Effects of marine Harmful Algal Blooms on bivalve cellular immunity and infectious diseases: a review

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Abstract

Bivalves were long thought to be "symptomless carriers" of marine microalgal toxins to human seafood consumers. In the past three decades, science has come to recognize that harmful algae and their toxins can be harmful to grazers, including bivalves. Indeed, studies have shown conclusively that some microalgal toxins function as active grazing deterrents. When responding to marine Harmful Algal Bloom (HAB) events, bivalves can reject toxic cells to minimize toxin and bioactive extracellular compound (BEC) exposure, or ingest and digest cells, incorporating nutritional components and toxins.

Several studies have reported modulation of bivalve hemocyte variables in response to HAB exposure. Hemocytes are specialized cells involved in many functions in bivalves, particularly in immunological defense mechanisms. Hemocytes protect tissues by engulfing or encapsulating living pathogens and repair tissue damage caused by injury, poisoning, and infections through inflammatory processes. The effects of HAB exposure observed on bivalve cellular immune variables have raised the question of possible effects on susceptibility to infectious disease. As science has described a previously unrecognized diversity in microalgal bioactive substances, and also found a growing list of infectious diseases in bivalves, episodic reports of interactions between harmful algae and disease in bivalves have been published. Only recently, studies directed to understand the metabolic basis of these interactions have been undertaken. This review compiles evidence from studies of harmful algal effects upon bivalve shellfish that establishes a framework for recent efforts to understand how harmful

algae can alter infectious disease, and particularly the fundamental role of cellular immunity, in modulating these interactions.

Experimental studies reviewed here indicate that HABs can modulate bivalve-pathogen interactions in various ways, either by increasing bivalve susceptibility to disease or conversely by lessening infection proliferation or transmission. Alteration of immune defense and global physiological distress caused by HAB exposure have been the most frequent reasons identified for these effects on disease. Only few studies, however, have addressed these effects so far and a general pattern cannot be established. Other mechanisms are likely involved but are under-studied thus far and will need more attention in the future. In particular, the inhibition of bivalve filtration by HABs and direct interaction between HABs and infectious agents in the seawater likely interfere with pathogen transmission. The study of these interactions in the field and at the population level also are needed to establish the ecological and economical significance of the effects of HABs upon bivalve diseases. A more thorough understanding of these interactions will assist in development of more effective management of bivalve shellfisheries and aquaculture in oceans subjected to increasing HAB and disease pressures.

Keywords: Bivalve; Harmful Algal Blooms (HABs); Pathogen; Hemocyte; Disease.

List of abbreviations

ASP: amnesic shellfish poisoning

AZA: azaspiracids

AZP: azaspiracid poisoning

BEC: bioactive extracellular compounds

BRD: brown ring disease

CFP: ciguatera fish poisoning

CTX: ciguatoxin

DA: domoic acid

DHC: differential hemocyte count

61 DMSP: dimethylsulfoniopropionate

62 DSP: diarrheic shellfish poisoning

63 DTX: dinophysistoxin

64 HAB: harmful algal bloom

65 LC: lytic compounds

66 NSP: neurotoxic shellfish poisoning

67 OA: okadaic acid

68 OIE: World Organisation for Animal Health (historically: Office International des Epizooties)

69 OsHV-1: ostreid herpesvirus-1

70 PAMP: pathogen-associated molecular pattern

71 PbTx: brevetoxin

72 PCR: polymerase chaine reaction

73 PLTX: palytoxin

74 PnTX: pinnatoxins

75 POMS: Pacific oyster mortality syndrome

76 PRP: receptor proteins

77 PSP: paralytic shellfish poisoning

78 PST: paralytic shellfish toxin

79 PTX: pectenotoxin

80 QPX disease: Quahog parasite unknown disease

81 QX disease: Queensland unknown disease

82 RLO: Rickettsia-like organisms

83 RNS: reactive nitrogen species

84 ROS: reactive oxygen species

85 SPX: spirolides

86 STX: saxitoxin

87 THC: total hemocyte count

YTX: yessotoxin

1 Introduction

Bivalve fisheries and aquaculture contribute to the economy of coastal countries worldwide. Mortality from infectious disease is the main threat to this industry, and mortality can be a consequence of interacting biotic and abiotic factors. Some evidence suggests the involvement of marine Harmful Algal Blooms (HABs) in bivalve disease outbreaks, particularly through effects upon bivalve immunity and defense against disease. This contribution reviews the published literature reporting effects of marine HABs upon cellular immunity and how they relate to bivalve infectious diseases, most of which have been studied under experimental conditions. Other mechanisms possibly involved in the effects of HABs on bivalve disease also are explored.

1.1 Bivalve diseases

Bivalve populations are affected by epizootics that decimate or weaken exploited stocks and therefore limit harvests (Barbosa Solomieu et al., 2015). Commercial trade between different regions of the world contributes to exotic species introduction and, as a consequence, to the spread of infectious diseases (Andrews, 1980; Renault, 1996). Bivalve diseases are caused by a variety of infectious agents (Zannella et al., 2017), mainly viruses (Arzul et al., 2017), bacteria (Travers et al., 2015), or protozoa (Robledo et al., 2014). A brief description of the most pathogenic agents for bivalves, mainly associated with OIE notifiable diseases, as well as occurrences and effects, follows.

In France, between 1967 and 1973, "gill disease" associated with an iridovirus, completely decimated populations of Portuguese oysters *Crassostrea angulata* (Comps, 1988), introduced from Portugal and Spain in 1868 (Marteil, 1976). This loss motivated the introduction in 1971 of the Pacific oyster *C. gigas* from Canada and Japan (Grizel and Héral, 1991); Pacific oyster resistance to this virus helped revive the French oyster industry. Nevertheless, in the early 1990s, Pacific oysters *C. gigas* were affected by “summer

mortality" events associated with a complex interaction between temperature, genetics, and physiological status (reproductive period) of the oyster, as well as the presence of opportunistic infectious agents, such as bacteria *Vibrio aesturianus* and *V. splendidus*, and the ostreid herpesvirus-1 (OsHV-1) (Samain, 2011). In 2008, this latter virus emerged as a more powerful variant (OsHV-1 µVar, Segarra et al., 2010), causing Pacific Oyster Mortality Syndrome (POMS), which strongly affected young *C. gigas* in France. POMS spread afterwards into many European countries as well as other countries in Oceania (New Zealand and Australia) (Barbosa Solomieu et al., 2015; Gittenberger et al., 2016; Mortensen et al., 2016). The OsHV-1 recently has been detected by PCR in *C. gigas* cultured in southern Brazil, however without any associated mortality (Mello et al., 2018), suggesting that environmental conditions can play an important role in the development of outbreaks. In Europe and Australia, Pacific oyster mortalities associated with OsHV-1 occur when temperature exceeds 16-18°C (de Kantzow et al., 2016; Panel and Health, 2015; Paul-Pont et al., 2014). Disbalance of environmental conditions combined with temperature stress also may contribute to the development of POMS. For example, in Australia, a POMS outbreak was correlated with heavy rainfall, presence of a pathogenic *Vibrio* sp., and a toxic phytoplankton bloom (Jenkins et al., 2013). In recent years, concerted efforts were made to understand the development of POMS, leading to recognition that OsHV1-µVar could weaken oyster defenses, thereby allowing opportunisitic bacteria of the genus *Vibrio* to infect the host, leading to mortality (de Lorgeril et al., 2018; Petton et al., 2015).

Vibriosis is a major concern for both oyster hatcheries and field production, causing larval and spat damage, depending upon species. Vibriosis can result in impairment of velum structure and function (necrosis and detachment of velar cells) and deterioration of soft tisues, which result in mortalities (Dubert et al., 2017; Travers et al., 2015). The most pathogenic vibrios belong to the *Splendidus* and *Harveyi* clades or to the species *V. aestuarianu*s, *V. tubiashii*, *V. coralliilyticus*, and *V. tapetis* (Travers et al., 2015). Although most *Vibrio* spp. can affect many bivalve species, *V. tapetis* appears to cause pathology only in Manila clams *Ruditapes philippinarum* and fishes (Levican et al., 2017; Reid et al., 2003). The resulting disease in clams is called Brown Ring Disease (BRD), because of the brown organic matrix deposit in the inner bivalve shell in responses to vibrio colonization. In advanced infections, *V. tapetis* can invade the circulatory system and lead to death (Paillard, 2004). The disease occurs in Europe, South Korea, and Japan (Travers et al., 2015).

Two species of protozoan parasite, *Marteilia refringens* and *Bonamia ostrea*, have strongly affected flat oyster *Ostrea edulis* production in France. *M. refringens* appeared in 1968 (Grizel et al., 1974) and *B. ostreae* in 1979 (Pichot et al., 1980), causing digestive gland and microcell diseases, respectively. Together these parasites caused a sharp decline in flat oyster production in France first, followed by in other countries in Europe (see special edition of the Diseases of Aquatic Organisms journal, vol.110, 2014). Recently, *B. ostrea* was reported for the first time in New Zealand (Lane et al., 2016). Another member of this genus, *Bonamia exitiosa,* also caused mortalities in *Ostrea chilensis* in New Zealand (Hine et al., 2001) and in *O. puelchana* from wild and cultured populations in Argentina (Oehrens Kissner et al., 2014). The protozoan parasite *B. exitiosa* also has been reported in European flat oysters and can contribute to disease (Ramilo et al., 2014). In Australia, Winter Mortality disease causes mortalities in 2 and 3 year-old Sydney rock oysters *Saccostrea glomerata* in winter and early spring (Dove et al., 2013). The disease initially was suspected to be caused exclusively by the protistan parasite *Bonamia roughleyi* (Hill et al., 2014); however, the disease may actually result from a confluence of factors, including environmental conditions (Spiers et al., 2014). Another disease, called Queensland unknown (QX) disease caused by the haplosporidia parasite *Marteillia sydneyi*, affects the *S. glomerata* industry in Australia (Carrasco et al., 2015; Perkins and Wolf, 1976). The parasite *M. sydneyi* enters the host by gill and palp epithelia, with the progression of infection reaching the digestive tubules where parasite sporulation proceeds. This process causes the breakdown of the digestive gland, compromising feeding processes and leading to death (Kleeman et al., 2002).

Protozoan parasites from the *Perkinsus* genus are among the most pathogenic for oyster species worldwide (Villalba et al., 2011). The first outbreak occurred in 1946 in Louisiana (USA) with reported mortalities (up to 100%) of American oysters *C. virginica* that resulted in significant economic losses (Goulletquer et al., 1994). The disease is commonly referred to as "Dermo" in reference to the belief that it was a fungus, *Dermocystidium* (Mackin and Owen, 1950). Prevalence and body burden of *Perkinsus marinus* in *C. virginica* populations in the northeastern United States present a seasonal pattern strongly related to temperature, wherein maximum prevalence and intensity are reached in late summer - early automn (Burreson and Ragone-Calvo, 1996). Occurrences of *P. marinus* in tropical regions, such as Mexico (Cáceres-Martínez et al., 2016) and Brazil (da Silva et al., 2014) were reported without mortalities of the native hosts, oysters *C. corteziensis* and *C. gasar*, respectively, but seasonal patterns of the disease seem to be similar to those in the USA. Intensities are

183 predominantly light to moderate, without strongly deleterious, histopathological effects
184 (Cáceres-Martínez et al., 2016; Queiroga et al., 2015; Scardua et al., 2017). Immunological
185 functions, however, were impaired in intense infections (Queiroga et al., 2013), and genetic
186 disturbances may occur because of widespread DNA methylation in *C. gasar* infected with
187 *Perkinsus* spp. (Farias et al., 2017). Another representative species of this genus is *Perkinsus*
188 *olseni* that affects clam *Ruditapes descussatus* and *R. philippinarum* populations in Europe
189 (Portugal, France, Spain and Italy) and Asia (South Korea and Japan). The intensity of the
190 effect of this parasite is variable, being milder in France, despite the high prevalence (up to
191 100%) (Dang et al., 2010) and in Spain. Strong effect is observed in Portugal (Ruano et al.,
192 2015), South Korea (Choi and Park, 2010) where mortalities were associated with stress of
193 high seawater temperature (Nam et al., 2018), and Japan where high prevalence (100%) and
194 intensity were associated with declining *R. philippinarum* populations (Waki et al., 2018).

195

196 **1.2 Harmful Algal Blooms and co-occurrence with bivalve infectious diseases**

197 HABs are a natural phenomenon characterized by localized and transient proliferation of
198 some microalgal species favored by certain environmental conditions (Sellner et al., 2003).
199 The frequency of HABs appears to have increased worldwide in recent decades and may be
200 partly related to global change and human activities (Anderson et al., 2008; Glibert, 2017;
201 Gobler et al., 2017; Hallegraeff, 1993; Wells et al., 2015). Toxic blooms in temperate areas
202 tend to be punctual and seasonal phenomena, most often in spring and summer, and can last a
203 few weeks to a few months. In tropical or sub-tropical areas, blooms can last much longer
204 where no strong seasonal environmental changes occur (e.g. blooms of *Karenia brevis*
205 persisted for over a year in Florida in 2018 (HABSOS, 2019)).

206 The harmful effect of HABs can either be direct (toxins or damaging algal morphology) or
207 indirect (high concentration of microalgal cells leading to hypoxia). In this paper, we will
208 discuss only HAB species producing described toxins (intra- or extracellular) and other
209 uncharacterized bioactive extracellular compounds (BEC) with cytotoxic properties, which
210 can affect bivalves.

211

The best-known microalgal biotoxins are those associated with symptoms in human consumers of contaminated seafood (see review from Berdalet et al., 2015; Gerssen et al., 2010; Lassus et al., 2016) as follows:

1) paralytic shellfish poisoning (PSP) is caused by saxitoxins (STXs, also refered to as Paralytic Shellfish Toxins, PSTs), produced by species of *Alexandrium*, *Gymnodinium* and *Pyrodinium*;

2) neurotoxic shellfish poisoning (NSP) caused by brevetoxins (PbTXs), mostly produced by *Karenia brevis*;

3) diarrheic shellfish poisoning (DSP) associated with okadaic acid (OA) and dinophysistoxins (DTXs) produced by species of the genera *Dinophysis* and *Prorocentrum*;

4) amnesic shellfish poisoning (ASP) caused by domoic acid (DA) and analogs produced by species of *Pseudo-nitzschia* and *Nitszchia*;

5) ciguatera fish poisoning (CFP) caused by ciguatoxins (CTXs), produced by *Gambierdiscus* species.

6) Other microalgal toxins implicated in human toxic symptoms include azaspiracids (AZA), mostly produced by *Azadinium* and *Amphidoma* spp. and responsible for azaspiracid poisoning (AZP); palytoxins (PLTXs) and analogues, produced by *Ostreopsis* spp., are associated with food-borne poisoning as well as irritative symptoms through contact or aerosol inhalation. Other phycotoxins possibly toxic to humans, as suggested by potency in mouse bioassay or *in vitro* toxicological tests, include: spirolides (SPXs) produced by *Alexandrium ostenfeldii* and *A. peruvianum*; yessotoxins (YTXs) produced by species of *Protoceratium*, *Gonyaulax* and *Lingulodinium*; pectenotoxins (PTXs) produced by species of *Dinophysis*; and pinnatoxins (PnTXs) produced by *Vulcanodinium rugosum*.

Other HABs, not toxic to humans but known for being deleterious to marine fauna, are referred to as ichthyotoxic or fish-killing algae because they are mainly involved in mortality of farmed fishes (although most also affect shellfish and other marine organisms). The harmful mechanism of some of these algae is associated with hypoxia from high bloom density, or through mechanical irritation, but most ichthyotoxic algae produce compounds with cytotoxic and lytic activity. Some ichthyotoxins have been described already (e.g. prymnesins, karlotoxins, karmitoxin), and other compounds such as reactive oxygen species

(ROS), polyunsaturated fatty acids, and muccopolysaccharides, appear to be involved in ichthyotoxic activity (Binzer et al., 2019; Dorantes-Aranda et al., 2015; Hallegraeff et al., 2017; Rasmussen et al., 2017, 2016). Most of the algal compounds responsible for ichthyotoxic activity, however, remain unknown or not well characterized (Rasmussen et al., 2016). Algae most involved in ichthyotoxic phenomena belong to the genera *Margalefidinium* (aka. *Cochlodinium)*, *Chatonella*, *Pseudochatonella*, *Prymnesium*, *Chrysochromulina*, *Karenia*, *Karlodinium*, *Pfiesteria*, *Heterocapsa, Heterosigma,* and *Akashiwo* (Hallegraeff et al., 2017; Lassus et al., 2016).

As sessile, filter-feeding organisms, bivalves interact directly with harmful microalgal blooms that occur along coasts worldwide. Bivalves can be in contact with both microalgal extracellular compounds, including BEC, as well as with intracellular toxins that can be released during digestion. Intracellular toxins often accumulate in bivalve tissues, mostly in the digestive gland (e.g. Lassudrie et al., 2014; Medhioub et al., 2012; see review of Landsberg, 2002). BEC have allelopathic, lytic, and oxidative activity reported upon microalgae, protists, or bivalve gametes (Arzul et al., 1999; Castrec et al., 2019; Flores et al., 2012; Le Goïc et al., 2014, 2013; Lelong et al., 2011; Long et al., 2018b; Tillmann and John, 2002). Toxins (intra- and extracellular) as well as BEC produced by HABs can be harmful to bivalves (e.g. Borcier et al., 2017; Castrec et al., 2018). HABs can affect physiological functions and ultimately survival of bivalves, at different life stages, and can result in major socio-economic and ecological problems (Landsberg, 2002; Shumway, 1990).

Considering spatial and temporal occurrence of HABs and infectious diseases, the probability for both potential stressors to affect bivalves simultaneously is high, as highlighted by Table 1, which lists (non-exhaustively) HABs reported to occur in regions and seasons where and when disease also occur. Only few studies, however, have reported co-occurrence of infectious disease outbreaks with HABs (Abi-Khalil et al., 2016; Jenkins et al., 2013). The low number of published observations probably is attributable more to a lack of reports than a lack of co-occurrence. The observations reported by these two field-studies suggested that *Alexandrium* spp. (Abi-Khalil et al., 2016; Jenkins et al., 2013) and/or *Pseudo-nitzschia* spp. (Jenkins et al., 2013) blooms in France and in Australia could increase oyster susceptibility to POMS. As causal relationship is difficult to infer from field observations, some experimental studies have focused on the interactive effects of both HABs and pathogen infection (summarized in Table 2).

The initial physiological status of the bivalve is one of the main conditions that modulates the outcome of a host-pathogen interaction (Samain and McCombie, 2007). Thus, the physio-pathological responses of bivalves exposed to both HABs and pathogens are the results of the interaction between: 1) the initial physiological status of the bivalve, 2) the effect of HABs, and 3) the effect of the pathogen upon the bivalve.

Since HABs interfere with bivalve immune cell variables and likely co-occur with disease infection, we review here the effects of HABs on hemocytes, including in bivalves co-exposed to pathogens, and their relationship with disease modulation. Other mechanisms by which infectious diseases can be modulated by HABs, through alteration of bivalve physiology, and through direct interactions between HABs and pathogens, are also explored.

2. Effects of HABs on bivalve cellular immunity and involvement in disease modulation

Compromised immunological status is a fundamental condition that contributes to disease acquisition and progression. Bivalve immune cells, called hemocytes, are responsive to disease infection, but can also be affected by environmental factors (e.g. temperature, salinity), including HABs. Therefore, the resulting effect on immunity and disease susceptibility has often been questioned.

In this section, after a brief description of the basics of bivalve immunity, we review the reported effects of HABs upon bivalve cellular effectors of immunity, the hemocytes, through the study of dual HAB-bivalve interactions (Table 3) and tripartite HAB-bivalve-pathogen interactions (Table 4).

2.1 Bivalve immunity and hemocytes

The immune system of bivalves is exclusively innate, lacking an adaptive memory as in vertebrates, although the existence of a form of immune memory in invertebrates is now being discussed, including in bivalves (see for example Lafont et al., 2019, 2017, for *C. gigas*). The

303 immune cells, hemocytes, are implicated in multiple physiological functions in bivalves,
304 including nutrition, shell mineralization and tissue repair and, the most important, immunity.
305 These circulating cells perform defense functions against infectious agents, mainly by
306 phagocytosis or encapsulation of infective agents (Cheng, 1996). The immune systems of
307 bivalves also include soluble molecules in the hemolymph and mucus secretions that act in
308 the recognition and destruction or inactivation of invading organisms (Allam and Raftos,
309 2015; Song et al., 2010). It is now accepted that the immune system of bivalves is
310 sophisticated and complex, presenting a high diversity of recognition molecules (Guo et al.,
311 2015). Receptor proteins (PRPs) are inducible and secreted or are membrane proteins that
312 recognize evolutionarily conserved pathogen-associated molecular patterns (PAMPs) (Allam
313 and Raftos, 2015; Guo et al., 2015; Song et al., 2010). The ability to destroy microorganisms
314 is associated with several immune molecules, including: hydrolytic enzymes, reactive oxygen
315 and nitrogen species (ROS and RNS), and especially peptides and antimicrobial proteins
316 which are widely studied in *C. gigas* (Destoumieux-Garzón et al., 2016; Schmitt et al., 2016,
317 2012b, 2012a). Hemocytes ontogeny, however, remains a mystery (Dyachuk, 2016; Li et al.,
318 2017). Hemocytes circulate through the open circulatory system in the hemolymph and reach
319 bivalve organs. Hemocytes are able to infiltrate tissues in response to infectious agents, such
320 as bacteria and protozoa in a response termed inflammation (Carella et al., 2015; De Vico and
321 Carella, 2012), and even in some cases transiting epithelial barriers and inadvertently bringing
322 pathogens, such as *P. marinus*, inside the body (Lau et al., 2018) or expulsion of *M. sydneyi*
323 (Kleeman et al., 2002). Total (THC) and differential hemocyte counts (DHC, granulocytes
324 and hyalinocytes, aka. agranulocytes, discriminated by cell size and internal complexity), and
325 functional measurements, phagocytosis activity particularly, are good indicators of bivalve
326 immune status (Fournier et al., 2000; Vargas-Albores and Barracco, 2001).

327

328 **2.2 Effects of HABs on bivalve hemocyte variables involved in immunity**

329 In this review we focused on the most studied bivalve hemocyte characteristics modulated by
330 HABs or associated toxins (section 2.2), as well as by combined exposure to HAB and
331 pathogens (section 2.3). As we focused on immunological aspects of bivalves, articles
332 reporting genotoxic effects on hemocytes were not included in this review. The most relevant
333 results presented in 38 articles are summarized in Table 3 and 4.

334 THC, DHC, size, complexity, phagocytosis, and ROS production of circulating cells in the
335 hemolymph are the most studied and common variables among the papers. Other hemocyte or
336 plasma variables also were included, such as adhesion/aggregation, agglutination titer,
337 phenoloxidase activity, viability, lysosomal membrane stability (cytotoxicity variables), and
338 apoptosis. Apoptosis was added because programmed cell death may be particularly
339 implicated in the immune defense against oyster intracellular pathogens (Sokolova, 2009),
340 which has been most-thoroughly investigated in the *P. marinus – C. virginica* model (Hughes
341 et al., 2010; Lau et al., 2018c). The studies summarized in Table 3 include the most important
342 commercial bivalve species worldwide, i.e., oysters primarily, followed by mussels, clams,
343 and pectinids. A good representation of HAB species is included in published studies, such as
344 producers of PSP toxins (*Alexandrium* spp.), DSP toxins (*Prorocentrum* and *Dynophysis*
345 spp.), gymnodimin (*Karenia selliformis*), palytoxin (*Ostreopsis ovata*), karlotoxins
346 (*Karlodinium veneficum*), and other toxic compounds still not well characterized from
347 *Karenia mikimotoi*, *Heterosigma akashiwo,* and *Heterocapsa circularisquama*. The effects of
348 purified phycotoxins were evaluated by *in vitro* incubation with hemocytes (STX, OA and
349 PbTx) or by injection into the living bivalve (DA). No studies on hemocyte responses were
350 carried out with algal producers of DA, YTX, CTX, or AZA toxins thus far (Table 3).

351 Bivalve hemocyte responses to a harmful alga depend upon the physiological state of the
352 bivalve, but also on algal morphology and density, intraspecific variability of algal toxicity,
353 and experimental conditions, which altogether may affect exposure to algal compounds,
354 including through pre-and post-ingestive selection. Therefore, it is sometimes difficult to
355 identify similar hemocyte response patterns, even considering the same alga and bivalve
356 species. Two good examples of diversity of bivalve responses were obtained with the most-
357 studied harmful algae *A. minutum* and *P. minimum*. In one experiment exposing *C. gigas* to *A.*
358 *minutum,* only an increase in hemocyte phagocytosis was observed (Haberkorn et al., 2014).
359 In contrast, in another study, THC and granulocytes increased and ROS production and
360 phenoloxidase activity were not consistent (Haberkorn et al., 2010a). Regarding *P. minimum*,
361 in one study, a simulated bloom increased *C. virginica* hemocyte phagocytosis, THC,
362 granulocyte counts and viability, and aggregation decreased, while ROS varied (Hégaret and
363 Wikfors, 2005a); whereas, the other experiment did not promote any hemocyte modulation
364 (Hégaret and Wikfors, 2005b). Difference in hemocyte responses in these studies were
365 attributed to differences between oyster populations and the means of algal exposure, i.e.,

366 cultured cells or a natural bloom. The latter study was later corroborated by an *in vitro* assay
367 (Hégaret et al., 2011).

368 The species *A.catenella* (= *A. fundyense* as refered to in these studies; see last nomenclature in
369 Fraga et al. 2015; Litaker et al. 2018) caused only mild effects upon hemocytes of adult *C.*
370 *virginica* and *C. gigas* (Hégaret et al., 2007b) and *M. edulis* (Galimany et al., 2008b). In
371 contrast, *A. catenella* and *A. tamarense* caused cytotoxic effects in addition to impairment of
372 immune responses in blue mussels *M. edulis* (Bianchi et al., 2019). Cytotoxic effects,
373 however, were not directly related to PSTs. Indeed, both PST and non-PST strains that
374 produced BEC (also refered to as lytic compounds, LC), caused similar responses (Bianchi et
375 al., 2019). Similarly, a highly-toxic, PST-producing strain of *A. catenella* (named *A.*
376 *tamarense* in the study; see new nomenclature in John et al., 2014; Fraga et al., 2015; Litaker
377 et al., 2018) had no effects upon *R. philippinarum* or *M. arenaria* hemocytes*;* whereas, a non-
378 PST strain of *A. tamarense* did have effects, probably caused by bioactive compounds (Ford
379 et al., 2008). Castrec et al. (2018) compared the effects of three *A. minutum* strains with
380 contrasting PST and BEC characteristics. This study detected clear effects of PST on
381 hemocyte mortality, hypothesized to involve apoptosis. PST effects upon hemocyte apoptosis
382 were reported previously from *in vivo* (PST injection) and *in vitro* (PST exposure of
383 hemocytes) assays with lions-paw scallops *Nodipecten subnodosus* (Estrada et al., 2014), in
384 *C. gigas*, *in vivo* (*A. pacificum* exposure) (Medhioub et al., 2013), and *in vitro* (PST exposure
385 of hemocytes) (Abi-Khalil et al., 2017). In other work with *A. minutum* and *C. gigas,* using *in*
386 *vitro* exposures, similar responses, phagocytosis and ROS inhibition, were observed when
387 hemocytes were exposed to PST-producing strains of *Alexandrium* spp. or directly to PSTs
388 (Hégaret et al., 2011; Mello et al., 2013). The effects of PSTs themselves upon hemocytes
389 seem to be relatively consistent, reducing phagocytosis (Astuya et al., 2015; Cao et al., 2018;
390 Mello et al., 2013) and ROS (Astuya et al., 2015; Mello et al., 2013), regardless of bivalve
391 species and administration mode (direct exposure or injection).

392 Separating effects of intracellular toxins and BEC has been recognized only recently because
393 of a lack of awareness of the existence of BEC, and for practical reasons (availability of algal
394 strains with different toxin and BEC characteristics). Correlations between hemocyte
395 variables and toxin accumulation in tissues indicated that specific hemocyte responses to PST
396 occur in *C. gigas* exposed to *Alexandrium* spp. (Haberkorn et al., 2010a; Lassudrie et al.,
397 2016). This was later confirmed using different *A. minutum* strains with contrasting PST and
398 BEC characteristics, showing some distinct hemocyte responses to PST *vs.* BEC (Bianchi et

al., 2019; Castrec et al., 2018). Results of Lassudrie et al.(2016) with the oyster *C. gigas* exposed to *A. pacificum* (named *A. catenella*, in this study; see last nomenclature in John et al. 2014; Fraga et al. 2015; Litaker et al. 2018) indicated a relationship between PST levels and hyalinocyte variables, suggesting a particular role for this hemocyte type in response to PST; whereas, granulocyte modulations may respond to putative BEC. Other studies with *A. minutum*, however, did not support the hypothesis of a specific role of hyalinocytes in PST response (Castrec et al., 2018; Haberkorn et al., 2010a). Further studies are needed to decipher the functional responses of the different hemocyte types to PST *vs*. other bioactive compounds.

The toxic dinoflagellate *P. minimum* was also reported to have different effects upon *C. virginica* (Hégaret and Wikfors, 2005a, 2005b). Results of some experiments indicated increased phagocytosis and decreased aggregation and mortality (Hégaret and Wikfors, 2005a), other experiments did not detect any alteration in hemocyte variables (Hégaret and Wikfors, 2005b). A decrease of phagocytosis and of apoptosic hemocytes could be observed in clams *R. philippinarum* exposed to *P. minumum* (Hégaret et al., 2009). However, no effect on hemocyte was observed also in *M. edulis* exposed to *P. minimum*, (Galimany et al., 2008c). In contrast, a simulated bloom of *P. minimum* strongly affected all hemocyte variables of scallops *A. irradians irradians* (Hégaret and Wikfors, 2005b). This could indicate a higher sensivity of scallops to some HABs like *P. minimum* than other bivalves, such as *C. virginica*. More studies are needed to support this hypothesis. The dinoflagellate *P. lima* and associated OA toxin were tested against mussels and clams and were shown to induce hemocyte apoptosis (Prado-Alvarez et al., 2013; Prego-Faraldo et al., 2016, 2015), except in one case of a natural bloom of *Prorocentrum* sp. and *Dinophysis* sp., and OA *in vitro* exposure (Prado-Alvarez et al., 2012). Effects of a simulated bloom of *P. lima* upon hemocyte functions were tested recently in the mussel *Perna perna*, and impaired phagocytosis, induced ROS production, and decreased THC were observed (Neves et al., 2019).

Although simulating a HAB under laboratory conditions may be a good approximation of reality, it is unquestionable that the best way to evaluate HAB effects upon bivalve cellular immune functions will be during a natural bloom; however, only three studies were conducted under those circumstances (Mello et al., 2010; Prado-Alvarez et al., 2012; Simões et al., 2015). During a natural bloom of *Dinophysis acuminata* in Santa Catarina state, South Brazil, some immune responses of three bivalve species belonging to different families were studied (Table 3). A reference group, animals collected at same site 30 days after the HAB exposure,

were used for comparisons. Despite the differences in the concentration of algae during the blooms, it was clear that the bivalve species responded differently, *C. gigas* was the most resilient species; whereas, the mussel *P. perna* was the most affected, suggesting that this mussel may be a good bioindicator species. The sentinel candidature of mussels for environmental change and now for HABs was corroborated in another study with the mussel *M. galloprovinciallis* exposed to the bentic dinoflagellate *Ostreopsis* cf. *ovata* with strong impairment (reduction) in granulocyte counts, phagocytosis activity, and lysosomal membrane stability as cytotoxic effects (Gorbi et al., 2013). In contrast, a study exposing oyster *C. gigas* hemocytes to brevetoxin did not reveal any cytotoxic effect (viability and apoptosis were evaluated) (Mello et al., 2012). Even though no *Pseudo-nitzschia* or *Nitszchia* spp. blooms have been evaluated for effects upon immune cellular responses of bivalves, *M. edulis* was exposed to DA by intra-muscular injection (Dizer et al., 2001). The acute effects of DA were seen in THC and phagocytosis, which increased initially, but after 7 days post-injection, variables normalized and hemocyte viability increased in a dose dependent manner during recovery.

2.3 Involvement of HAB effects on bivalve hemocytes in disease modulation?

The several effects of HABs upon hemocyte variables documented above led many authors to wonder about HAB effects upon immune functions and eventually upon disease susceptibility. These effects upon hemocytes have been hypothesized to modify the efficiency of bivalve immune functions, either by causing immunosuppression, particularly when functions such as phagocytosis are affected, or immunostimulation when considering increased THC or viability, for example. Few papers, however, report the combined effects of HABs and infectious agents upon immune functions of bivalves (Table 4). Most studied is the host-parasite model *R. philippinarum-P. olseni* under the secondary effect of HABs *K. selliformis* and *K. mikimotoi* (da Silva et al., 2008; Hégaret et al., 2007a), *P. minimum* (Hégaret et al., 2009) and *A. ostenfeldii* (Lassudrie et al., 2014). Others evaluated the effects of HAB *A. catenella* (=*A. fundyense*), on *P. marinus* and *Bucephalus* sp. in oysters *C. virginica* (Lassudrie et al., 2015b), on trematodes Gymnophalidae in mussels *M. edulis* (Galimany et al., 2008b), on BRD caused by *V. tapetis* in clams *R. philippinarum* (Bricelj et al., 2011). The effect of *P. minimum* on Quahog Parasite Unknown (QPX) disease in clams *M. mercenaria* also was studied (Hégaret et al., 2010).

464 Many of these studies reported a repression of hemocyte responses during the interaction of
465 bivalve – pathogen – HAB, which cannot be explained simply. Indeed, the combination of the
466 two biotic factors causes hemocyte responses that might not correspond to the cumulative
467 effect of each isolated factor, leading to antagonistic or synergistic responses. Additionally,
468 the existence of combined effects of HAB and pathogen can modulate the bivalve response.
469 For example *K. selliformis,* in a short exposure experiment, inhibited *R. philippinarum*
470 hemocyte phagocytosis and increased hemocyte count in clams heavily infected with *P.*
471 *olseni;* whereas, the parasite itself did not affect the host (Hégaret et al., 2007a). Another toxic
472 dinoflagellate, *A. ostenfeldii* had a very mild effect itself upon *R. philippinarum* hemocyte
473 variables, but the combination with *P. olseni* infection induced ROS production in lightly-
474 infected clams comparable with the levels found in the heavily-infected animals unexposed to
475 HAB (Lassudrie et al., 2014). Likely, the interference between hemocyte responses to HAB
476 and to pathogens are related to different functions.

477 It was hypothesized initially that effects of HABs upon hemocyte functionality would induce
478 an immunocompromised state associated with increased susceptibility to disease. Such
479 immunodepression, indicated by immunological changes and inflammatory response, was
480 hypothesized by Galimany et al. (2008c) after observation of increased prevalence of
481 trematodes in mussels exposed to *A. catenella* (= *A. fundyense*). Increase in parasite *P.*
482 *marinus* prevalence was detected in the Eastern oysters exposed to *A. catenella* and
483 concomitantly infected by trematodes *Bucephalus* sp. (Lassudrie et al., 2015b). This increase
484 in parasite prevalence was associated with repression of hemocyte responses to the trematode
485 infestation (Lassudrie et al., 2015b). The authors concluded that this higher susceptibility to *P.*
486 *marinus* was likely the result of immunosuppression caused by HAB exposure in oysters
487 already weakened by trematode infestation, as indicated by histological evidence.

488 Other studies reviewed in Table 4 could not link the hemocyte alteration caused by HABs
489 with disease modulation.

490

491

3. Other bivalve physiological variables affected by HABs and possibly involved in disease modulation

HAB exposure can affect several physiological variables in bivalves. Here, we discuss the variables most likely involved in disease transmission or proliferation that have been reported to be modulated by HABs: feeding activity, and tissue alterations, often associated with inflammatory response.

3.1 Effects of HABs on feeding processes: possible involvement in pathogen transmission?

Filtration and ingestion rates could play an important role in the modulation of the tripartite interactions. Indeed, infection process is deeply related to the entry of pathogenic agents into the bivalve body. Thus, it can be speculated that the lower the filtration rate, the lower the level of parasite inside the host.

Bivalves have the ability to adapt filtration and ingestion rates (feeding activity) to plankton composition. Indeed, decreases in clearance and filtration rates of several bivalve species in the presence of toxic microalgae have been widely reported in the literature (e.g. Contreras et al., 2011; Hégaret et al., 2007c; Jauffrais et al., 2012; Lassus et al., 2007, 1999; Shumway, 1990).

In oysters, reduction of *A. minutum* consumption seems to be mostly associated with algal BEC production, rather than to PST (Castrec et al., 2018). BECs irritate gills and, therefore, likely interfere with filtration or sorting functions and induce a protective behavioral response consisting of increased frequency of valve micro-closures (Castrec et al., 2018; Haberkorn et al., 2011; Tran et al., 2010). Conversely, contact with intracellular PSTs occurs mainly in the digestive organs after algal cell lysis. Pousse et al. (2018), however, demonstrated that a PST, non-BEC-producing strain of *A. minutum* also caused a decrease in feeding activity, thus suggesting the involvement of PST in filtration response. Furthermore, a recent study exposing mussels to *Alexandrium* spp. strains with different PST and BEC characteristics, also suggested that PSTs cause lower feeding activity (Bianchi et al., 2019). Such differences

may, indeed, be caused by variability in both BEC and PST quality and quantity exposure in the two studies, or to different sensitivity of mussels and oysters.

Reduction in herpesvirus infection, associated with POMS, in juvenile *C. gigas* oysters was hypothesized to be associated with filtration decrease (Lassudrie et al., 2015a). No study to date, however, has investigated the specific links between effects of HABs upon feeding processes and infectious agent transmission and proliferation.

3.2 Tissue degeneration and inflammatory response caused by HABs: overall physiological weakness favorizing disease susceptibility?

Despite the ability of bivalves to avoid or reduce ingestion of some HAB species, they show histopathological effects resulting from the HAB exposures.

The most common tissues affected are epithelia from mantle, gills, digestive gland or foot, and the most common alterations found are: vacuolation, oedema, melanization of gills and mantle (putatively associated with oxidative stress), signs of irritation (mucus production), and digestive tubules sloughing and atrophy (Haberkorn et al., 2010b; Hégaret et al., 2012, 2010, 2009; Lassudrie et al., 2014; Medhioub et al., 2012; Neves et al., 2019). Depending upon the organ, effects upon epithelia can be attributed to: (a) the extracellular compounds released by HABs, and (b) the intracellular toxins released after cell lysis at the end of the bloom or after direct contact with gills, or as a consequence of digestion. Indeed, the digestive gland is the organ accumulating most of the algal intracellular toxins (e.g. Lassudrie et al., 2014; Medhioub et al., 2012; see review of Landsberg, 2002).

Additionally, exposure to PST-producing HABs, or to purified toxins, can affect muscle integrity (Estrada et al., 2010; Haberkorn et al., 2010b; Hégaret et al., 2012, 2009), sometimes associated with altered escape response (Hégaret et al., 2012) or paralysis (Estrada et al., 2010).

Inflammatory response, consisting of hemocyte infiltration, often is observed in response to HAB or associated toxin exposure and likely is involved in repairing damaged tissues (e.g. Estrada et al., 2010; Hégaret et al., 2010; Hermabessiere et al., 2016; Lassudrie et al., 2015b, 2014; Medhioub et al., 2012). Hemocyte diapedesis through the digestive epithelia, and significative presence of hemocytes in the lumen of the intestine or around the gills,

surrounding algal cells, and in the faeces, also suggest a mechanism comparable to encapsulation to protect the internal tissues from algal toxic compounds (Galimany et al., 2008c; Hégaret et al., 2009). These observations also lead some authors to assume an additional role for hemocytes in detoxification, i.e., transporting toxins or their products outside the tissues (Galimany et al., 2008c, 2008b; Hégaret et al., 2009). Detection of a type of lipohphilic algal toxin, yessotoxins, in the hemocytes of mussels (Franchini et al., 2003), supports this hypothesis.

Degeneration of tissues and inflammatory response caused by HAB exposure are likely to increase susceptibility to pathogens by physiologically weakening bivalves and possibly interfering with hemocyte immune functions by recruiting hemocytes for tissue repair. This mechanism was suggested previously by Hégaret et al. (2012) and Lassudrie et al. (2015a) who observed concomitant tissue alterations and disease modulation under HAB exposure (Table 2).

4. Modulation of bivalve disease through direct effect of HABs on infectious agents

Direct interactions between HABs and infectious agents in the environment may affect bivalves indirectly by interfering with infectious agent transmission or proliferation. Two possible types of interactions are considered here: (a) effects of algal toxins and extracellular compounds on bivalve pathogens, which could either be beneficial or deleterious to pathogens, and (b) the possibility of microalgae, including HABs, to act as pathogen carriers.

4.1 Effects of algal toxins and extracellular compounds to bivalve pathogens

Bivalve pathogens may be in contact with toxic algal cells and associated toxic compounds directly before infecting the host (dissolved toxins or BEC) or during infection, within bivalve tissues (BEC or accumulated toxins).

Efforts to characterize the deleterious effects of extracellular compounds from HAB species upon various microorganisms have highlighted cytotoxic activity towards auto- and hetero-

trophic protists (Adolf et al., 2007; Arzul et al., 1999; Flores et al., 2012; Lelong et al., 2011; Long et al., 2018b, 2018a; Tillmann, 2003; Tillmann et al., 2008; Tillmann and John, 2002). As many species of HABs are mixotrophic, but also serve as prey, such extracellular bioactivity is believed to be related to predation and/or defense (anti-grazing) behavior (e.g. Adolf et al., 2007; Tillmann, 2003; Tillmann et al., 2008). Similarly, many other microalgae, including HAB species, can also feed on bacteria (Burkholder et al., 2008; Mitra et al., 2014).

Effects of HABs specifically upon protists, bacteria, and viruses pathogenic to bivalves have rarely been investigated (Table 2). Reports of decreased infections suggest that HABs could alter viability or virulence of bivalve pathogens (see further examples below, in da Silva et al., 2008; Hégaret et al., 2010; Lassudrie et al., 2015a). Another scenario considered is that HAB compounds could promote growth of pathogenic bacteria, as bacteria can consume organic nutrients excreted by microalgae (Seymour et al., 2017; Zhou et al., 2018). Among compounds excreted by microalgae, dimethylsulfoniopropionate (DMSP) is an organosulfur compound that is a potent chemoattractant to bacteria, which can metabolize it and use it as carbon and sulfur sources (Kiene et al., 2000; Simó, 2001). Not incidentally, harmful algal species are mostly represented by dinoflagellates, which are important DMSP producers among phytoplankton groups (Caruana and Malin, 2014).

Many studies reported the allelopathic, lytic, and oxidative properties of *Alexandrium* spp. extracellular compounds toward different cells, such as microalgae, protists, or bivalve gametes (Arzul et al., 1999; Castrec et al., 2019; Flores et al., 2012; Le Goïc et al., 2014, 2013; Lelong et al., 2011; Long et al., 2018b; Tillmann and John, 2002). Although PST can be released extracellularly (Lefebvre et al., 2008; Persson et al., 2012), many studies reported the bioactivity of extracellular compounds produced by non-PST *Alexandrium* strains, demonstrating that these effects are independent from PSTs (Bianchi et al., 2019; Borcier et al., 2017; Castrec et al., 2019, 2020; Ford et al., 2008; Long et al., 2018b; Tillmann et al., 2007; Tillmann and John, 2002). Only a few studies focused on the characterization of these compounds, and their precise nature remains unknown (Flores et al., 2012; Ma et al., 2011, 2009).

Antibacterial compounds produced by microalgae have been widely reported in the literature (see for example Amaro et al., 2011; Kellam and Walker, 1989), including upon bacteria pathogenic to aquacultured species, in particular *Vibrio* spp. (Kokou et al., 2012). Antibacterial effects of HAB species, however, have rarely been studied. Lauritano et al.

612 (2016) did not detect any activity of intracellular extracts of *Pseudo-nitzschia*
613 *pseudodelicatissima, Alexandrium tamutum*, *A. andersonii* and *A. minutum* against different
614 Gram-negative and Gram-positive bacteria infecting humans. PSTs target voltage-gated
615 sodium channel receptors, resulting in modulations of sodium and potassium fluxes in many
616 organisms, such as mammals (Catterall, 2000), bivalves (Boullot et al., 2017), and certain
617 bacteria (Pomati et al., 2003). Such effects were also demonstrated in the bacterium *Vibrio*
618 *fischeri* (Pomati et al., 2003). Therefore, it could be hypothesized that PST released by algal
619 cells may interact with certain pathogenic bacteria *in situ* and result in modulation of infection
620 in bivalves, although no study has demonstrated such effects so far.

621 Extracellular compounds from microalgae, including recognized HAB species, can have
622 antiviral activity (see review by Amaro et al., 2011). For example, extracellular sulphated
623 polysaccharides produced by *Gymnodinium impudicum* and *Margalefidinium polykrikoides*
624 were reported to affect viruses pathogenic to human and other mammalian hosts (Hasui et al.,
625 1995; Yim et al., 2004). The observation of a decrease in intensity of herpesvirus OsHV-
626 1µVar infection in juvenile oysters *C. gigas* exposed experimentally to *A. pacificum* led the
627 authors to propose that the dinoflagellate extracellular compounds may also induce
628 deleterious effects in viruses (Lassudrie et al., 2015a). The hypothesis was advanced that ROS
629 produced in extracellular compounds of *Alexandrium* spp. (as evidenced by Flores et al.,
630 2012) could have altered the OsHV-1 lipidic envelope and thereby infectivity. Despite these
631 hypotheses, no study so far has confirmed the direct effects of HABs upon viruses pathogenic
632 to bivalves.

633 Deleterious effects of other dinoflagellates upon bivalve parasites were reported. An *in vitro*
634 experiment reported toxicity of a culture of *K. selliformis* to the Manila clam parasite *P.*
635 *olseni*, as indicated by observation of a higher percentage of dead *P. olseni* cells and altered
636 morphology (da Silva et al., 2008). These effects were believed to be responsible for
637 decreasing intensity of *P. olseni* infection in clams *R. philippinarum* exposed experimentally
638 to this alga (da Silva et al., 2008). Similarly, Hégaret et al. (2009) reported toxic effects of
639 extracellular compounds from *P. minimum* to *P. olseni* cells during an *in vitro* experiment.
640 These authors, however, did not observe any modulation of the *P. olseni* infection in Manila
641 clams exposed to this alga, possibly because of the short duration of the exposure (6 days)
642 (Hégaret et al., 2009).

643 Exposure to HABs were reported to modulate disease infections in bivalve, but only few
644 studies have focused on the direct interaction between HABs and pathogenic agents so far
645 (Table 2). Additional, *in vitro* exposures of pathogenic microorganisms to toxic microalgae
646 and associated compounds are needed to better understand how microalgal extracellular
647 compounds can alter bivalve infectious agent viability or virulence. Such methods, however,
648 are limited by the inability to cultivate several pathogenic agents without the host
649 (herpesvirus, certain bacteria and parasites). Field studies and developments in environmental
650 DNA analyses may overcome this limitation.
651

652 **4.2 Microalgae as vectors of infectious agents?**

653 Phytoplankton dynamics may participate in disease transmission in bivalves as infectious
654 agents may be attached to planktonic food particles. For example, viral particles of OsHV-1
655 were reported to attach to particles *in situ*, including algal food particles, leading the authors
656 to hypothesize that plankton dynamics plays a key role in POMS transmission (Evans et al.,
657 2015, 2014; Paul-Pont et al., 2013). Similarly, the acute viral necrobiotic disease virus,
658 pathogen to the scallop *Chlamys farreri*, was shown to be carried by microalgae (Zhang et al.,
659 2010).

660 Toxic dinoflagellates were reported to be vectors of human infectious agents, such as
661 *Legionella pneumophila* or *Vibrio cholerae* (see review of Doucette, 1995; Rivera et al.,
662 2013). No published study has researched so far the specific ability of toxic dinoflagellates to
663 transport and disseminate bivalve pathogenic agents. The hypothesis of toxic microalgae
664 acting as vectors for bivalve pathogenic agents could be further investigated to explore these
665 phenomena.

666

667

668 # 5. Discussion and future research recommendations

669

670 This review, mainly based upon experimental studies, highlighted that HABs can modify
671 disease processes in bivalves through several mechanisms (summarized in Figure 1).
672 Modulation of hemocyte immune functions by HABs and associated compounds is one

673 reported mechanism leading to the effects of HABs on disease in bivalves. HAB exposure can
674 cause immunosuppression that promotes pathogen proliferation. Conversely, HAB exposure
675 could stimulate immune responses. However, other mechanisms are likely involved, but are
676 under-studied thus far, and need more attention in the future. Indeed, HAB exposure can
677 decrease bivalve filtration rate, which may in turn decrease pathogen acquisition. HABs can
678 also cause tissue and organ lesions, increasing bivalve global physiological weakness and
679 decreasing defense against pathogens. Pathogen viability or pathogenicity can be affected
680 directly by HAB toxins or compounds in the seawater, which suggest they could also be
681 affected in bivalve tissues exposed to HAB compounds. Finally, HABs could act as pathogen
682 carriers and favor pathogen transmission.

683 Modulation of pathological condition in bivalves exposed to HABs and pathogens is the result
684 of the interaction between the initial physiological status of the bivalve, the effects of the
685 HABs, and the effects of the pathogen. It is challenging, therefore, to identify unique
686 mechanisms applicable to all bivalves, and conclusions should be made for each bivalve
687 population of interest and the specific HAB-pathogen combination. To best address a specific
688 situation, we recommend experimental studies that simulate as close as possible the natural
689 conditions. For example, experiments should be consistent with the seasonality of HABs and
690 pathogen appearance in the field. To better understand the mechanisms involved, and for
691 purposes of comparison with other studies, extensive information should be provided
692 regarding the bivalve initial condition (reproduction stage, age, origin, etc), and the HABs and
693 pathogens (strain information, origin, growing conditions and stage, toxin production, etc)
694 studied.

695

696 The ecological and economical significance of the effects of HABs upon bivalve disease are
697 not well established, although experiments have shown clearly that such effects are likely.
698 The study of these interactions in the field, and at the population level, is now needed to
699 answer these questions.

700 The experimental studies and the field observations reported here only consider the immediate
701 effects of a HAB exposure upon pathogen infections. Whether these acute effects can durably
702 affect the dynamics of the host-pathogen interaction is a question that remains to be answered.
703 From a selected number of HAB-bivalve-pathogen interaction studies reviewed herein,

conceptual models of evolution of the host-pathogen dynamics can be proposed (Figure 2). We propose that the effect of a HAB on bivalve infectious disease would depend upon the temporal dynamics of both the disease and the HAB.

In the studies reviewed here, bacterial and viral infections led to rapid and intense consequences, i.e., acute effects (Figure 2A, B). POMS in France induces each year a mortality peak over a few weeks in oyster *C. gigas* spat. This disease is associated with herpesvirus and/or bacteria such as *V. tasmaniensis*. Lassudrie et al. (2015a) showed experimentally that a bloom of *A. pacificum* starting before herpesvirus exposure could alter transmission or proliferation of the virus. Conversely, Abi-Khalil et al. (2016) experimental results indicated that an *A. pacificum* bloom starting before injection of *V. tasmaniensis* could increase oyster mortality induced by the infection. These two experimental studies suggest that at the population level, mortality events could be modulated by toxic blooms occuring before the outbreak (Figure 2A, B).

Other papers reviewed here studied the effects of HABs on diseases associated with parasites *P. olseni* (da Silva et al., 2008; Lassudrie et al., 2014), *P. marinus* (Lassudrie et al., 2015b) and bacteria RLO (Rickettsia-like organisms; Hégaret et al., 2012). In the bivalve populations studied, these diseases do not induce severe mortality, resulting in long-lasting host-pathogen interactions. In the short-term, a toxic bloom can modulate the development of a bacterial (Hégaret et al., 2012) or parasitic (da Silva et al. 2008; Lassudrie et al., 2015b) infections (Figure 2C, D). Specifically, Lassudrie et al. (2015b) results indicated that an *A. catenella* (= *A. fundyense*) bloom could promote *P. marinus* infection in oysters *C. virginica* that were already weakened by trematode infestation. The parasitic levels were not surveyed after the toxic algal exposure, it is therefore questionable wether this HAB would durably disrupt the *P. marinus* - *C. virginica* interaction, or wether the initial *P. marinus* levels would be quickly restored (Figure 2C). Nevertheless, it does not seem realistic that a short-term HAB exposure could have a long-term consequence. The equilibrium of the host-pathogen interaction would probably recover after exposure, as suggested by the results of da Silva et al. (2008) (Figure 2D). In this study, the intensity of infection by *P. olseni* in clams *R. philippinarum* decreased after 2 and 3 weeks of exposure of toxic dinoflagellate *K. selliformis.* Then, after 3 weeks of exposure at a lower *K. selliformis* concentration, the intensity of infection was restored to its original level (Figure 2D).

Another point to consider is that HABs are usually recurrent phenomena, whereas most studies assess the effect of a single HAB exposure. Long-term effects of repeated toxic blooms upon host-pathogen interaction dynamics at the population level should therefore be considered. Effects of HABs upon bivalve reproduction and on physiology through parental exposure were reported recently (e.g. Basti et al., 2013; Castrec et al., 2019, 2020; Rolton et al., 2015), and could ultimately alter bivalve population fitness in the case of repeated blooms. Adaptations of bivalve populations to recurrent toxic blooms, reflected by differential physiological responses between populations (Navarro et al., 2014), can lead to the emergence of resistant genotypes (Bricelj et al., 2010, 2005). The use of *in situ* monitoring and epidemiological models could contribute to understanding of effects of HABs upon the host-pathogen interactions at the population level.

Climate change conditions have been reported experimentally to alter physiology of bivalves and interaction with HABs (Farrell et al., 2015; Turner et al., 2016). Therefore, the HAB-bivalve-pathogen interaction likely will evolve under future climate conditions.

6. Conclusion

Increased disease susceptibility in bivalves caused by HAB exposure has been related to altered immune functions and global physiological distress. This pattern, however, is not always verified, as direct deleterious effects of HABs upon certain pathogenic agents can result in lower pathogen infection. Other processes likely interfere with disease infection under HAB exposure, such as filtration and direct interactions between pathogens and HABs. More studies are needed to understand the role of these processes in the complex tripartite bivalve-pathogen-HAB interaction. Future research should also focus on field observations to verify experimental results, and to identify the effect of HABs upon disease dynamics at the bivalve population level. Such considerations may provide clues for unexplained mortalities, and eventually improve shellfish management.

Declaration of interest

Nothing to declare.

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Figure 1

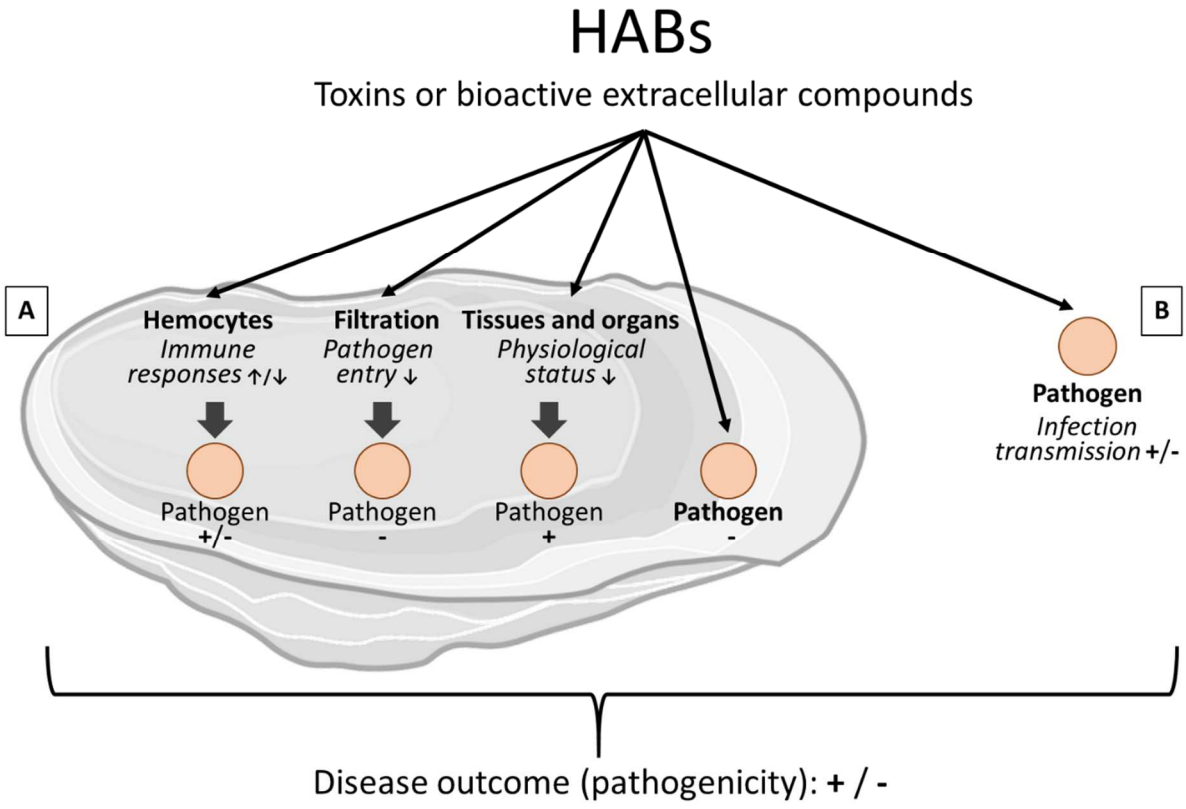
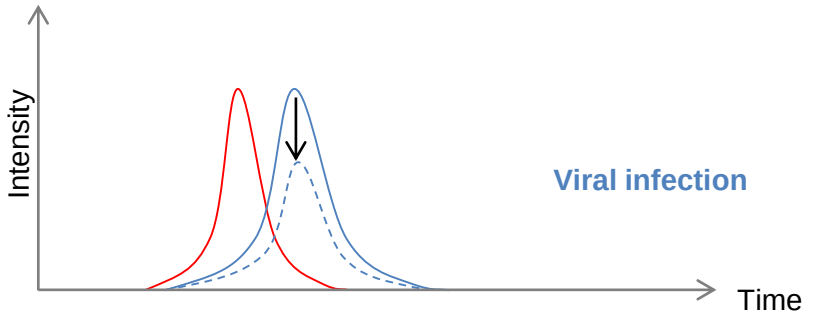
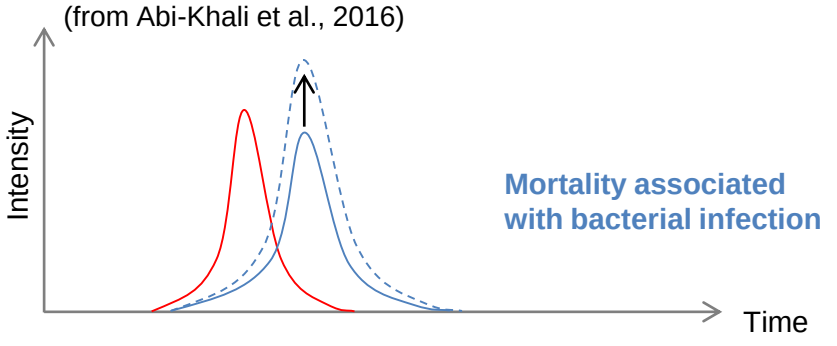

HABs
Toxins or bioactive extracellular compounds
A
Hemocytes
Immune responses ↑/↓
Filtration
Pathogen entry ↓
Tissues and organs
Physiological status ↓
Pathogen
+/-
Pathogen
-
Pathogen
+
Pathogen
-
B
Pathogen
Infection transmission +/-
Disease outcome (pathogenicity): + / -

Figure 2

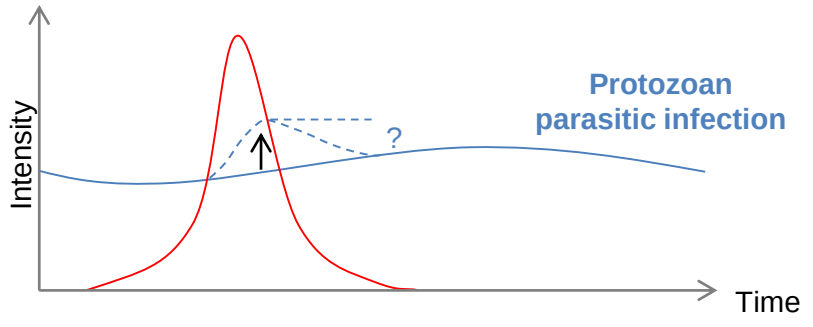
A Proposed long-term effect of *A. pacificum* on herpesvirus infection in oyster *C. gigas* (from Lassudrie et al., 2015a)



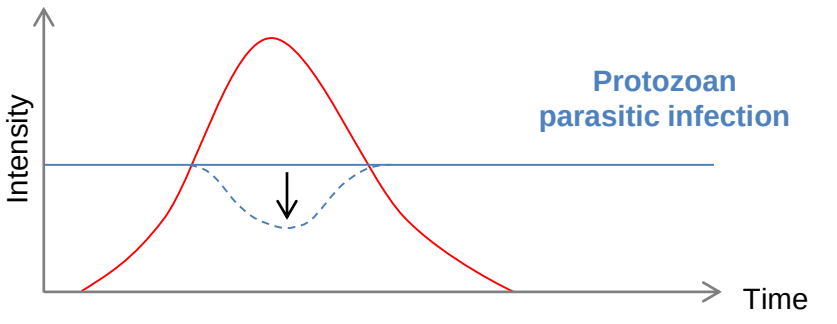
B Proposed long-term effect of *A. pacificum* on mortality related to *V. tasmaniensis* infection in oyster *C. gigas* (from Abi-Khali et al., 2016)



D Proposed long-term effect of *A. catenella (=A. fundyense)* on *P. marinus* infection in oyster *C. virginica* also infested with trematodes (from Lassudrie et al., 2015b)



C Proposed long-term effect of *K. selliformis* on *P. olseni* infection in clam *R. philippinarum* (from da Silva et al., 2008)



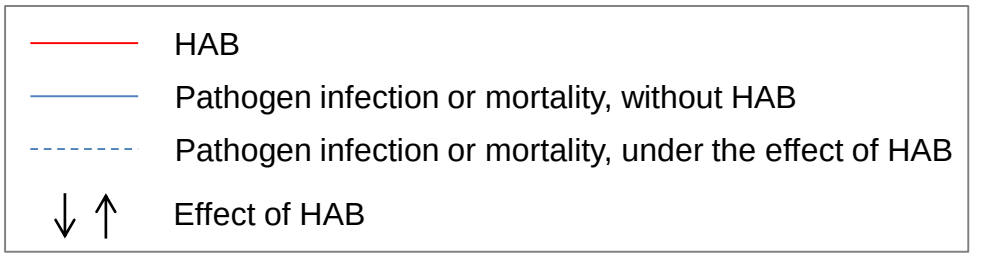


Table 1: Main bivalve diseases (mainly OIE notifiable diseases), associated pathogen, distribution and temporal dynamics, main marine HAB genera hypothetically co-occurring with disease (HABs reported to occur in regions and seasons where and when disease also occur, suggesting that both HABs and disease co-occur), and marine HAB species reported to co-occur with disease outbreaks in the field.

Bivalve species	**Disease**	**Pathogen**	**Effect**	**Distribution**	**Seasonal dynamic**	**Reference for disease reports**	**Hypothetical co-occurrence of main HAB genera ***	**Reported co-occurrence of HABs with disease outbreak**
Crassostrea gigas (juvenile-spat)	Pacific Oyster Mortality Syndrome (POMS)	OsHV-1 microvariants (virus) and *Vibrio* spp. (bacteria)	Lethal	Southern and Western Europe	Summer to fall	(Barbosa Solomieu et al., 2015)	*Alexandrium*, *Pseudo-nitzschia*, *Dinophysis*, *Ostreopsis*, *Azadinium, Vulcanodinium, Protoceratium, Lingulodinium, Gonyaulax, Karlodinium*	*Alexandrium* spp. (Abi-Khalil et al., 2016)
Crassostrea gigas (juvenile-spat)	Pacific Oyster Mortality Syndrome (POMS)	OsHV-1 microvariants (virus) and *Vibrio* spp. (bacteria)	Lethal	Australia (Southern and Eastern coast), New-Zealand (Northern coast)	Summer to fall	(Barbosa Solomieu et al., 2015)	*Alexandrium*, *Pseudo-nitzschia, Ostreopsis, Gambierdiscus, Karenia, Karlodinium, Protoceratium, Gymnodinium, Dinophysis, Prorocentrum, Amphidinium, Vulcanodinium* (Ajani et al., 2017, 2013, 2016; Rhodes and Smith, 2019; Rhodes et al., 2019)	*Alexandrium* spp. and *Pseudo-nitzschia* spp. (Jenkins et al., 2013)
Crassostrea gigas (juvenile-spat)	Pacific Oyster Mortality Syndrome (POMS)	OsHV-1 microvariants (virus) and *Vibrio* spp. (bacteria)	Non-lethal	Brazil (South coast)	Unknown	(Mello et al., 2018)	*Dinophysis* spp., *Gymnodinium*, *Pseudo-nitzschia*, *Alexandrium*, *Prorocentrum*, *Chatonella*, *Heterosigma*, *Fibrocapsa* (Branco et al., 2019; Cuellar-Martinez et al., 2018; Mafra et al., 2015, 2006; Menezes et al., 2018; Moreira-González et al., 2019; Proença et al., 2001, 2007; Simões et al., 2015; Tavares et al., 2009; Tibiriçá et al., 2015)	NA
Crassostrea gigas	Perkinsosis	*Perkinsus marinus* (protozoan parasite)	Lethal	Mexico (Gulf of California)	Unknown	(Enríquez-Espinoza et al., 2010)	*Margalefidinium, Pseudo-nitzschia*, *Prorocentrum*, *Gymnodinium, Chatonella Akashiwo, Heterosigma* (Núñez-Vázquez et al., 2011)	NA
Crassostrea virginica	Dermo / Perkinsosis	*Perkinsus marinus* (protozoan parasite)	Lethal	USA (East coast)	Maximum in summer and autumn	(Burreson and Ragone-Calvo, 1996; Ford and Smolowitz, 2007)	*Alexandrium*, *Karenia, Margalefidinium Karlodinium*, *Pseudo-nitzschia*, *Prorocentrum, Prymnesium*, *Dinophysis*	NA
Crassostrea corteziensis	Perkinsosis	*Perkinsus marinus* (protozoan parasite)	Non-lethal	Mexico (Pacific coast)	Maximum in summer	(Cáceres-Martínez et al., 2016)	*Margalefidinium Pseudo-nitzschia*, *Prorocentrum, Pyrodinium, Dinophysis, Gambierdiscus*	NA

Crassostrea gasar	Perkinsosis	*Perkinsus marinus* and *P. beihaiensis* (protozoan parasites)	Sub-lethal	Brazil (Northeast coast)	Sergipe State: Maximum in summer and autumn Other States: no seasonal pattern	(da Silva et al., 2014; Queiroga et al., 2015, 2013)	*Nitzschia, Dinophysis, Alexandrium, Ostreopsis, Prorocentrum, Gambierdiscus* (Aquino et al., 2015; De Carli, 2014; Jales et al., 2013; Machado et al., 2018; Menezes et al., 2018; Nascimento et al., 2012; Santiago et al., 2010) **	NA
Ostrea edulis	Digestive gland disease	*Marteilia refringens* (protozoan parasite)	Lethal	Europe	Maximum in summer (>17°C). Winter and early spring: absence or few parasites.	(Berthe et al., 2004; Carrasco et al., 2015)	*Alexandrium*., *Pseudo-nitzschia*., *Dinophysis*, *Ostreopsis*, *Azadinium, Vulcanodinium, Protoceratium, Lingulodinium, Gonyaulax, Karlodinium*	NA
Ostrea edulis	Microcell disease	*Bonamia ostrea* (protozoan parasite)	Lethal	Europe	Unclear. Maximum prevalence in winter.	(Arzul and Carnegie, 2015)	*Alexandrium*., *Pseudo-nitzschia*., *Dinophysis*, *Ostreopsis*, *Azadinium, Vulcanodinium, Protoceratium, Lingulodinium, Gonyaulax, Karlodinium*	NA
Saccostrea glomeraa	Winter mortality disease	*Bonamia roughleyi* (protozoan parasite)	Lethal	Australia (East coast)	Winter and early spring	(Dove et al., 2013; Farley et al., 1988; Spiers et al., 2014)	*Alexandrium*, *Pseudo-nitzschia, Ostreopsis, Gambierdiscus, Karlodinium, Prorocentrum, Dinophysis, Amphidinium* (Ajani et al., 2017, 2013)	NA
Saccostrea glomeraa	Queensland unknown (QX) disease	*Marteillia sydneyi* (protozoan parasite)	Lethal	Australia (East coast)	Unclear	(Adlard and Wesche, 2005; Green et al., 2011; Nell, 2001; Perkins and Wolf, 1976)	*Alexandrium*, *Pseudo-nitzschia, Ostreopsis, Gambierdiscus, Karlodinium, Prorocentrum, Dinophysis, Amphidinium* (Ajani et al., 2017, 2013)	NA
Ruditapes philippinarum	Perkinsosis	*Perkinsus olseni* (protozoan parasite)	Lethal (Portugal) and sub-lethal	Europe (Western and South)	Spain, and Portugal: Maximum in spring and summer. France: no seasonality.	(Ruano et al., 2015; Villalba et al., 2011)	*Alexandrium*., *Pseudo-nitzschia*., *Dinophysis*, *Ostreopsis*, *Azadinium, Protoceratium, Lingulodinium, Gonyaulax, Karlodinium*	NA
Ruditapes philippinarum	Perkinsosis	*Perkinsus olseni* (protozoan parasite)	Lethal	East Asia (Korea, Japan, China)	South Korea: Maximum late summer; Japan: Maximum in summer and autumn	(Choi and Park, 2010; Waki et al., 2018)	*Margalefidinium, Chatonella, Karenia, Heterocapsa, Gymnodinium, Heterosigma, Alexandrium, Dinophysis, Prorocentrum, Gambierdiscus,* (Lee et al., 2013)	NA
Ruditapes philippinarum	Brown Ring Disease (BRD)	*Vibrio tapetis* (bacterium)	Lethal	Korea and Japan	Undertemined	(Park et al., 2008, 2006)	*Margalefidinium, Chatonella, Heterosigma, Prorocentrum, Alexandrium, Akashiwo* (Lee et al., 2013)	NA
Ruditapes philippinarum	Brown Ring Disease (BRD)	*Vibrio tapetis* (bacterium)	Lethal	France, Spain	Winter and spring: high prevalence and mortality	(Paillard, 2004)	*Alexandrium*., *Pseudo-nitzschia*, *Dinophysis*, *Ostreopsis*, *Azadinium, Protoceratium, Lingulodinium, Gonyaulax, Karlodinium*	NA
Most bivalves	Vibriosis	*Vibrio* spp. (bacteria)	Lethal – sub-lethal	Worldwide	Variable and undetermined	(Travers et al., 2015)	Potentially all HABs	NA

* Main references used in this column are HAEDAT: Harmful Algae Events Database (http://haedat.iode.org/index.php), and (Lassus et al., 2016), in addition to other references mentioned.
** Important HAB taxa mays be unlisted due to scarce information related to absence of HAB monitoring in this region
NA: Not available

Table 2. Literature survey of the main studies reporting the effects of marine harmful algal blooms (HABs) on bivalve infectious diseases or pathogens. This table summarizes HAB effects on pathogen infection in bivalves, effects of direct HAB exposure to pathogens, effects of HABs and their combination with pathogens on bivalve physiological variables, and mechanisms identified to induce disease modulation. Individual effects of pathogens on bivalves are not listed here. Detailed hemocyte responses are listed in Table 4.

Bivalve species; stage	**Pathogen (infection type; conditions compared)**	**HAB species Exposure type**	**Effects of HAB on pathogen infection**	**Direct effects of HAB on pathogen**	**Bivalve variables studied**	**Main effects of HAB and combination with pathogen on physiology of bivalves**	**Identified reason for disease modulation**	**Reference**
Crassostrea virginica; adult	*Perkinsus marinus* (*P.m.*) (natural; non infected *vs.* infected); *Bucephalus* sp. (*B.*) (natural; non infected *vs.* infected)	*Alexandrium catenella* (= *A. fundyense* as refered to in this study)* Simulated bloom ; $2x10^3$ cells mL^{-1} 4 times a day ; 3 weeks	Effect of HAB alone*:* Prevalence & intensity (=, *P.m.* & *B.*) Combined effect HAB-*B*: Prevalence of *P. m.* (↑) in *B.*-infected oysters, Intensity (=).	NA	Viability; Condition index; Circulating hem.; Histopathology; Expression of targeted immune-related genes in gills; Toxin accumulation; Pathogen infection	Effect of HAB in *B.*-uninfected bivalves - Hem. infiltration (kidney) Combined effect HAB - *B.*-infected bivalves: - Antagonistic: Suppression of hem. inflammatory response to *B.* by HAB (circulating hem. and infiltration in tissues) - Synergistic: Tissue degeneration in adductor muscle	Immunosuppression caused by HAB exposure combined to physiological weakness caused by *B.* infection	(Lassudrie et al., 2015b)
Crassostrea gigas; juvenile	Herpesvirus OsHV-1µVar (experimentally by cohabitation (*Exp.*) or naturally (*Nat.*); non infected *vs.* infected)	*Alexandrium pacificum* (named *A. catenella* in this study)* Simulated bloom ;- $3.5x10^2$ cells mL^{-1} continuously ; 4 days	*Exp.*: Prevalence (↓), Intensity (=); *Nat.*: Prevalence (=), Intensity (↓)	NA	Viability; Toxin accumulation; Pathogen infection	Combined effect HAB-pathogen: Toxin accumulation (↓)	NA	(Lassudrie et al., 2015a)
Crassostrea gigas; juvenile	*Vibrio tasmaniensis* LGP32. (experimental by injection; infected *vs.* non infected)	*Alexandrium pacificum* (named *A. catenella* in this study)*, (*A.p.*, PST strain) *Alexandrium tamarense**, (*A.t.*, non-PST strain)	NA	NA	Viability; Toxin accumulation	Effect of HAB for all infection status: none Combined effect HAB-pathogen: Viability (↓ *A.p.*; = *A.t.*)	NA	(Abi-Khalil et al., 2016)

		Simulated bloom; 1-$3x10^3$ cells mL^{-1} continuously ; 10 days						
Mytilus edulis; larva	*Vibrio splendidus* (*V.s.*); *Vibrio coralliilyticus* (*V.c.*) (experimentally by incubation; infected *vs* non infected)	*Prorocentrum lima* (*P.l.*) ; *Prorocentrum micans* (*P.m.*) ; *Alexandrium ostenfeldii* (*A.o.*) ; *Alexandrium minutum* (*A.m.*) ; *Karenia mikimotoi* (*K.m.*) ; *Protoceratium reticulatum* (*P.r.*) ; *Prorocentrum cordatum* (*P.c.*) Simulated bloom ; 10^2, $5x10^2$, $2.5x10^3$ & $1.2x10^4$ cells mL^{-1} once ; 5 days	NA	NA	Viability; Larval development; Phenoloxydase activity (except for *A.m, A.o, P.r,* with *V.s.* and *V.c.,* and for *P.m., K.m.* with *V.s.*)	<u>Effect of HAB (at highest concentrations) for all infection status:</u> - Larval viability and development rate ↓ (except *P.c.*) - Immune function: modulation of phenoloxydase activity depending on algal species (↑ *P.c.* and *P.m.*, ↓ *K.m.* and *P.l.*) <u>Combined effect of HAB-pathogen</u>: none	NA	(De Rijcke et al., 2016)
Mytilus edulis; adult	Gymnophallidae trematodes (natural; not considered as a factor)	*Alexandrium catenella* (= *A. fundyense* as refered to in this study)* Simulated bloom; $3x10^3$ cells mL^{-1} every 90min; 9 days.	Prevalence (↑)	NA	Viability; Histopathology; Circulating hem.; Toxin accumulation; Pathogen infection	<u>Effect of HAB for all infection status:</u> - Inflammatory response: hem. infiltration in gonad, and stomach and intestine lumen, circulating hem. modulations. - Mucus secretory cells in gills - Oxidative stress: ceroidosis in tissues	Immunosuppression caused by HAB exposure	(Galimany et al., 2008b)
Perna perna; adults	RLO, copepods (*Cop.*), Nematopsis sp. (*Nem.*), Trematodes (*Trem.*), Tylocephalum sp. (*Tyl.*); (natural; not considered as a factor)	*Prorocentrum lima* Simulated bloom; $9x10^2$ cells mL^{-1} once a day; 1, 2 & 4 days.	*RLO*, *Cop.*: Prevalence (↓) *Others:* Prevalence (=)	NA	Survival; Shell-valve closure response; Circulating hem.; Histopathology (incl. pathogen infection)	<u>Effect of HAB for all infection status:</u> - Alteration of shell valve-closure response - Circulating hem. modulations - In digestive gland, alteration (atrophy of digestive tubules) and inflammatory response (hem. infiltrations)	NA	(Neves et al., 2019)

Ruditapes philippinarum; adult	*Perkinsus olseni* (natural; 2 classes of infection: very light-light *vs.* moderate-heavy)	*Alexandrium ostenfeldii* Simulated bloom ; 10^3 cells mL^{-1} continuously; 7 days	Prevalence (=); Intensity (NS trend ↓)	NA	Viability; Condition index; Circulating hem. and plasma; Histopathology; Activity of antioxidant and digestive enzymes; Toxin accumulation; Pathogen infection	<u>Effect of HAB for all infection status:</u> - Tissue alterations in digestive gland, gills and mantle - Inflammatory response: hem. infiltration in gills and digestive gland, hem. diapedesis in digestive gland epithelia, circulating hem. modulations - Metabolic and oxidative processes: modulation of antioxidant enzyme activity in gills and hem. modulations - <u>Combined effect HAB - highest infection class:</u> Antagonistic: Suppression of anti/pro-oxidative responses to highest parasite burden (CAT activity in gills, ROS in hem.)	NA	(Lassudrie et al., 2014)
Ruditapes philippinarum; adults	*Perkinsus olseni* (natural; 2 classes of infection: null-light *vs.* moderate-heavy)	*Karenia selliformis* <u>Bivalve exposure</u>: simulated bloom; 10^2-10^3 cells mL^{-1} continuously; 6 weeks. <u>Pathogen exposure</u>: *in vitro*, HAB whole culture or exudates, cell ratio 1:250 (HAB:pathogen); 30 min, 1h30, 3h30.	Prevalence and intensity (↓) after 2 and 3 weeks, and recovery after decrease of HAB concentration	Mortality (whole culture; exudates), altered morphology (whole culture)	Viability; Condition index; Circulating hem. and plasma; Pathogen infection	<u>Effect of HAB for all infection status</u> Circulating hem. modulations <u>Combined effect HAB-pathogen</u>: none	Direct toxicity of HAB to pathogen	(da Silva et al., 2008)
Ruditapes philippinarum; adults	*Perkinsus olseni* (natural; 2 classes of infection: null-light *vs.* moderate-heavy)	*Prorocentrum minimum* <u>Bivalve exposure</u>: simulated bloom; 10^5 cells mL^{-1} continuously; 6 days. <u>Pathogen exposure</u>: *in vitro*, HAB whole culture or exudates, cell ratio 1:50 (HAB:pathogen); 30 min	Prevalence and intensity (=)	Mortality and altered morphology (whole culture; exudates)	Viability; Condition index; Circulating hem. and plasma; Histopathology; Apoptosis; Pathogen infection	<u>Effect of HAB for all infection status</u> - Condition index (↓) - Circulating hem. modulations - Tissue alterations (adductor and foot muscles, digestive gland, ova); hem. infiltration in gonad; bacteria and hem. (viable and apoptotic) in intestine lumen. <u>Combined effect HAB-pathogen</u>: - Synergistic: Tissue degeneration in gonad	NA	(Hégaret et al., 2009)

Ruditapes philippinarum, adults	*Perkinsus olseni*, (natural, 2 classes of infection: null-light *vs.* moderate-heavy)	*Karenia mikimotoi (K.m.); Karenia selliformis (K.s.)* Simulated bloom; *K.m.*: 10^3 cells mL^{-1}; *K.s.*: 5 x 10^2 cells mL^{-1}; continuously: 3 & 6 days	Prevalence and intensity (=)	NA	Condition index; Circulating hem.; Plasma; Pathogen infection;	<u>Effect of HAB for all infection status:</u> Circulating hem. modulations, stronger for *K.s.* than *K.m.* <u>Combined effect HAB-pathogen:</u> Synergistic effects: circulating hem. modulations for *K.s.* after 3 days	NA	(Hégaret et al., 2007a)
Ruditapes philippinarum; juveniles (*Juv.*); adults (*Ad.*)	*Vibrio tapetis* (*Juv.*: experimental by injection; *Ad.*: natural, 4 stages)	*Alexandrium catenella* (named *A. tamarense* in this study)* Simulated bloom. *Juv.*: $5x10^1$ cells mL^{-1} continuously; 3 days. *Ad.:* 10^2 cells mL^{-1} continuously; 16h.	*Juv.*: Apparent prevalence and intensity (↓) (assessed by shell mark symptoms). *Ad.:* None	NA	*Juv.* & *Ad.:* Viability; Burrowing; Toxin accumulation; Disease stage (based on shell-mark symptoms); *Juv.:* Growth; *Ad.*: Condition index, Circulating hem.	<u>Effect of HAB</u>., all infection status: *Juv:* Viability (↓); Burrowing incapacitation; Growth (↓); *Ad.*: Burrowing incapacitation; Circulating hem. modulations <u>Combined effect HAB-pathogen</u>: *Juv.:* Cumulative: Higher mortality	*Juv.*: Unclear if apparent decrease of disease severity traduces host-pathogen modulation, or a decrease of defense mechanisms (possibly related to shell mark symptoms)	(Bricelj et al., 2011)
Mercenaria mercenaria; adults	QPX (natural; infected *vs.* non infected)	*Prorocentrum minimum* Simulated bloom; $2x10^4$ cells mL^{-1} continuously; 5 days.	NA	NA	Viability; Circulating hem. and plasma; Histopathology; Pathogen infection	<u>Effect of HAB in non-infected bivalves:</u> - Circulating hem. modulations - Tissue alteration and inflammatory response (hem. infiltrations) in gills, hemocytic aggregates in all organs <u>Effect of HAB in infected bivalves:</u> - Circulating hem.: morphology - Hem. infiltrations in tissues	NA	(Hégaret et al., 2010)
Argopecten purpuratus, adults	RLO, (natural; not considered as a factor)	*Alexandrium catenella** Simulated bloom; $5x10^3$ cells mL^{-1} continuously; 6 days	Prevalence (↑)	NA	Survival; Escape response, Heat-shock protein (hsp70); Histopathology (incl. pathogen infection); Toxin accumulation	<u>Effect of HAB for all infection status:</u> - Altered escape response to predator - Tissue alteration in muscle - Melanization of epithelia	Physiological weakness and decreased defense associated to pathologies caused by HAB	(Hégaret et al., 2012)

(↑): increase; (↓): decrease; no change: (=); NA: not available (not investigated); NS: non significant; Hem.: hemocytes; QPX: Quahog Parasite Unknown; RLO: Rickettsia-like organisms; incl.: including. *: Nomenclature for species within the *A. tamarense* complex has changed since the publication of these studies, current accepted names indicated here were deduced from John et al. (2014); Fraga et al. (2015); Litaker et al. (2018), where *A. catenella* corresponds to group I, *A. tamarense* to group III, *A. pacificum* to group IV).

Table 3. Literature survey of most recently reported effects of marine harmful algal blooms (HABs) or their toxins on bivalve hemocyte variables involved in cellular immunity.

Bivalve species	HAB/phycotoxin	Experiment type	Hemocyte parameters	Reference
Mytilus chilensis	Saxitoxins	*In vitro* 1–100 nM, 4h and 16h.	Viability (=), ROS (↓ 10 nM, ↑ 100 nM), phagocytosis (↓)	(Astuya et al., 2015)
Crassostrea gigas	Saxitoxins	*In vitro* 0.8, 1 and 3.3 µM, 3.5h.	Apoptosis (↑).	(Abi-Khalil et al., 2017)
Crassostrea gigas (*C.g.*) *Chlamys farreri* (*C.f.*)	Saxitoxins	Injection 10–20 µg STX eq. 100 g^{-1} shellfish meat, 12, 48, and 96 h p.i.	Phagocytosis (↓ 12 and 96h, *C.g.* and *C.f.*), ROS (↑ 48h and 96h, *C.f.*).	(Cao et al., 2018)
Crassostrea gigas	*Alexandrium minutum* (*A.m.*); Saxitoxins (*STX*)	*In vitro* *A.m:* 2 x 10^4 cells mL^{-1}. STX: 0.05 µg L^{-1} for 4h.	Size (↑ GR, *A.m.*), and complexity (=), viability (=), phagocytosis (↓), ROS (↓) for *A.m* and *STX*	(Mello et al., 2013)
Crassostrea gigas (diploid and triploid, in April and in May)	*Alexandrium minutum*	Simulated bloom 5 x 10^3 cells mL^{-1}, for 4 days.	THC (↑) GRC (↑), viability (=), phagocytosis (=), ROS (↑ April GR, ↓ May GR and HY), agglutination titer (=), phenoloxidase (↓ April, ↑ May).	(Haberkorn et al., 2010a)
Crassostrea gigas	*Alexandrium minutum*	Simulated bloom 5 x 10^3 cells mL^{-1}, flow of 14 mL min^{-1}, for 4 days.	THC (=), phagocytosis (↑), ROS (=), phenoloxidase (=).	(Haberkorn et al., 2014)
Crassostrea gigas	*Alexandrium minutum* (PST, BEC, and PST+BEC strains)	Simulated bloom 3.1 x 10^3 cells mL^{-1}, for 4 days (no control algae).	THC (=), HYC (PST < PST+BEC, BEC), Size (=), complexity (=), viability (PST < PST+BEC, BEC), phagocytosis (=), ROS (=).	(Castrec et al., 2018)
Crassostrea virginica (*C.v.*) *Crassostrea gigas* (*C.g.*)	*Alexandrium catenella* (= *A. fundyense* as refered to in this study*; *A.c.*) *A. pacificum* (named *A. catenella* in this study*; *A.p.*)	Simulated bloom *A.c.*: 1, 2.5, 5 x 10^2 cells mL^{-1}, for 1, 7 days. *A.p.*: 75 cells mL^{-1}, for 14 h, then 1.5 x 10^2 cells mL^{-1}, for 10 h day for 4 days.	THC (=), size (=), complexity (=), viability (=), phagocytosis (=), ROS (=), for *C.v* and *C.g*.	(Hégaret et al., 2007b)
Crassostrea gigas (juveniles)	*Alexandrium pacificum* (named *A. catenella* in this study)*	Simulated bloom 10^2 cells mL^{-1}, for 4 to 9 days.	THC (↑), GRC (↑), HYC (↑), size (↑ HY, ↑ GR day 4), complexity (↑ HY, ↑ GR), viability (=), ROS (↑).	(Lassudrie et al., 2016)
Ruditapes philippinarum, Mya arenaria	*Alexandrium catenella* (named *A. tamarense* in this study)* (PST) *Alexandrium tamarense* (nonPST)	*In vitro* Filtered extracts of 5 x 10^5 cells mL^{-1}	Adherence (↓ nonPST), phagocytosis (↓ nonPST).	(Ford et al., 2008)
Mytilus edulis	*Alexandrium catenella* (PST and PST+LC strains) *A. tamarense* (LC strain)	Simulated bloom 500 cells mL^{-1}, for 3 and 7 days.	THC (↓ PST and LC, = PST+LC, 3 days ; = PST, PST+LC and LC, 7 days), viability and lysosomal membrane stability (↓ for all, 3 and 7 days), phagocytosis (↑ PST, 3 days ; = for all, 7 days), ROS (↓ for all, 3 days).	(Bianchi et al., 2019)

Crassostrea virginica (native and non-native populations)	*Prorocentrum minimum*	Natural and simulated bloom 10^4 cells mL^{-1}, 2 days. Native: exposed to recurrent blooms; Non-native: naïve from bloom exposure.	THC (↑), GRC (↑), viability (↑), phagocytosis (↑), ROS (↑ native, = non-native), aggregation (↓).	(Hégaret and Wikfors, 2005a)
Crassostrea virginica (*C.v.*), *Argopecten irradians irradians* (*A.i.i.*)	*Prorocentrum minimum*	Simulated bloom 10^5 cells mL^{-1}, for 1h, and 1, 2, 4 and 7 days.	*C.v.*: THC (=), size (=), complexity (=), viability (=), phagocytosis (=), ROS (=), aggregation (=). *A.i.i.*: GRC (↓), HYC (↑), viability (↑ GR, ↓ HY), phagocytosis (↓), ROS (↑), aggregation (↑ HY, ↓ GR).	(Hégaret and Wikfors, 2005b)
Mytilus edulis	*Prorocentrum minimum*	Simulated bloom 10^4 cells mL^{-1}, for 9 days.	Viability (=), phagocytosis (=), ROS (=), adhesion (=), apoptosis (=).	(Galimany et al., 2008c)
Perna perna	*Prorocentrum lima*	Simulated bloom 900 cells mL^{-1}, for 1, 2 and 4 days.	THC (↓ 2 & 4 days), size (↑2 & 4 days), phagocytosis (↑ 2 days), ROS (↑ 4 days).	(Neves et al., 2019)
Ruditapes decussatus	*Prorocentrum lima* (*P.l.*); Okadaic acid (OA)	*P.l.*: Simulated bloom 2 x 10^2 and 2 x 10^4 cells mL^{-1}, for 24h and 48h. OA: *In vitro* 10, 50, 100 and 500 nM, for 2 and 4h.	*P.l.*: Viability (↓ 24 h), apoptosis (↑ 24 h). OA: Viability (↓ 100 and 500 nM, 2 and 4 h), phagocytosis (↓ all concentrations), apoptosis (↑ 100 and 500 nM, 4 h).	(Prado-Alvarez et al., 2013)
Mytilus galloprovincialis	*Prorocentrum lima*	Simulated bloom 10^3 and 10^5 cells mL^{-1}, 24h and 48h.	Apoptosis (↑ 48h, both concentrations).	(Prego-Faraldo et al., 2016)
Mytilus galloprovincialis	*Prorocentrum* and/or *Dinophysis;* OA	Natural bloom; OA: *In vitro* 10, 50 and 100 nM, for 2 and 4 h.	Natural bloom: Apoptosis (↓) OA: Apoptosis (↓ 100 nM, 4h).	(Prado-Alvarez et al., 2012)
Mytilus galloprovincialis	OA	*In vitro* 10, 50, 100, 200 and 500 nM, for 1 and 2 h.	Apoptosis (↑ 500 nM, 2h).	(Prego-Faraldo et al., 2015)
Perna perna (*P.p.*), *Crassostrea gigas* (*C.g.*)	*Dinophysis acuminata*	Natural bloom 2 sites: PA: 2950 cells L^{-1} PZ: 4150 cells L^{-1}	*P.p.*: THC (↓ PA, ↑ PZ), DHC (=), hemagglutinating titter (=), phenoloxidase (↑PA, = PZ), *C.g.*: THC (=), DHC (=), hemagglutinating titter (=), phenoloxidase (↓ PZ).	(Simões et al., 2015)
Perna perna (*P.p.*), *Anomalocardia brasiliana* (*A.b.*), *Crassostrea gigas* (*C.g.*)	*Dinophysis acuminata*	Natural bloom 17,600 cells L^{-1}.	*P.p.*: THC (↑), GRC (↓), phenoloxidase (↓). *A.b.*: THC (↑), GRC (=), phenoloxidase (=). *C.g.*: THC (=), GRC (=), phenoloxidase (=). Apoptosis and hemagglutinating titter (=, all spp.).	(Mello et al., 2010)

Mercenaria mercenaria (*M.m.*), *Mya arenaria* (*M.a.*), *Crassostrea virginica* (*C.v.*), *Crassostrea gigas* (*C.g.*), *Ruditapes philippinarum* (*R.p.*)	*Heterosigma akashiwo* (*H.a.*) *Prorocentrum minimum* (*P.m.*) *Alexandrium catenella* (= *A. fundyense* as refered in this study) (*Ac.*) *Alexandrium minutum* (*A.m.*) *Karenia selliformis* (*K.s.*) *Karenia mikimotoi* (*K.m.*)	*In vitro* *H.a.*: 10^5 cells mL^{-1} *P.m.*: 10^5 cells mL^{-1} *A.c.*: 10^4 cells mL^{-1} *A.m.*: 5 x 10^4 cells mL^{-1} *K.s.*: 4-7 x 10^3 cells mL^{-1} *K.m.*: 4-7 x 10^3 cells mL^{-1} For 4 h	*H.a*: *M.m.*: viability (↓ WC), phagocytosis (=), ROS (=), adhesion (↓ S); *M.a.*: phagocytosis (=), ROS (↑ WC), adhesion (=); *C.v.*: viability (↓ WC), phagocytosis (=), adhesion (=). *P. m.*: *M.m.*: size (↓ WC), complexity (↓ WC), adhesion (↑ S), phagocytosis (↓ WC); *M.a.*:, ROS (=), adhesion (=), phagocytosis (↓ WC); *C.v.*: All parameters (=). *A.c.*: *M.m.*: phagocytosis (↓ WC and S), ROS (=), adhesion (↓ WC); *M.a.*: phagocytosis (↓ WC), ROS (=), adhesion (=); *C.v.*: viability (↓ WC), remaining parameters (=). *A.m.*: *C.g.*: viability (↓ WC and S), ROS (↓ WC), remaining parameters (=). *K.s.*: *R.p.*: size (↓ WC), viability (↓ WC and S), phagocytosis (↓ WC), ROS (↓ WC and S), adhesion (↓ WC). *K.m.*: *R.p.*: ROS (↓ WC), adhesion (↓ WC), other parameters (=).	(Hégaret et al., 2011)
Crassostrea gigas	Brevetoxin	*In vitro* 3, 30, 100, 300 and 1000 µg L^{-1}, for 1, 4 and 12 h.	Viability (=), apoptosis (=).	(Mello et al., 2012)
Mytilus galloprovincialis	*Ostreopsis* cf. *ovata*	Simulated bloom 1 x 10^5 cells L^{-1}, for 7 and 14 days.	GRC (↓), HYC (↑), phagocytosis (↓), lysosomal membrane stability (↓), for both durations.	(Gorbi et al., 2013)
Mytilus edulis	Domoic acid	Injection 1, 10, 100 and 500 ng g body $weight^{-1}$, 48h and 7 days p.i.	THC (↑ 48h, 500 ng), viability (all concentrations: = 48h; ↑ 7 days), phagocytosis (↑ 48h, 100 ng).	(Dizer et al., 2001)
Ruditapes philippinarum	*Heterocapsa circularisquama*	Simulated bloom 10^3 cells mL^{-1}, for 24 and 48h.	THC (↑ 24h).	(Basti et al., 2011)
Crassostrea gigas	*Alexandrium pacificum* (named *A. catenella* in this study)* (PST) *Alexandrium tamarense* (nonPST)	Simulated bloom, 10^3 cells mL^{-1}, for 48h.	Apoptosis (PST>nonPST, 29h)	(Medhioub et al., 2013)
Nodipecten subnodosus	Saxitoxins	Injection: 140 µg STX eq per 0.2 mL injection, 24h p.i. *In vitro:* 10–20 µg STX eq.mL^{-1}, 24h p.i.	Apoptosis (↑)	(Estrada et al., 2014)
Nodipecten subnodosus	Saxitoxins	Injection Low dose: 6.25 MU, 0.2mL, 12-72h p.i. High dose: 100 MU, 0.2mL, 40 days p.i.	THC (↓) (low dose, 12-24h p.i., high dose 10-40 days p.i.)	(Estrada et al., 2010)
Mytilus edulis	*Karlodinium veneficum*	Simulated bloom 6.25 x 10^1 cells mL^{-1}, for 3 and 6 days	GRC (↓3 days, = 6 days), HYC (↑ 3 days, = 6 days), ROS (↑), phagocytosis (↑ 6 days)	(Galimany et al., 2008a)

THC: total hemocyte count; DHC: differential hemocyte count; GR: granulocytes; HY: hyalinocytes (a.k.a. agranulocytes); GRC: granulocyte count; HYC: hyalinocyte count; ROS: reactive oxygen species production; PST: paralytic shellfish toxin; STX: Saxitoxin; LC: lytic compounds; BEC: bioactive extracellular compounds; OA: Okadaic acid; PA: Praia Alegre, Brazil; PZ: Praia de Zimbros, Brazil; MU: mouse units; p.i.: post injection; ↓: decrease,↑: increase, or = : no difference compared to control non-toxic treatments; < decrease

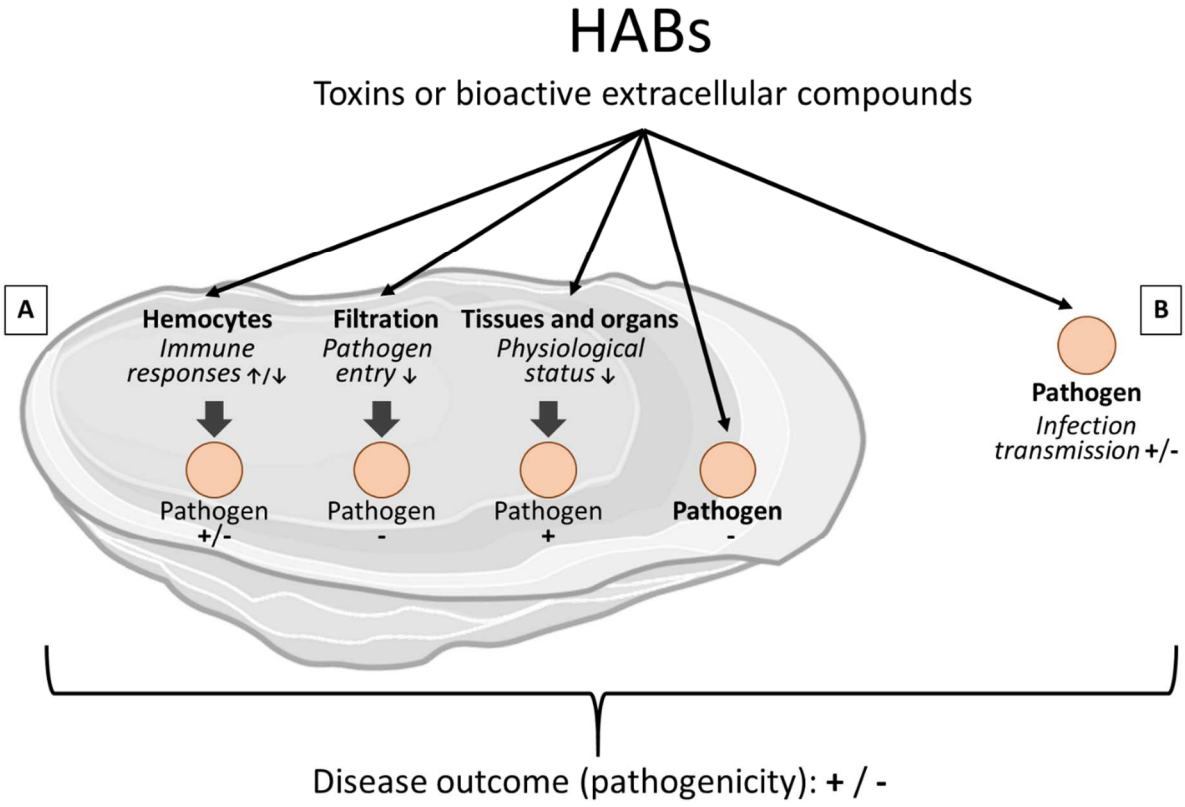
or > increase compared to other treatments. *: Nomenclature for species within the *A. tamarense* complex has changed since the publication of these studies, current accepted names are indicated here and were deduced from John et al. (2014), Fraga et al. (2015) and Litaker et al. (2018), where *A. catenella* (= *A. fundyense*) corresponds to group I, *A. tamarense* to group III, *A. pacificum* to group IV.

Table 4. Literature survey of most recently reported effects of marine harmful algae blooms (HABs) combined with pathogen infection on bivalve hemocyte variables involved in cellular immunity.

Bivalve species	**Pathogen**	**HAB species**	**Experiment type**	**Effects of HABs and pathogens on hemocytes**	**Effect of HAB on pathogen infection** ([h] : considered to be related to hemocytes)	**Reference**
Ruditapes philippinarum	*Perkinsus olseni*	*Karenia mikimotoi* (*K.m.*) *Karenia selliformis* (*K.s.*)	Simulated bloom *K.m.:* 10^3 cells mL^{-1}, *K.s.*: 5 x 10^2 cells mL^{-1}, for 3 and 6 days.	Effect of HAB: viability (↑, *K.s.*, *K.m.*), size and complexity (↓, *K.s.*), phagocytosis (=), ROS (=), agglutination titer (=). Effect of parasite: all parameters (=). Combined effect: THC (M-H: ↑ *K.s.*), phagocytosis (M-H: ↓ *K.s*) (after 3 days).	Prevalence (=), intensity (=).	(Hégaret et al., 2007a)
Ruditapes philippinarum	*Perkinsus olseni*	*Karenia selliformis*	Simulated bloom 10^2 - 10^3 cell mL^{-1}, for 6 weeks.	Effect of HAB: viability (=), size (↓), phagocytosis (=), ROS (=), agglutination titter (=), apoptosis (↓). Effect of parasite: all parameters (=). Combined effect: none	Intensity of infection (↓, after 2 & 3 weeks), associated with direct toxicity of HAB to parasite *in vitro*	(da Silva et al., 2008)
Ruditapes philippinarum	*Perkinsus olseni*	*Prorocentrum minimum*	Simulated bloom 10^3 cells mL^{-1}, for 6 days. *In vitro* *P. mínimum - P. olseni* – (1:500)	Effect of HAB: THC (=), size (↓), complexity (=), viability (=), phagocytosis (↓), ROS (=), agglutination titter (=). Effect of parasite: all parameters (=). Combined effect: none	Prevalence (=), intensity (=).	(Hégaret et al., 2009)
Ruditapes philippinarum	*Perkinsus olseni*	*Alexandrium ostenfeldii*	Simulated bloom 10^3 cells mL^{-1}, for 7 days.	Effect of HAB: THC (=), size (↑), complexity (=), viability (=), phagocytosis (=), ROS (↑), agglutination titter (=). Effect of parasite: M-H, size (↑) ROS (↑) Combined effect: ROS (antagonistic: repression of ↑).	Intensity of infection (↓ non-significant) [h]	(Lassudrie et al., 2014)
Crassostrea virginica	*Perkinsus marinus* (*P.m.*) *Bucephalus* sp. (*B.*)	*Alexandrium catenella* (= *A. fundyense* as refered to in this study)*	Simulated bloom 1-2 x 10^3 cells mL^{-1}, for 3 weeks.	Effect of HAB: THC (=), size (=) and complexity (=), ROS (=). Effect of *B.*: THC (↑), viability (↑). Effect of *P.m.*: all parameters (=). Combined effect HAB-*B*: THC (repression of ↑ normally induced by *B.*)	Prevalence of *P. m.* ↑ in *B.* infected oysters [h]	(Lassudrie et al., 2015a)
Mercenaria mercenaria	QPX	*Prorocentrum minimum*	Simulated bloom 2 x 10^4 cells mL^{-1}, for 5 days.	Effect of HAB: THC (=), size (↑), complexity (=), viability (=), phagocytosis (↓), ROS (↑), adhesion (=), apoptosis (=). Combined effect: phagocytosis (↓), size (↓).	NA	(Hégaret et al., 2010)

Mytilus edulis	Gymnophallidae trematode	*Alexandrium catenella* (= *A. fundyense* as refered to in this study)*	Simulated bloom 4 x 10^3 cells mL^{-1}, for 9 days.	Effect of HAB: THC (↓), GRC (↓), phagocytosis (=), ROS (=), complexity (↓, GR and HY), size (GR ↓, HY =). Combined effect: none	Prevalence (↑) [h]	(Galimany et al., 2008b)
Ruditapes philippinarum (adults)	*Vibrio tapetis*	*Alexandrium catenella* (named *A. tamarense* in this study)*	Simulated bloom. 10^2 cells mL^{-1}, for 16h.	Effect of HAB: THC (↑), GRC (↑), phagocytosis (↓)	None	(Bricelj et al., 2011)

THC: total hemocyte count; GR: granulocytes; HY: hyalinocytes (a.k.a. agranulocytes); GRC: granulocyte count; ROS: reactive oxygen species production; VL-L: very-light and light *P. olseni* infection intensity; M-H: moderate to heavy *P. olseni* infection intensity; QPX: Quahog Parasite Unknown; ↓: decrease; ↑: increase or =: no difference compared to control non-toxic algal treatments. *: Nomenclature for species within the *A. tamarense* complex has changed since the publication of these studies, current accepted names are indicated here and were deduced from John et al. (2014), Fraga et al. (2015) and Litaker et al. (2018), where *A. catenella* (= *A. fundyense*) corresponds to group I.


HABs
Toxins or bioactive extracellular compounds
A
Hemocytes
Immune responses ↑/↓
Filtration
Pathogen entry ↓
Tissues and organs
Physiological status ↓
Pathogen +/-
Pathogen -
Pathogen +
Pathogen -
B
Pathogen
Infection transmission +/-
Disease outcome (pathogenicity): + / -