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# Mortality of marine mussels *Mytilus edulis* and *M. galloprovincialis*: systematic literature review of risk factors and recommendations for future research

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## Abstract

The aim of this study was to summarise the literature reporting the risk factors for mortality in the mussel species *Mytilus edulis* and *Mytilus galloprovincialis* in order to identify potential science-based solutions to prevent or mitigate mussel mortality outbreaks. We followed the PRISMA methodology: Preferred Reporting Items for Systematic Reviews and Meta-Analyses. The studied corpus of 91 publications (114 studies) was highly heterogeneous with respect to the methodological approaches used to define or estimate mussel mortality and the related putative risk factors. Results showed that the mortality risk of both mussel species *M. edulis* and *M. galloprovincialis* varied across the seasons, increased with an elevated seawater temperature above a thermal threshold of 20 and 24°C, respectively, decreased by protecting mussels from predation, and was associated with the presence of pathogens in *M. edulis*. For *M. galloprovincialis*, using mussel spat from the same area where the farming is carried out and farming them together with another mussel species appears to reduce the mortality risk. However, for *M. edulis*, this could be achieved by using pure crosses and in particular mussel spat having a selected genotype. For wild bed conservation, sand accumulation and anthropogenic sedimentation should be minimised. Our analysis showed that current approaches to this research topic are limited and are unlikely to yield actionable evidence to identify mussel mortality prevention or mitigation strategies. Therefore, recommendations are offered to increase the ability of future eco-epidemiological research to identify multiple exposures associated with mussel mortality, underpinned by standardised efforts and cooperative initiatives.

**Key words:** eco-epidemiology, environment, husbandry practices, mussel health, pathogens.

## Introduction

Over the last decade, massive mortalities have been reported on a recurrent basis in different marine bivalve species along the French coastline: spat of the Pacific oyster (*Crassostrea gigas*; Miossec *et al.*, 2009), wedge clam (*Donax trunculus*; Garcia *et al.*, 2018), marketable-size Pacific oysters (Garcia *et al.*, 2014), cockles (*Cerastoderma edule*; Garcia *et al.*, 2019) and mussels (*Mytilus* sp.; Garcia *et al.*, 2015; Lupo & Prou, 2016). The aetiology of these mortalities is often unknown, and the current consensus within the scientific community is that their origins are multifactorial. These mass mortalities may reflect a marine disturbance and thus damaged health of the marine coastal ecosystem (Sherman, 2000). Additionally, these recurrent mortalities cause an imbalance in the entire coastal socio-ecosystem, and stakeholders need to adapt permanently to ensure the sustainability of their socio-economic activities (Guillotreau *et al.*, 2017). Representative bodies of the shellfish industry often alert the government authorities about these sustainability concerns, asking either for research to be conducted to explain these mass mortality events and to mitigate the outbreaks, or for financial compensation to mitigate their effects on socio-economic activities. For example, during the massive mortality events that occurred in mussels along the Atlantic coastline of France in 2014, several regional-scale studies were rapidly launched by various research groups (Bernard & Allain, 2016; SMI-DAP, 2016; Travers *et al.*, 2016).

After almost a decade of research on shellfish mortalities, the French Ministry in charge of Agriculture decided to coordinate research efforts at the national level by establishing a research programme and in 2016 set up a national expert panel (called the Scientific and Technical Council, STC) to supervise this project, which consisted of the co-authors of this manuscript. The STC panel brought together all the scientific and technical bodies and institutions in France that have expertise in key related areas, including laboratory diagnostic analyses, shellfish farming and fishery practices, the chemistry of coastal and marine environments, economics, ecotoxicology, epidemiology, genetics, hydrodynamic modelling, shellfish pathology, shellfish physiology and ecosystem quality. The formulated objective of the research programme was ‘to understand the interactions between the physicochemical conditions (abiotic factors) and the biotic factors in the environment, and the infectious status, as well as the impact of these interactions on the mortalities of the farmed and wild shellfish. [...] The programme should explore how contaminants from the terrestrial and marine environments, currents and sediment fluxes, and physicochemical changes in seawater, contribute, as a function of the presence of pathogens, to influence the level of survival of Pacific

oysters, mussels and other shellfish species affected by unexplained massive mortality events, at different physiological stages, and taking into account farming or fishing practices and genetics, if necessary’ (Anon, 2016). The first step was to review the knowledge related to the risk factors for shellfish mortalities in order to identify potential solutions to limit the impact of mortality events. If required, a second step would be to conduct a large eco-epidemiological study at the national level. As massive mortalities in marine mussels were reported at that time (Garcia *et al.*, 2015; Lupo & Prou, 2016), the STC chose to carry out a literature review on these species. The STC panel started its activities in November 2016 and submitted its final report in January 2019.

The objective of this study was to summarise the current literature reporting the risk factors for mortality in the mussel species exploited in France, *Mytilus edulis* and *Mytilus galloprovincialis*, in order to identify potential solutions to prevent or mitigate mussel mortality outbreaks, using the systematic review methodology. A systematic review is an overview of existing evidence relevant to a clearly formulated and specific question, which uses prespecified standardised methods to identify and critically appraise relevant research, and to collect, report and analyse data from the studies that are included in the review (Moher *et al.*, 2009). Methodological rigour, transparency and reproducibility are the fundamental principles underlying a systematic review. This method follows a series of steps to reduce bias in the selection and inclusion of the studies that address the review question and to objectively summarise the quantity and the quality of evidence. Systematic reviews can be helpful when there is a large amount of evidence because they can guide funding decisions for future research and reduce unnecessary duplication of research. If the evidence is scarce, systematic reviews can be particularly helpful to formally identify knowledge gaps and to identify evidence not previously known to exist. If the research findings identified are of poor quality, then this method will document the limitations and weaknesses of the existing evidence and make informed proposals for the design of future research (European Food Safety Agency, 2010). Thus, as part of the review process, this study also aimed to identify gaps in knowledge on mussel mortality risk factors and to formulate recommendations to help target future research.

## Methods

### Scope of the study and research question

This review was conducted following a protocol developed *a priori* to minimise the subjective decisions that could be made during the review process and was reported according to the Preferred Reporting Items for Systematic Reviews

and Meta-Analyses (PRISMA) guidelines (Moher *et al.*, 2009).

Based on the terms of reference formulated by the French Ministry in charge of Agriculture (Anon, 2016), this review covers risk factors for marine mussel mortalities, with the following question: ‘What are the risk factors for mussel mortality included in the topics of animal characteristics, farming or fishery practices, seawater characteristics, contaminants from the terrestrial and marine environments, pathogens, climate characteristics, and geographical characteristics of the farming/fishing site?’ Thus, the specific research question was defined including the key elements for review of risk factors, using the PECO format:

- *Population of interest (P)*: mussel species exploited for human consumption in France, that is *Mytilus edulis* and *M. galloprovincialis*;
- *Exposure (E)*: any exposure to factors pertaining to the following seven topics: animal characteristics, farming or fishery practices, seawater characteristics, contaminants from the terrestrial and marine environments, pathogens, climate characteristics and geographical characteristics of the farming/fishing site;
- *Comparator (C)*: only explanatory studies employing some form of comparison or control group against which the exposure can be compared were included;
- *Outcome of interest (O)*: mortality.

#### Literature search strategy

An exhaustive literature search, including electronic and manual searching, was performed. To ensure completeness of the search, key PECO elements were combined in a search algorithm using Boolean operators. Search equations were adapted to the different databases explored (Appendix S1).

Searches were carried out in the following online bibliographic databases: Web of Science, Scopus, Aquatic Sciences and Fisheries Abstracts, CAS Abstracts, Pascal and Francis, and Environmental Sciences and Pollution Management, on 03 May 2017; the search was updated on 05 April 2018 and 13 November 2018. Manual searches were also performed in available online databases and proceedings of the following conferences: Society for Veterinary Epidemiology and Preventive Medicine (SVEPM), International Symposia on Veterinary Epidemiology and Economics (ISVEE), National Shellfisheries Association (NSA), World Aquaculture Society (WAS), European Aquaculture Society (EAS), European Association of Fish Pathologists (EAFP), Annual Meeting of the European Union Reference Laboratories for Mollusc Diseases, International Symposium on the Advances in Marine Mussel Research (AMMR), Annual Council of the French Shellfish Industry and Annual Ifremer Meeting of Surveillance and Reference

for Mollusc Diseases. To identify grey literature (i.e. unpublished studies) focused on risk factors for mussel mortalities, regional and national representative bodies for shellfish farmers and those for fishermen, regional technical institutes and private consulting engineers were contacted and data were requested in February 2017; the search was updated in November 2018. These bodies belonged to the SCT panel or to their networks. Manual searching of the reference lists in all of the citations that met the eligibility criteria (see below) was conducted as the review progressed.

A unique code was attributed to each captured citation. Citations captured by the search on the online bibliographic databases were saved in .ris format. All the identified citations were gathered in a single electronic database. Duplicate citations were removed by electronic and manual scanning. The final unit of this work was no longer the citation but the study, identified by a unique study code derived from the citation code.

#### Study selection: inclusion and exclusion criteria

Inclusion and exclusion criteria were built using the key PECO elements. Both laboratory and observational studies were included. The following additional exclusion criteria were applied: citations published in languages other than English or French, or before 2006 (to account for progress in the techniques used for pathogen or chemical detection), or concerning mussel larvae (i.e. before their fixation on a collector), or concerning human foodborne pathogens (e.g. *Vibrio parahaemolyticus*), or purely descriptive or case report studies. Only original research studies were included; review articles were excluded.

#### Review process

The purpose of relevance screening in the systematic review methodology is to rapidly remove citations not relevant to the review, as the literature search process should be highly sensitive, with low specificity. This first step was based on title and abstract screening of the identified citations. Citations excluded at this stage were not assessed further. The study selection was conducted unmasked, that is the reviewers had access to the authors' names. Screening of the whole corpus was conducted by a single reviewer, with a second reviewer independently examining the first reviewer's work for a random sample of the identified citations, with 30 citations per member of the STC ( $N = 13$ ). The second step was based on the full-text examination of the citation. Citations excluded at this stage were documented for the reason behind their exclusion in a dedicated table (Appendix S2). The full-text screening was conducted by a single reviewer, with a

second reviewer validating the first reviewer's work for two citations per member of the STC ( $N = 11$ ).

When disagreements on study selection occurred, the reviewers discussed and sought consensus. At each step, the kappa coefficient was calculated to evaluate the agreement between the inclusion/exclusion decisions of the first reviewer and the STC, using the interpretation of Landis and Koch (1977), where values  $<0$  indicate no agreement, 0–0.20 slight, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 substantial and 0.81–1 almost perfect agreement.

### Study methodological quality and field transposition assessment

For each included study, we built a quality score based on key features of the study design, to assess the appropriateness of the methodological aspects to identify a risk factor. Three levels (low, moderate or high) were assigned to this methodological quality score, based on a combination of key study design features for observational and experimental studies. For observational studies, criteria were the random selection of epidemiological units and the strength of proof of causal association provided by the study design. A moderate strength of proof was attributed to transversal and single cohort studies, whereas a high strength of proof was attributed to exposed/nonexposed cohort and case–control studies. For experimental studies, criteria were the use of a control during the experiment or a design of experiments (when several risk factors were investigated), and the number of replicates of the experiment. At least three replicates were considered as strength to assess the variations in experiment outcomes.

For laboratory studies, an additional criterion was built to evaluate the relevance of the results to 'real-world' conditions. Two levels (low or satisfactory) were assigned to this field transposition score, based on the environmental relevance of the physical parameters of the seawater and of the tested chemical concentrations, and the route of exposure to the pathogens, and by excluding intramuscular injection that forced the natural barriers of the mussels. To assess the environmental relevance of the physical parameters of the seawater, we used the ocean monitoring indicators collected by the EU Copernicus Marine Service Information (EU Copernicus Marine Service Information, 2019) for the 1993–2017 period for seawater temperature and salinity, and 2001–2016 period for seawater pH. To assess the environmental relevance of the chemical concentrations, we used the chronic predicted no-effect concentration (PNEC) in marine waters, which is the concentration of a substance in any environment below which adverse effects will most likely not occur during long-term exposure (INERIS, 2019). Results of studies using chemical concentrations greater than 250 times the PNEC were considered

as not relevant to the 'real-world' conditions, except when the studies mimicked a field pollution event. In addition, studies using the stress on stress (SOS) test, that is survival in air test, to identify the negative effects of chemicals were excluded.

Scoring for methodological quality and field transposition assessment was conducted by one reviewer. The studies with low-quality scores or low field transposition scores were excluded from the review (Appendix S2).

### Data extraction from the included studies

Data were extracted and collated in a Microsoft<sup>®</sup> Excel spreadsheet. Two templates, for either laboratory or observational studies, were developed *a priori* to standardise the extraction of information from the selected studies as far as possible. The unit was no longer the citation but the study. The templates were further reviewed and enriched by all co-authors and pilot-tested before use. Some fields were standardised, using drop-down lists, and others were left open because the related information was considered difficult to predict. Table 1 lists all extracted data, if available, from the selected corpus.

For each putative risk factor, the effect of exposure on mussel mortality risk was extracted and categorised as increasing, decreasing or no effect. The absence of effect referred to comparisons between controls and treatment/cases that were statistically nondifferent. Seven topics concerning mortality risk factors were defined based on a consensus among the STC members: pathogens, mussel characteristics, seawater characteristics, characteristics of the farming or fishing site, farming or harvesting practices, pollutants from the terrestrial and marine environments, and climate characteristics.

Data extraction was conducted by a single reviewer and was checked by a second reviewer for two citations per member of the STC.

### Data analyses

Summary distributions of extracted characteristics were examined by mussel species and study conditions (i.e. observational or experimental). A qualitative analysis of open fields was conducted *a posteriori*, to build categorical variables having different response modalities. Each categorical variable was then described in terms of numbers and frequency of its modalities. These were used to write a narrative synthesis of the results, summarising information on the characteristics of the included studies, such as study conditions and design, and the outcome and exposure effect measures used.

Multiple correspondence analysis (MCA) was used to identify groups of studies with similar profiles regarding

**Table 1** Characteristics extracted from the studies included in the systematic review of the risk factors for mussel mortality

Characteristics	Standardised modalities
All studies	
Authors' names	Open field
Title	Open field
Journal name and volume	Open fields
Year of publication	Open field
Type of document	Journal, conference paper/abstract, report and thesis
Mussel species†	<i>Mytilus edulis</i> and <i>Mytilus galloprovincialis</i>
Country and region	Open field
Study conditions	Laboratory and observational
Population type†	Farmed, wild, hatchery and others
Mussel age class†	Juveniles and adults
Mussel size	Open field
Epidemiological unit	Individual and group
Frequency of mortality estimation	Open field
Risk factor topic†	Animal characteristics, site characteristics, climate characteristics, seawater characteristics, contaminants, pathogens and farming/fishery practices
Risk factor(s) studied	Open field
Interactions addressed	Yes, no
Methodological quality score	Poor, moderate and satisfactory
Field transposition score	Poor and satisfactory
Measure of association between the mortality and the exposure of interest	Open field
Effect of exposure to the factor on the mortality risk	Increasing, decreasing and no effect
Observational studies	
Study design	Cross-sectional, case-control, exposed/nonexposed cohorts and single prospective cohort
Random sampling	Yes, no
Mortality estimation	Open field
Mortality counting method	Open field
Laboratory studies	
Control presence	Yes, no
Triplicate of the trial	Yes, no
Mortality definition criteria	Open field

†Several choices were possible.

the extracted characteristics (i.e. categorical variables) and the associations between studies and characteristics (Greenacre, 1984). This method is used to detect and represent underlying structures in a data set, by representing data as points in a low-dimensional Euclidean space. It produces graphs on which the studies are represented by points which tend to group together if the studies are similar; differences, on the contrary, tend to produce distance.

Fourteen active variables were used for the MCA: year of publication, mussel species, study conditions, geographical location, mussel population type, quality score, the seven themes of mortality risk factors and interaction considerations between risk factors. When the frequency of studies in a variable category was <10%, this category was grouped with another category, if relevant. The contributions of the variables to each factorial axis and the plots of the MCA were used to interpret each factorial axis.

The descriptive analysis was conducted by using R software, version 3.6.1 (R Core Team, 2019). Study screening based on the title and abstract was conducted using the Metagear package (Lajeunesse, 2016). MCA was carried out using the FactoMineR (Lê *et al.*, 2008) and Factoextra (Kassambra & Mundt, 2017) packages. Plots were built using the ggplot2 package (Wickham, 2016).

## Results

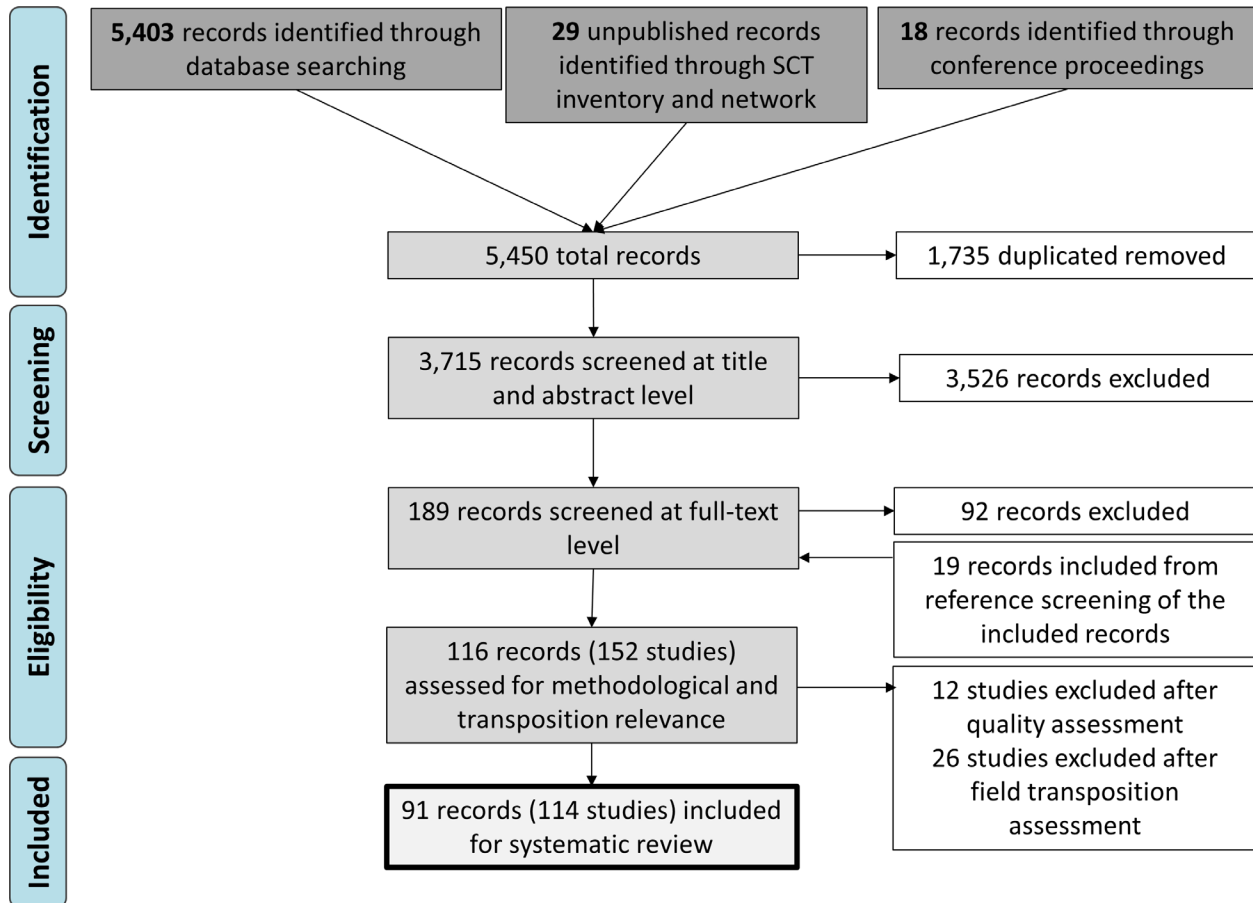
### Literature search and selection

The initial search identified 5450 citations in the electronic databases and through manual searching in the conferences and referrals from the SCT, published between 2006 and 2018. After removal of duplicates, 3715 remained for further screening. Screening the titles and abstracts excluded another 3526 citations, leaving 189 citations for a full-text review. Subsequently, an additional 92 citations were excluded. We included 19 articles by scanning the reference lists of included citations. These 116 citations contained reports on 152 studies that were critically appraised individually. Assessment of the methodological quality and field transposition excluded an additional 12 and 26 studies, respectively. Appendix S2 lists the studies that were rejected on full-text screening, methodological quality and field transposition assessments, together with the reasons for exclusion. Finally, a total of 91 citations met the eligibility criteria for inclusion in the systematic review. They reported on 114 studies, listed in Appendix S3. Figure 1 shows the selection process workflow.

Agreement between reviewers was substantial at the abstract and title screening level (kappa coefficient = 0.66, 95% CI [0.58–0.75] calculated on 9.9% (366/3715) of the identified citations), and almost perfect at the full-text screening level (kappa coefficient = 0.92, 95% CI [0.78–1] on 14.3% (27/189) of the citations).

### Description of the included studies

Among the 91 included citations, 82 were scientific journal articles, 6 unpublished study reports, 2 Ph.D. thesis reports and 1 conference proceedings. Among the 114 included studies, almost half of the studies about *M. edulis* (44%;



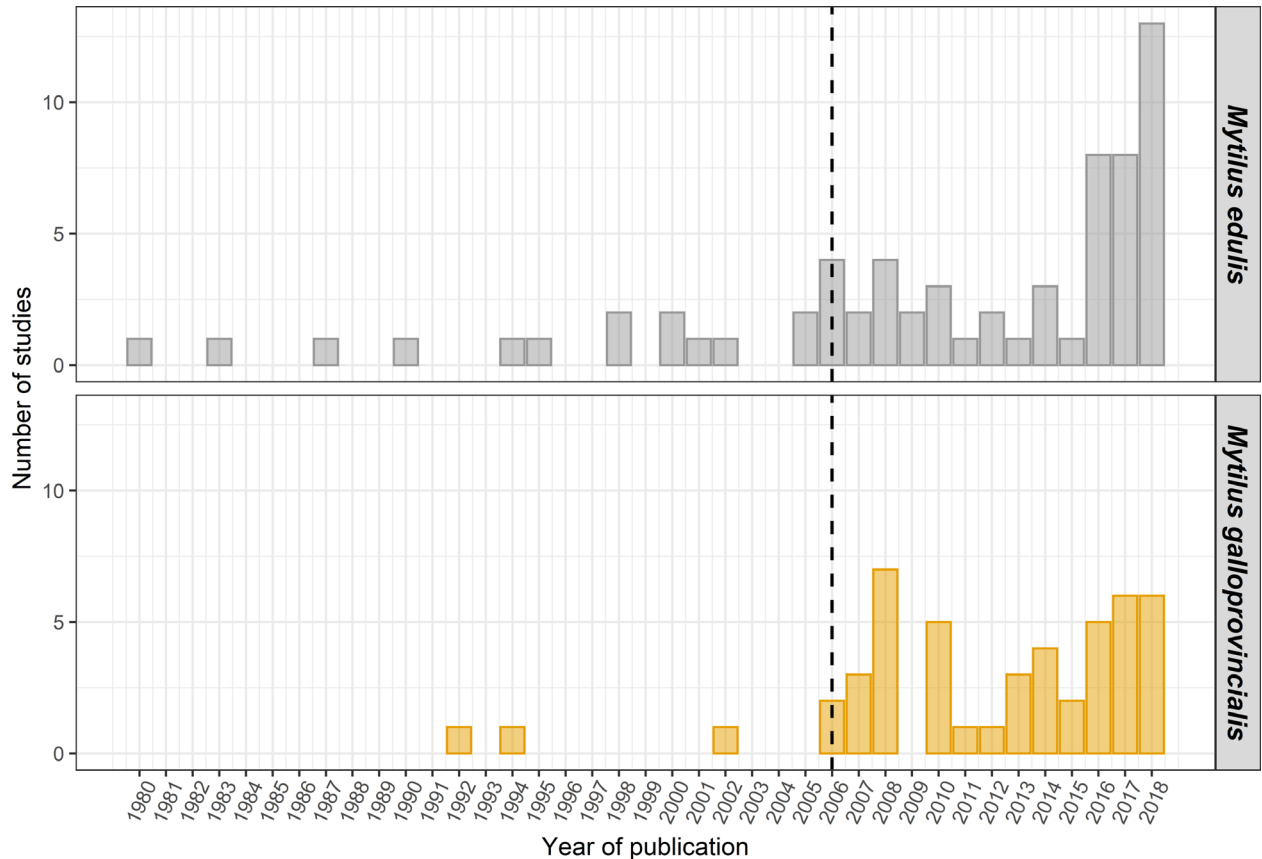
**Figure 1** PRISMA workflow diagram representing the study selection process.

29/66) were conducted after 2015, whereas the annual number of studies on *M. galloprovincialis* varied regularly over the last decade (Fig. 2). Almost one-quarter of the studies about *M. edulis* were conducted in France and about one third in North America (Fig. 3a). For *M. galloprovincialis*, almost half of the studies were conducted in Southern Europe (particularly in Spain) and in South Africa (Fig. 3b). Overall, the included studies aimed to understand mussel production losses (45%; 52/114), mussel species distribution and habitat segregation (21%; 24/114), or they used mussels as bio-indicators to assess environment quality or climate change effects (33%; 38/114).

Table 2 describes the main characteristics of the corpus. The species *M. edulis* was mainly studied under observation conditions (58%; 38/66 studies), whereas *M. galloprovincialis* was equally studied under either experimental or observation conditions (48%; 23/48 and 52%; 25/48 studies, respectively). For the two species, the studied populations were mainly farmed mussels or mussels from wild beds. The age class of the studied mussel populations was not reported for two thirds of the studies, as most of them

rather described mussel size, especially for *M. galloprovincialis*. Only 34% of the studies showed a high methodological quality score to identify a risk factor. The vast majority of observation studies did not select the mussels at random (48/63) and used a study design with a low strength of proof to identify a risk factor (47/63). One-quarter (13/51) of the laboratory studies did not use a control, and half of them (26/51) did not reproduce the experiment in triplicate.

The first two factorial axes, which explained the larger amount of variance of all the 14 variables used to run the MCA, were used to interpret the pattern of relationships of the descriptive characteristics of the studies. They represented 28.0% of the total inertia (i.e. total variance of all variables included in the analysis), with 15.5% and 12.5% of variance explained, respectively. The 114 studies could be differentiated based on the modalities of all the variables used to run the MCA, except the geographical location, when the ellipses of the variable modalities were distinct (Fig. 4). This figure also shows that the studies could be divided into two main groups. On the left quadrants, a first



**Figure 2** Yearly distribution of the number of studies on risk factors for mussel mortalities from 1980 to 2018, per mussel species ( $N = 114$ ). The dotted black line separates included studies using the initial temporal inclusion criteria (i.e. published after 2006) from additional older studies.

group gathered studies conducted on *M. edulis* in observational conditions, with a satisfactory methodological score, and investigating mortality risk factors pertaining to animal characteristics, and characteristics of the site and farming or harvesting practices. On the right quadrants, the second group gathered studies conducted on *M. galloprovincialis* in laboratory conditions in the Black Sea or the Mediterranean, exploring the effects of seawater characteristics and pollutants on the mussel mortality risk. The absolute contributions of the variables and their modalities are reported in Appendix S4.

#### Definition and estimation of mussel mortality

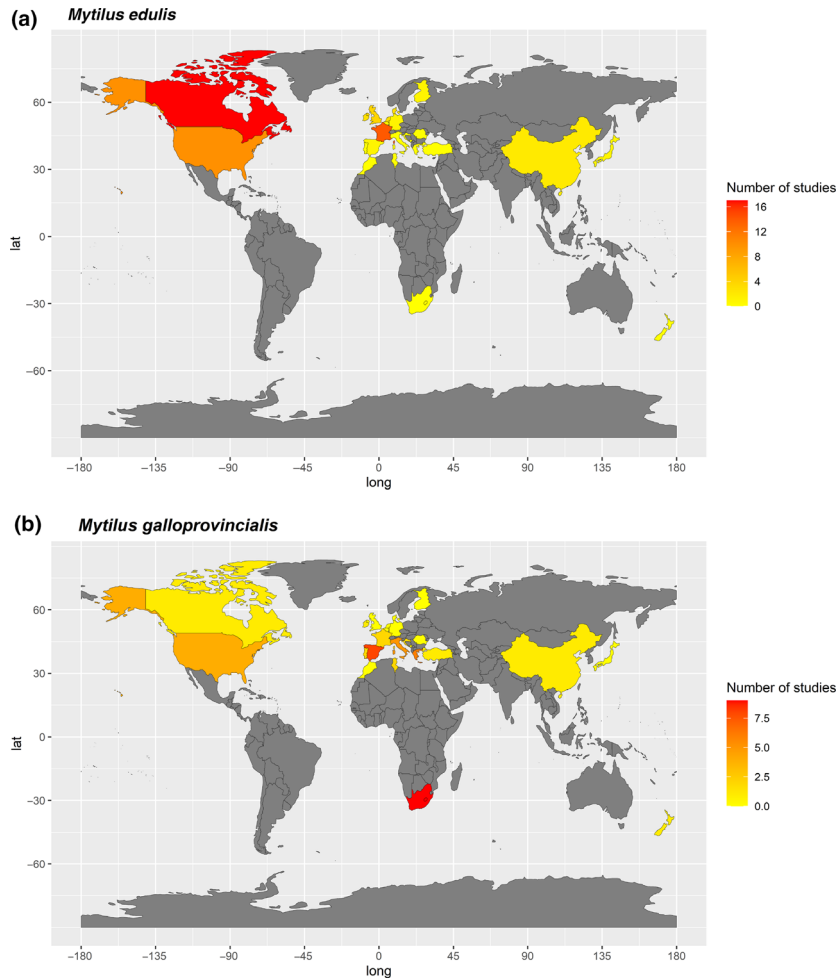
Even though all the 114 studies dealt with mussel mortality, a broad variation in terms of methodological approaches to define or estimate this outcome was found (Table 2). In laboratory studies, experimental mussel mortality was defined at the animal level as a binary outcome, the mussel being dead or alive. Half of the studies did not define criteria to assess the death of a mussel, and the other half used varying criteria. In the vast majority of observational

studies, mortality was quantified at the mussel population level and expressed as a proportion, using a number of dead mussels as the numerator, and a total number of mussels as a denominator. For most of the studies in both mussel species (59/63), this proportion was a final prevalence or a cumulative prevalence, monitored throughout the study. No studies used mortality incidence as an outcome. To estimate the mortality proportion, most of the studies (52/63) used counts, but counting methods varied greatly among the studies. Almost three-quarters of the studies measured mussel mortality regularly throughout the study course. Mussel mortality was mainly reported on a monthly basis in observational conditions and on a daily basis in laboratory conditions.

#### Association measures between mortality and risk factors

Studies used various statistical associations between the outcome of interest (mussel mortality) and the exposures of interest (e.g. factor modalities, treatments and concentrations) (Table 3). For qualitative factors of interest, comparison of mortality means, medians or proportions was





**Figure 3** Geographical distribution of the included studies about (a) *Mytilus edulis* ( $N = 66$ ) and (b) *Mytilus galloprovincialis* ( $N = 48$ ). Grey shading indicates countries without included research about mussel mortality risk factors. The other colours represent the number of studies for each country.

used, whereas for quantitative factors of interest (e.g. chemical compound concentrations), several types of correlations were used. Laboratory studies, in particular those investigating the impact of pollutants, used substance concentrations causing 50% mortality ( $LC_{50}$ ) within a fixed period of time (24 or 96 h) or time leading to 50% mortality ( $LT_{50}$ ).

### Risk factors for mussel mortality

In total, 102 putative risk factors were examined in the 114 studies, with 62 factors for *M. galloprovincialis* (Table 4) and 67 factors for *M. edulis* (Table 5), pertaining to seven topics: pathogens, mussel characteristics, seawater characteristics, characteristics of the farming or fishing site, farming or harvesting practices, contaminants from the terrestrial and marine environments, and climate

characteristics. The key results of the studies included in the following narrative review are provided in Appendix S3.

#### *Factors related to pathogens*

The effect of pathogens on the mortality risk was studied equally in *M. edulis* (11 factors by 8 studies, Table 5) and in *M. galloprovincialis* (9 factors by 8 studies, Table 4).

In *M. edulis*, horizontal transmission of a putative causal agent of mortality was reproduced in laboratory conditions between two wild mussel stocks sampled after mortality events (Benabdelmouna *et al.*, 2018). An additional experimental reproduction of this phenomenon was reported between wild mussels sampled after mortality events and sentinel hatchery-produced mussels (Pépin *et al.*, 2017). However, in both studies, pathogen identification was not successful.

Across the investigated pathogens in both mussel species, evidence of the absence was consistently reported for

**Table 2** Characteristics and numbers of included studies investigating risk factors of marine mussel mortality ( $N = 114$ )

Characteristics	<i>M. edulis</i>		<i>M. galloprovincialis</i>	
	Number of observational studies ( $N = 38$ )	Number of experimental studies ( $N = 28$ )	Number of observational studies ( $N = 25$ )	Number of experimental studies ( $N = 23$ )
Geographical focus				
North Sea	3	10	0	1
Black Sea/Mediterranean	0	0	8	11
Atlantic Ocean	31	16	15	9
Pacific Ocean	4	2	2	2
Population type†				
Farmed	22	7	10	12
Wild	11	20	15	11
Hatchery	6	1	1	0
Not reported	0	1	0	0
Mussel age class‡				
Juveniles	6	3	2	2
Adults	5	10	2	10
Not reported	28	15	21	11
Mussel size				
<20 mm	4	5	7	2
20–30 mm	6	5	5	4
30–40 mm	5	6	8	4
40–50 mm	4	4	5	3
50–60 mm	3	7	7	8
60–70 mm	2	1	4	1
>70 mm	1	0	4	2
Not reported	22	10	10	1
Epidemiological unit				
Individual	0	4	1	0
Group	38	24	24	23
Study design				
Cross-sectional	2		2	
Case-control	0		0	
Exposed/nonexposed cohorts	10		6	
Single prospective cohort	26		17	
Strength of proof of causal association provided by the study design				
Low	28		19	
High	10		6	
Random sampling				
Yes	7		8	
No	31		17	
Control presence				
Yes		19		19
No		9		4
Triplicate of the trial				
Yes		15		10
No		13		13
Quality score				
Moderate	24	20	16	15
High	14	8	9	8
Mortality definition criteria§				
Failure to close the valves in response to external stimuli		10		9
Widely open valves		7		7
Not defined		18		14
Mortality estimation methods				
Counting	34		18	

Table 2 (continued)

Characteristics	<i>M. edulis</i>		<i>M. galloprovincialis</i>	
	Number of observational studies (N = 38)	Number of experimental studies (N = 28)	Number of observational studies (N = 25)	Number of experimental studies (N = 23)
Analysis of digital pictures of quadrats	0		2	
Drop-in density of live mussel	1		0	
Not reported	3		5	
Mortality counting methods				
Dead and live mussels	6		2	
Remaining live mussels	7		4	
Dead mussels	1		3	
Freshly dead mussels	0		1	
Empty shells	3		1	
Not reported	17		7	
Mortality statistics				
Final prevalence	14		12	
Cumulative prevalence	21		12	
Instantaneous proportion	2		0	
Half-stock index	1		1	
Frequency of mortality estimation¶				
Daily	2	9	2	10
Weekly	3	3	1	3
Bimonthly	5	1	0	0
Monthly	15	2	11	3
Quarterly	5	0	5	0
Biannually	1	0	0	0
Annually	1	0	0	0
At the end of the study	9	5	6	6
Not reported	3	12	1	3
Risk factor topics**				
Pathogens	2	6	5	3
Animal characteristics	17	3	5	2
Seawater characteristics	4	11	0	9
Site characteristics	18	7	13	1
Farming or fishery practices	21	2	10	3
Contaminants	0	3	1	6
Climate characteristics	6	2	3	5

†Several population types could be examined in a single study; thus, the sum of studies per population type could be greater than the total number of studies.

‡Several age classes could be examined in a single study; thus, the sum of studies per age class can be greater than the total number of studies.

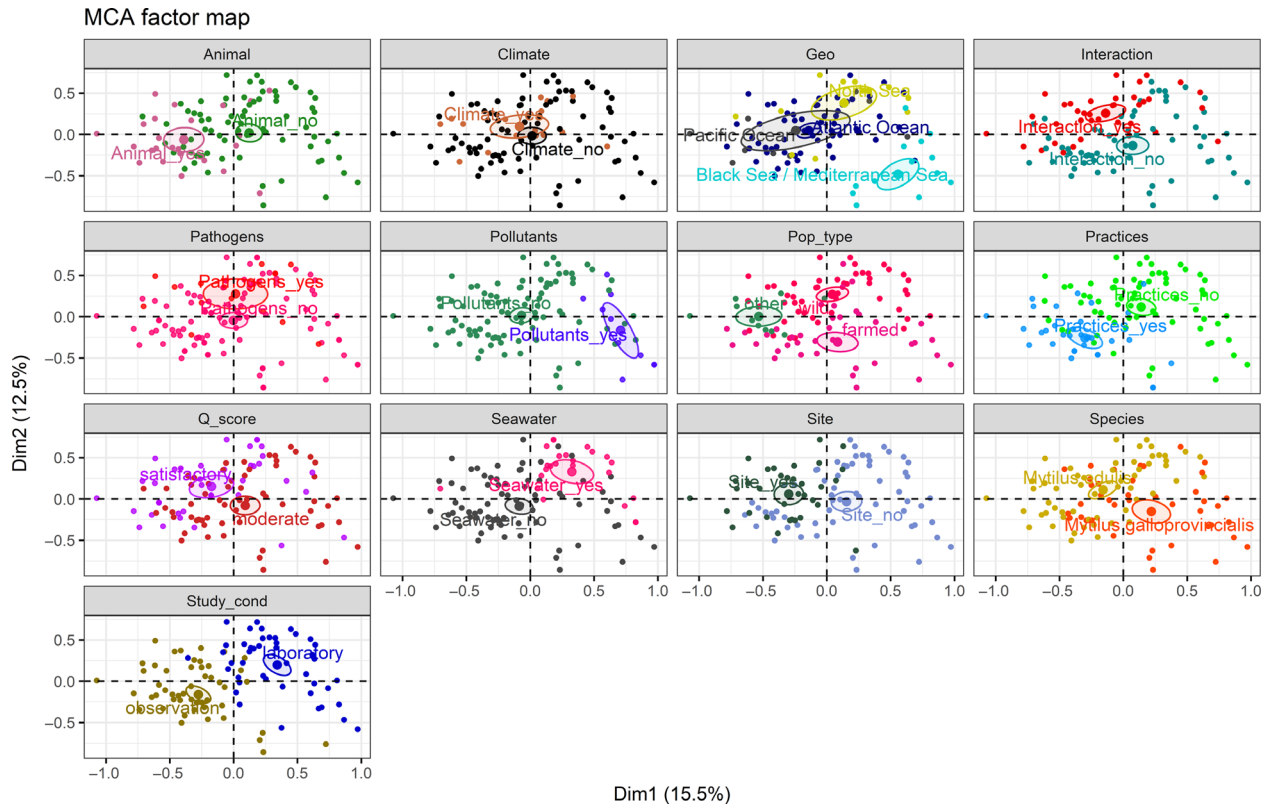
§Several criteria could be used in a single study; thus, the sum of studies per criterion can be greater than the total number of studies.

¶Mussel mortality could be measured at several frequencies in a single study; thus, the sum of studies per frequency can be greater than the total number of studies.

\*\*Several risk factor topics could be investigated in a single study; thus, the sum of studies per topic can be greater than the total number of studies.

ostreid herpesvirus OsHV-1 (Benabdelmouna *et al.*, 2018) and the OIE listed parasite *Marteilia refringens* (Benabdelmouna *et al.*, 2018; Bernard *et al.*, 2018b). However, results reported for bacteria were not straightforward. In both mussel species, no effect of the overall bacteriological profile of the mussels was shown on the mortality risk (Bernard *et al.*, 2018b). In *M. edulis*, the bacterium *Vibrio aestuarianus* was not detected in moribund mussel tissues (Benabdelmouna *et al.*, 2018), whereas a possible association with mortality risk was suspected for anaerobic

bacteria (Babarro & De Zwaan, 2008), opportunistic heterotrophic bacteria present in the seawater (Eggermont *et al.*, 2014) or bacteria belonging to the genus *Photobacterium* (Eggermont *et al.*, 2017). Bacteria belonging to the *Splendidus* clade of the genus *Vibrio* were inconsistently detected in moribund mussel tissues or haemolymph, challenging their role in mortality risk (Eggermont *et al.*, 2017; Benabdelmouna *et al.*, 2018). In *M. galloprovincialis*, conflicting results were reported regarding the effect of the presence of bacteria *Vibrio aestuarianus* or *Vibrio* belonging



**Figure 4** Graphical solution of the MCA on the first and second factorial axis, which explained, respectively, 15.5% and 12.5% of the total inertia of the 14 variables, for the 13 descriptive characteristics of  $N = 114$  studies related to risk factors of mussel mortality. Each variable is plotted on the graph according to the coordinates on factorial axes 1 (horizontal) and 2 (vertical).

**Table 3** Association measures between mussel mortality and factors of interest ( $N = 114$  studies)

Association measure	No. of studies	
	<i>Mytilus edulis</i> (66)	<i>Mytilus galloprovincialis</i> (48)
Comparison of mortality means	20	15
Comparison of mortality proportions	34	20
Comparison of survival curves	7	3
Median survival	1	0
Correlation	2	4
Concentration leading to 50% mortality	2	5
Time leading to 50% mortality	0	1

to the *Splendidus* clade on the mortality risk, even when mussels were exposed to high concentrations of bacteria in the seawater ( $10^{10}$  CFU mL<sup>-1</sup>) (Romero et al., 2014). To induce mussel mortality, additional exposures to an elevated temperature of the seawater (25°C) and to 8 h emersion to reproduce hypoxia stress were needed.

Algae effects were also investigated. Lethal effects of toxic dinoflagellate algae were reported in *M. galloprovincialis* with *Ostreopsis cf ovata* (Carella et al., 2015) and in *M. edulis* with *Karlodinium armiger* (Binzer et al., 2018). On sheltered rocky shores, the presence of epibiotic algae on the shell was reported to increase the mortality risk in both mussel species (O'Connor, 2010). In *M. galloprovincialis*, conflicting results were reported concerning the effect of parasitic phototrophic shell-degrading endoliths, showing a protective effect against heat stress mortality by decreasing their body temperature (Zardi et al., 2016) or a sublethal effect because of induced shell weakening (Marquet et al., 2013) or of energy trade-off between shell repair and other physiological constraints (Nicastro et al., 2018).

*Factors related to mussel characteristics*

The effect of mussel characteristics on the mortality risk was more commonly studied in *M. edulis* (15 factors by 22 studies, Table 5) than in *M. galloprovincialis* (4 factors by 7 studies, Table 4).

Among these factors, genetic characteristics were the main factors investigated, in particular species and genotype. The mortality risk of *M. edulis* did not differ from

**Table 4** Factors studied in *M. galloprovincialis* and reported effect on the mortality risk (23 experimental studies and 25 observation studies). Experimental studies are underlined; studies accounting for interactions between factors are in bold; in the last column, NR stands for nonrelevant

Studied factors	No. of studies	Effect on mortality risk			Consistency of study results
		Increase	Decrease	No effect	
Pathogens	8				
Nonidentified infectious agent	1	<u>Benabdelmouna et al. (2018)</u>			NR
Bacteriological profile	1			Bernard et al. (2018b)	NR
Bacteria <i>Vibrio aestuarianus</i>	3	<b><u>Romero et al. (2014)</u></b> <sup>1</sup>		<u>Benabdelmouna et al. (2018)</u> ; <b><u>Romero et al. (2014)</u></b> <sup>2</sup>	No
Bacteria <i>Vibrio Splendidus</i> clade	3	<b><u>Romero et al. (2014)</u></b> <sup>1</sup>		<u>Benabdelmouna et al. (2018)</u> ; <b><u>Romero et al. (2014)</u></b> <sup>2</sup>	No
Ostreid herpesvirus OsVH-1	1			<u>Benabdelmouna et al. (2018)</u>	NR
Parasite <i>Marteilia refringens</i>	1			<u>Benabdelmouna et al. (2018)</u>	NR
Toxic algae dinoflagellate <i>Ostreopsis cf ovata</i>	1	<u>Carella et al. (2015)</u> <sup>3</sup>			NR
Presence of epibiotic algae on the shell	2	<b>O'Connor (2010)</b> <sup>4</sup>		<b>O'Connor (2010)</b> <sup>5</sup>	No
Endolithic infestation	3	<u>Marquet et al. (2013)</u> ; <u>Nicastro et al. (2018)</u> <sup>5</sup>	<b>Zardi et al. (2016)</b> <sup>7</sup>		No
Animal characteristics	7				
Species vs. <i>M. trossulus</i>	3		<u>Dowd and Somero (2013)</u> ; <u>Schneider (2008)</u>	<u>Shields et al. (2008)</u>	No
Intraspecific vs. interspecific genotype	2		<u>Fuentes et al. (2002)</u> <sup>8</sup>	<u>Shields et al. (2008)</u> <sup>9</sup>	No
High frequency of individuals having more than 10% cytogenetic abnormalities in haemocytes in the population	1	<u>Benabdelmouna and Ledu (2016)</u>			NR
Small size	2			<u>Lok et al. (2007)</u> ; <b>O'Connor (2010)</b> <sup>10</sup>	Yes
Seawater characteristics	9				
Elevated temperature	4	<u>Anestis et al. (2007)</u> <sup>11</sup> ; <u>Dowd and Somero (2013)</u> <sup>12</sup> ; <u>Gazeau et al. (2018)</u> <sup>13</sup>		<u>Gestoso et al. (2016)</u> <sup>14</sup>	No
Increased number of thermal stresses	1			<u>Lenz et al. (2018)</u> <sup>15</sup>	NR
Decreased salinity	2	<b><u>Hamer et al. (2008)</u></b> <sup>16</sup>		<b><u>Hamer et al. (2008)</u></b> <sup>17</sup>	NR
Decreased pH/Acidification	4	<u>Bressan et al. (2014)</u> <sup>18</sup> ; <b><u>Gestoso et al. (2016)</u></b> <sup>19</sup>		<b><u>Gazeau et al. (2018)</u></b> <sup>20</sup> ; <u>Bressan et al. (2014)</u> <sup>21</sup>	No
Decreased dissolved oxygen/hypoxia	2	<b><u>Romero et al. (2014)</u></b> <sup>22</sup>		<b><u>Romero et al. (2014)</u></b> <sup>23</sup>	No
Characteristics of the farming/fishing site	14				
General effect	5	<u>Bownes and McQuaid (2010)</u> ; <u>Fuentes et al. (1994)</u> ; <u>Gardner (2013)</u> ; <u>Moschino et al. (2017)</u>		<u>Fuentes et al. (1992)</u>	No
Coast vs. bay	2	<u>Nicastro et al. (2008)</u> ; <u>Nicastro et al. (2010)</u>			Yes
Sand burial or accumulation	4	<u>Nicastro et al. (2010)</u> ; <u>Zardi et al. (2006)</u> ; <u>Zardi et al. (2006)</u>		<u>Zardi et al. (2008)</u>	No
Wave exposure	2	<b>O'Connor (2010)</b> <sup>4</sup>		<b>O'Connor (2010)</b> <sup>5</sup>	No
Wave height	3	<u>Zardi et al. (2008)</u> ; <b><u>Nicastro et al. (2010)</u></b> <sup>24</sup>		<b><u>Nicastro et al. (2010)</u></b> <sup>25</sup>	No
High position on the shore	2			<u>Bownes and McQuaid (2010)</u> ; <u>Marquet et al. (2013)</u> <sup>2</sup>	Yes
Border vs. central position in the bed	1			<u>Nicastro et al. (2008)</u>	NR

**Table 4** (continued)

Studied factors	No. of studies	Effect on mortality risk			Consistency of study results
		Increase	Decrease	No effect	
Predation	2	Gammoudi <i>et al.</i> (2017) <sup>27</sup> ; Plass-Johnson <i>et al.</i> (2010)			Yes
Farming/harvesting practices	13				
Geographical origin of the spat: local. vs transplanted	7	Shields <i>et al.</i> (2008)	Bernard <i>et al.</i> (2018a); Fuentes <i>et al.</i> (1992); Fuentes <i>et al.</i> (1994); Gardner (2013); Kovacic <i>et al.</i> (2017); Ramon <i>et al.</i> (2007)		No
Position inside the farming structure	2		Fuentes <i>et al.</i> (1994)	Fuentes <i>et al.</i> (1992)	No
Mixed mussel species	2		<u>Gestoso <i>et al.</i> (2016)<sup>28</sup></u> ; Olabarriall <u><i>et al.</i> (2016)<sup>28</sup></u>		Yes
Polyculture (fish)	1	Gvozdenovic <i>et al.</i> (2017)			NR
Polyculture (algae <i>Gracilaria verrucosa</i> )	1		<u>Ajjabi <i>et al.</i> (2018)</u>		NR
Re-immersion duration of the mussels before sale >11 days	1	Theodorou <i>et al.</i> (2017)			NR
Stocking density during immersion before transport for sale (kg per bag)	1			Theodorou <i>et al.</i> (2017)	NR
Increasing intensity of human trampling during bed harvesting	1	Nicastro <i>et al.</i> (2018)			NR
Contaminants from the terrestrial and marine environments	7				
Total metals (As, Cd, Cr, Cu, Hg, Ni, V, Pb, Zn, Al, Fe)	1	Moschino <i>et al.</i> (2016) <sup>29</sup>			NR
Al	1	Moschino <i>et al.</i> (2016) <sup>29</sup>			NR
As	1			Moschino <i>et al.</i> (2016) <sup>29</sup>	NR
Cd	1			Moschino <i>et al.</i> (2016) <sup>29</sup>	NR
Cr	1			Moschino <i>et al.</i> (2016) <sup>29</sup>	NR
Cu	1			Moschino <i>et al.</i> (2016) <sup>29</sup>	NR
Fe	1	Moschino <i>et al.</i> (2016) <sup>29</sup>			NR
Hg	1			Moschino <i>et al.</i> (2016) <sup>29</sup>	NR
Ni	1			Moschino <i>et al.</i> (2016) <sup>29</sup>	NR
Pb	1	Moschino <i>et al.</i> (2016) <sup>29</sup>			NR
V	1			Moschino <i>et al.</i> (2016) <sup>29</sup>	NR
Zn	1			Moschino <i>et al.</i> (2016) <sup>29</sup>	NR
Polycyclic aromatic hydrocarbons (PAHs)	1	Moschino <i>et al.</i> (2016) <sup>29</sup>			NR
Polychlorinated biphenyls (PCBs)	1			Moschino <i>et al.</i> (2016) <sup>29</sup>	NR
Carbamazepine (anti-epileptic pharmaceutical drug)	1	<u>Oliveira <i>et al.</i> (2017)</u>			NR
Phthalates (plasticisers)	1			Moschino <i>et al.</i> (2016) <sup>29</sup>	NR
Alkylphenols (detergents, fuel and oil additives, and resins)	1			Moschino <i>et al.</i> (2016) <sup>29</sup>	NR
Zinc oxide nanoparticles (ZnO)	1	<u>Li <i>et al.</i> (2018)</u>			NR
2,4,6-trinitrotoluene (TNT, explosive compound)	1	<u>Rosen and Lotufo (2007)</u>			NR
Hexahydro-1,3,5,-triazine (RDX, explosive compound)	1			<u>Rosen and Lotufo (2007)</u>	NR
Octahydro-1,3,5,7-tetranitro-1,3,5,7- tetrazocine (HMX, explosive compound)	1			<u>Rosen and Lotufo (2007)</u>	NR

Table 4 (continued)

Studied factors	No. of studies	Effect on mortality risk			Consistency of study results
		Increase	Decrease	No effect	
Imidazolium ionic liquids (1-butyl-3-methylimidazolium and 1-methyl-3-octylimidazolium tetrafluoroborate), alternative to conventional organic solvents	1	Tsarpali <i>et al.</i> (2015)			NR
Olive mill wastewater (by-product of olive oil production)	1	Danellakis <i>et al.</i> (2011)			NR
Landfill leachate	1	Tsarpali and Dailianis (2012)			NR
Climate characteristics	8				
Season	3	Bernard <i>et al.</i> (2018a) <sup>30</sup> ; Nicastro <i>et al.</i> (2008) <sup>31</sup> ; <b>Nicastro <i>et al.</i> (2010)</b> <sup>32</sup>			Yes
Elevated air temperature	1	Olabarri <i>et al.</i> (2016)			NR
Air vs. seawater thermal range	4	Anestis <i>et al.</i> (2010) <sup>33</sup> ; Dowd and Somero (2013) <sup>34</sup>	Schneider (2008) <sup>35</sup>	Schneider (2008) <sup>36</sup>	No
Increased number of aerial thermal stresses	1	Dowd and Somero (2013) <sup>37</sup>			NR

<sup>1</sup>Infection by exposure to contaminated seawater with  $10^{10}$  CFU mL<sup>-1</sup>, with seawater temperature at 25°C and in emersion for 8 h (to simulate hypoxia conditions).

<sup>2</sup>Infection by exposure to contaminated seawater with  $10^{10}$  CFU mL<sup>-1</sup>, with seawater temperature at 15°C or at 25°C.

<sup>3</sup>Dose effect.

<sup>4</sup>In sheltered rocky shores.

<sup>5</sup>In shores exposed to waves.

<sup>6</sup>Mortality due to trampling (anthropogenic stressor) in the context of recreational or harvesting use of wild beds.

<sup>7</sup>Mortality due to a heatwave.

<sup>8</sup>Different genotypes of *M. galloprovincialis* vs. different hybrid genotypes of *M. edulis* and *M. galloprovincialis*.

<sup>9</sup>Native genotype of *M. trossulus* vs. introgressed vs. introduced genotype of *M. galloprovincialis*.

<sup>10</sup>Mortality due to epibiotic algae on the shell.

<sup>11</sup>Thermal threshold at 24°C; elevation from 18 to 30°C by 0.1°C increase per minute (thus in 2 h in total).

<sup>12</sup>Seawater from 13 to 33°C.

<sup>13</sup>Thermal threshold at 25°C; variations from 15.7 to 27.8°C and elevation of 1°C per week for 3 weeks.

<sup>14</sup>Seawater at 21°C vs. 16°C.

<sup>15</sup>Seawater from 19 to 29°C, two thermal stresses separated by 14-day-long recovery phases.

<sup>16</sup>Salinity below 28 psu, with seawater temperature at 27°C.

<sup>17</sup>Salinity below 28 psu, with seawater temperature at 13°C.

<sup>18</sup>Constant pH of 7.4 for 6 months.

<sup>19</sup>When mussels *M. galloprovincialis* are mixed with mussels *Xenostrobus securis*.

<sup>20</sup>Gradual decrease of 0.3 pH units (from 8.01 to 7.98); decrease of 0.1 unit per week for 3 weeks then maintenance for 10 months; irrespective of the seawater temperature between 12 and 25°C.

<sup>21</sup>Constant pH of 7.4 for 3 months.

<sup>22</sup>With seawater temperature at 25°C.

<sup>23</sup>With seawater temperature at 15°C.

<sup>24</sup>Bay habitat.

<sup>25</sup>Coast habitat.

<sup>26</sup>Mortality due to endolith infestation.

<sup>27</sup>Mortality due to predation by the polyclad flatworm *Imogine mediterranea*.

<sup>28</sup>With *Xenostrobus securis*, invasive species in Galicia, Spain.

<sup>29</sup>In mussel tissues.

<sup>30</sup>In France, spring (March–May) vs. other seasons.

<sup>31</sup>In South Africa, end of summer (February) vs. other seasons.

<sup>32</sup>In South Africa, *on the coast*: mortality peaks at the end of summer (February) and in winter–spring (June–October)/*in the bay*: mortality peaks in summer (February) and in winter (June).

<sup>33</sup>Seawater at 18°C or 26°C and air at 32°C.

<sup>34</sup>Seawater at 13°C and air at 33°C.

<sup>35</sup>Seawater at 12°C and air from 20 to 30°C.

<sup>36</sup>Seawater at 18°C and air from 20 to 30°C.

<sup>37</sup>33°C, three times.

**Table 5** Factors studied in *M. edulis* and reported effect on the mortality risk (28 experimental studies and 38 observation studies). Experimental studies are underlined; studies accounting for interactions between factors are in bold; in the last column, NR stands for nonrelevant

Studied factors	No. of studies	Effect on mortality risk			Consistency of study results
		Increase	Decrease	No effect	
Pathogens	8				
Nonidentified infectious agent	2	<u>Benabdelmouna <i>et al.</i> (2018)</u> ; <u>Pépin <i>et al.</i> (2017)</u>			Yes
Bacteriological profile	1			Bernard <i>et al.</i> (2018b)	NR
Anaerobic bacteria	1	<u>Barbaro and De Zwaan (2008)</u>			NR
Opportunistic heterotrophic bacteria	1	<u>Eggermont <i>et al.</i> (2014)</u>			NR
Bacteria <i>Vibrio aestuarianus</i>	1			<u>Benabdelmouna <i>et al.</i> (2018)</u>	NR
Bacteria <i>Vibrio Splendidus</i> clade	2	<u>Eggermont <i>et al.</i> (2017)</u>		<u>Benabdelmouna <i>et al.</i> (2018)</u>	No
Bacteria <i>Photobacterium</i>	1	<u>Eggermont <i>et al.</i> (2017)</u>			NR
Ostreid herpesvirus OsVH-1	1			<u>Benabdelmouna <i>et al.</i> (2018)</u>	NR
Parasite <i>Marteilia refringens</i>	2			<u>Benabdelmouna <i>et al.</i> (2018)</u> ; Bernard <i>et al.</i> (2018b)	Yes
Toxic algae <i>Karlodinium armiger</i>	1	<u>Binzer <i>et al.</i> (2018)</u>			NR
Presence of epibiotic algae on the shell	2	<b>O'Connor (2010)<sup>1</sup></b>		<b>O'Connor (2010)<sup>2</sup></b>	No
Animal characteristics	22				
Species vs. <i>M. trrossulus</i>	3		Gardner and Thompson (2001)	Penney <i>et al.</i> (2006); Lowen (2008)	No
Interspecific genotype	2	Fuentes <i>et al.</i> (2002) <sup>3</sup> ; Lowen (2008) <sup>4</sup>			Yes
Intraspecific genotype	3		Pépin <i>et al.</i> (2017) <sup>5</sup> ; Pépin <i>et al.</i> (2017) <sup>5</sup>	Myrand and Gaudreault (1995)	No
Low degree of multiple-locus heterozygosity	1	Tremblay <i>et al.</i> (1998)			NR
High frequency of individuals having more than 10% cytogenetic abnormalities in haemocytes in the population	4	Benabdelmouna and Ledu (2016); <u>Pépin <i>et al.</i> (2017)</u> ; <u>Pépin <i>et al.</i> (2018)</u>		Pépin <i>et al.</i> (2017)	No
Neoplastic process in the haemocytes	2	<u>Pépin <i>et al.</i> (2018)</u>		Bernard <i>et al.</i> (2018b)	No
Small size	7	<b>Altieri and Witman (2006)<sup>6</sup></b> ; <b>Dionne <i>et al.</i> (2006)<sup>7</sup></b> ; Lauzon-Gay <i>et al.</i> (2005); Lauzon-Gay <i>et al.</i> (2005)		<b>O'Connor (2010)<sup>8</sup></b> ; Tremblay <i>et al.</i> (1998); Tsuchiya (1983)	No
Low growth rate	2	<b>Altieri and Witman (2006)<sup>6</sup></b> ; <u>Hiebenthal <i>et al.</i> (2013)</u>			Yes
Low condition index	1	<u>Hiebenthal <i>et al.</i> (2013)</u>			NR
Age (juveniles vs. adults)	1		Mallet <i>et al.</i> (1990)		NR
Low energetic resources/high energetic needs for maintenance	2	Myrand <i>et al.</i> (2000); Tremblay <i>et al.</i> (1998)			Yes
End of spawning period	1	Myrand <i>et al.</i> (2000)			NR
Spawning period	1	Pépin <i>et al.</i> (2017)			NR
Lipofuscin accumulation	1	<u>Hiebenthal <i>et al.</i> (2013)</u>			NR
Shell resistance	1			Hiebenthal <i>et al.</i> (2013)	NR
Seawater characteristics	17				



Table 5 (continued)

Studied factors	No. of studies	Effect on mortality risk			Consistency of study results
		Increase	Decrease	No effect	
Elevated temperature	12	Bernard <i>et al.</i> (2018a) <sup>9</sup> ; Clements <i>et al.</i> (2018) <sup>10</sup> ; Cottrell <i>et al.</i> (2016) <sup>11</sup> ; Hiebenthal <i>et al.</i> (2013) <sup>12</sup> ; <b>Hutchison <i>et al.</i> (2016)<sup>13</sup></b> ; <b>Incze <i>et al.</i> (1980)<sup>14</sup></b> ; Jones <i>et al.</i> (2009); Jones <i>et al.</i> (2010); Lenz <i>et al.</i> (2018) <sup>15</sup> ; Wang <i>et al.</i> (2018) <sup>16</sup>		<b>Ali and Taylor (2010)<sup>17</sup></b> ; <b>Stevens and Gobler (2018)<sup>18</sup></b>	No
Increased number of thermal stresses	2	Jones <i>et al.</i> (2009)	Lenz <i>et al.</i> (2018)		No
Decreased temperature	1	Wang <i>et al.</i> (2018) <sup>19</sup>			NR
Decreased salinity	1	<b>Ali and Taylor (2010)<sup>20</sup></b>			NR
Decreased pH/acidification	4	<b>Stevens and Gobler (2018)<sup>21</sup></b> ; Sun <i>et al.</i> (2016) <sup>22</sup>		Clements <i>et al.</i> (2018); <b>Stevens and Gobler (2018)<sup>21</sup></b>	No
Variations of dissolved oxygen concentration	2			<b>Stevens and Gobler (2018)<sup>23</sup></b> ; <b>Stevens and Gobler (2018)<sup>23</sup></b>	Yes
Low quantity of food	1	Incze <i>et al.</i> (1980) <sup>24</sup>			NR
Low phytoplankton diversity index	1	Travers <i>et al.</i> (2016)			NR
Characteristics of the farming/fishing site	25				
General effect	10	Bernard <i>et al.</i> (2018a); Glize <i>et al.</i> (2017); Glize and Gourmelen (2018); Penney <i>et al.</i> (2006); Pépin <i>et al.</i> (2017)		Lauzon-Guay <i>et al.</i> (2005); Mallet <i>et al.</i> (1987); Mallet <i>et al.</i> (1990); Myrand and Gaudreault (1995); Stirling and Okumus (1994)	No
Increased burial sediment depth	2	Hutchison <i>et al.</i> (2016)		Hutchison <i>et al.</i> (2016)	No
Increased burial sediment duration	3	Cottrell <i>et al.</i> (2016); Hutchison <i>et al.</i> (2016); Hutchison <i>et al.</i> (2016)			Yes
Fine burial sediment fraction (<0.3 mm)	2	Cottrell <i>et al.</i> (2016); Hutchison <i>et al.</i> (2016)			Yes
High concentration (1%) of organic matter in burial fine sediment	1	Cottrell <i>et al.</i> (2016)			NR
Wave exposure	2	<b>O'Connor (2010)<sup>1</sup></b>		<b>O'Connor (2010)<sup>2</sup></b>	No
Spatially complex habitat (with small interstructural spaces)	2		<b>Bertolini <i>et al.</i> (2018)<sup>25</sup></b>	<b>Bertolini <i>et al.</i> (2018)<sup>26</sup></b>	No
High position on the shore	2	Petrakis (1998) <sup>27</sup> ; Tsuchiya (1983)			Yes
Predation	10	Bertolini <i>et al.</i> (2018) <sup>25</sup> ; Bertolini <i>et al.</i> (2018) <sup>26</sup> ; Brousscau <i>et al.</i> (2014) <sup>28</sup> ; Brousscau <i>et al.</i> (2014) <sup>28</sup> ; Christensen <i>et al.</i> (2012); Christensen <i>et al.</i> (2012); Dionne <i>et al.</i> (2006) <sup>7</sup> ; Petrakis (1998) <sup>27</sup> ; <b>Waser <i>et al.</i> (2015)<sup>25</sup></b>		Altieri and Witman (2006) <sup>6</sup>	No

**Table 5** (continued)

Studied factors	No. of studies	Effect on mortality risk			Consistency of study results
		Increase	Decrease	No effect	
Presence of the oyster <i>Crassostrea gigas</i>	1		<b>Waser <u>et al.</u> (2015)<sup>25</sup></b>		NR
Farming/harvesting practices	22				
Geographical origin of the spat	7	Bernard <i>et al.</i> (2018a); Myrand and Gaudreault (1995); Mallet <i>et al.</i> (1987); Mallet <i>et al.</i> (1990)		Glize <i>et al.</i> (2017); Glize and Gourmelon (2018); SMIDAP (2016–2017)	No
Geographical origin of the spat: local. vs transplanted	7	SMIDAP (2016–2017) <sup>29</sup>		Glize <i>et al.</i> (2017) <sup>29</sup> ; Penney <i>et al.</i> (2006); Mallet <i>et al.</i> (1987); Mallet <i>et al.</i> (1990); Myrand and Gaudreault (1995); SMIDAP (2016) <sup>29</sup> ; Stirling and Okumus (1994)	No
Origin of the spat: use of mussels collected in suspended culture vs. mussels collected from natural bottom beds (for bottom culture production)	2		<b>Christensen <u>et al.</u> (2012)<sup>25</sup></b>	<b>Christensen <u>et al.</u> (2012)<sup>25</sup></b>	No
Depth of the farming structure: deep vs shallow	2		Myrand <i>et al.</i> (2000) <sup>30</sup>	Karayucel and Karayucel (2000) <sup>31</sup>	NR
Position inside the farming structure	1			Karayucel and Karayucel (2000) <sup>32</sup>	NR
High farming density	3	<b>Lauzon-Guay <u>et al.</u> (2005)<sup>33</sup></b>		Lauzon-Guay <i>et al.</i> (2005); Lowen (2008) <sup>34</sup>	No
Protective socking material	1		<b>Dionne <u>et al.</u> (2006)<sup>7</sup></b>		NR
Thermal assay of spat (<10 mm) before field deployment	1		LeBlanc <i>et al.</i> (2008) <sup>35</sup>		NR
48H pretransportation depuration vs. no depuration of the mussels	1			Barrento and Powell (2016) <sup>36</sup>	NR
48H depuration pretransportation vs. no depuration of the mussels, either with ice storage or at ambient temperature during transport	1			<b>Barrento and Powell (2016)</b>	NR
48H pretransportation depuration + ice storage during transport vs. no depuration pretransportation + storage at ambient temperature during transport	1		<b>Barrento and Powell (2016)<sup>37</sup></b>		NR
Mixed mussel species	1		Lowen (2008) <sup>38</sup>		NR
Anti-biofouling treatment with potassium monopersulfate triple salt	1			<b>Paetzold and Davidson (2011)</b>	NR
24H pretransportation anti-biofouling treatment (vinegar, brine or lime), with or without seawater rinsing	1			Vickerson (2009)	NR
After transportation anti-biofouling treatment (vinegar, brine or lime)	1			Vickerson (2009)	NR
Contaminants from the terrestrial and marine environments	3				
Cd	1	<b>Ali and Taylor (2010)<sup>20</sup></b>			NR
Zn	1	<b>Ali and Taylor (2010)<sup>20</sup></b>			NR

Table 5 (continued)

Studied factors	No. of studies	Effect on mortality risk			Consistency of study results	
		Increase	Decrease	No effect		
Untreated municipal sewage	1	<u>Akaishi et al. (2007)</u>			NR	
Diesel oil	1	<u>Suni et al. (2007)</u>			NR	
Climate characteristics	8					
Season	3	Bernard et al. (2018a) <sup>39</sup> ; Myrand et al. (2000) <sup>40</sup>		Mallet et al. (1987)	No	
Elevated air temperature	4	<u>Jones et al. (2009)</u> ; Jones et al. (2010); Tsuchiya (1983)		Travers et al. (2016)	No	
Increased number of thermal stresses	3	<u>Jones et al. (2009)</u> ; Jones et al. (2010)	<b>Peden et al. (2018)</b> <sup>41</sup>		No	
Pluviometry	1				Travers et al. (2016)	NR

<sup>1</sup>In sheltered rocky shores.

<sup>2</sup>In shores exposed to waves.

<sup>3</sup>Different hybrid genotypes between *M. edulis* and *M. galloprovincialis* vs. pure crosses of *M. galloprovincialis*.

<sup>4</sup>Hybrid genotypes between *M. edulis* and *M. trossulus* vs. pure crosses of *M. edulis* vs. pure crosses of *M. trossulus*.

<sup>5</sup>Selected (i.e. which parents survived a previous mortality event) vs. nonselected genotype.

<sup>6</sup>Under hypoxia conditions.

<sup>7</sup>Mortality due to predation by diving ducks.

<sup>8</sup>Mortality due to epibiotic algae on the shell.

<sup>9</sup>Over 19–20°C.

<sup>10</sup>22°C vs. 16°C.

<sup>11</sup>20°C vs. 15°C.

<sup>12</sup>Over 20–25°C.

<sup>13</sup>From 8°C to 20°C; with several burial depths.

<sup>14</sup>Thermal threshold at 20°C, with a rapid decline of total chlorophyll concentration.

<sup>15</sup>From 15°C to 28°C, two thermal stresses separated by 14-day-long recovery phases.

<sup>16</sup>35°C.

<sup>17</sup>6°C or 12°C; mortality due to zinc (Zn) or cadmium (Cd) exposure; with a low salinity of 20 psu.

<sup>18</sup>20°C vs. 26°C.

<sup>19</sup>4°C.

<sup>20</sup>20 psu; mortality due to zinc (Zn) or cadmium (Cd) exposure.

<sup>21</sup>pH = 7.2 vs. 9.7.

<sup>22</sup>pH = 6.5.

<sup>23</sup>2.0 mg L<sup>-1</sup> vs. 8.0 mg L<sup>-1</sup> during 4 weeks.

<sup>24</sup>Rapid decline of total chlorophyll concentration.

<sup>25</sup>Mortality due to predation by the shore crab *Carcinus maenas*.

<sup>26</sup>Mortality due to predation by the starfish *Asterias rubens*.

<sup>27</sup>Mortality due to the predatory snail *Nucella lapillus*.

<sup>28</sup>Mortality due to predation by the Asian shore crab *Hemigrapsus sanguineus*.

<sup>29</sup>Local origin with mortality events vs. transplanted origin without mortality events, France.

<sup>30</sup>Suspended cages at 16 m (open water) vs. 6 m depth (lagoon).

<sup>31</sup>Lantern nets at 6 m vs. 2 m depth.

<sup>32</sup>Inflow or outflow of the raft.

<sup>33</sup>273 mussels/30-cm section of a sock, small-sized mussels.

<sup>34</sup>30 mussels per cage (15 *M. edulis* and 15 *M. trossulus*).

<sup>35</sup>Elevated seawater temperature.

<sup>36</sup>Mortality before transport.

<sup>37</sup>Mortality during rewatering, after transport.

<sup>38</sup>With *M. trossulus*.

<sup>39</sup>France, spring (April–June) vs. other seasons.

<sup>40</sup>Canada, summer (June–September) vs. other seasons.

<sup>41</sup>From 20 to 35°C; mussels collected from a heavily polluted area.

that of *M. trossulus* in field conditions (Penney *et al.*, 2006; Lowen, 2008), whereas it was lower in a laboratory study reproducing coastal and estuarine conditions (Gardner & Thompson, 2001). In the field, the mortality risk of *M. galloprovincialis* did not differ from that of *M. trossulus* (Shields *et al.*, 2008), whereas a lower mortality risk was observed in two laboratory studies where animals were exposed to either air or seawater thermal stress (Schneider, 2008; Dowd & Somero, 2013). In *M. galloprovincialis*, the effect of the genotype on the mortality risk depended on the species crossed. On the one hand, the mortality risk of mussels having a hybrid genotype of *M. galloprovincialis* and *M. trossulus* showed no difference when compared to pure native *M. trossulus* and to pure introduced *M. galloprovincialis* (Shields *et al.*, 2008). On the other hand, hybrids of *M. galloprovincialis* and *M. edulis* showed a higher mortality risk than the populations from pure crosses (Fuentes *et al.*, 2002). Hybrids of *M. edulis* and *M. trossulus* also showed a higher mortality risk than the pure populations (Lowen, 2008). In *M. edulis*, a selected intraspecific genotype showed inconsistent effects on mortality risk, perhaps depending on the number of selected generations. In fact, the first selected generation, that is the survivor mussels of a preceding mortality event, still presented an increased mortality risk in subsequent years (Myrand & Gaudreault, 1995), whereas two studies reported a lower mortality risk for spat descending from parents that had survived a previous mortality event, compared to spat with a nonselected genotype (Pépin *et al.*, 2017; Pépin *et al.*, 2018). A low degree of multiple-locus heterozygosity was associated with an increased risk of mortality in *M. edulis* (Tremblay *et al.*, 1998). A high percentage of genomic abnormalities in haemocytes was found to be associated with an increased mortality risk in *M. galloprovincialis* (Benabdelmouna & Ledu, 2016), although inconsistent association was reported in *M. edulis* (Benabdelmouna & Ledu 2016; Pépin *et al.*, 2017; Pépin *et al.*, 2018).

Physiological characteristics were also explored, mainly in *M. edulis*. The effect of mussel size on the mortality risk was the most commonly investigated factor. Although no effect was observed in the two studies on *M. galloprovincialis* (Lok *et al.*, 2007; O'Connor, 2010), inconsistent results were reported for the effect of this trait on the mortality risk of *M. edulis*. Discrepancies may be explained by different study conditions: mussel size was sometimes studied in combination with hypoxic conditions (Altieri & Witman, 2006), in the context of new socking material to protect mussels from predation (Dionne *et al.*, 2006) or in the context of exploration of massive mortalities of wild beds (Tsuchiya, 1983) or cultivated mussels (Tremblay *et al.*, 1998). A study also explored the effect of the initial seed size, showing that

small seed had a higher mortality risk than larger seed (Lauzon-Guay *et al.*, 2005). These types of differences in study conditions prevented any direct comparison or synthesis of the results. Individual traits related to a poor condition were also investigated in *M. edulis* to a lesser extent. A low condition index (Hiebenthal *et al.*, 2013), low energy reserves due to depleted reserves after spawning (Myrand *et al.*, 2000) and high bio-energetic needs for maintenance metabolism (Tremblay *et al.*, 1998) were reported to be associated with an increased mortality risk in *M. edulis*. This is further supported by reported synchronous timing between mortality and gametogenesis (Pépin *et al.*, 2017), when the mussels use high bio-energetic resources for reproduction.

#### *Factors related to seawater characteristics*

The effect of seawater characteristics on the mortality risk was more often studied in *M. edulis* (8 factors by 17 studies, Table 5) than in *M. galloprovincialis* (5 factors by 9 studies, Table 4).

In *M. galloprovincialis*, these factors were exclusively studied under laboratory conditions. As the only study showing no effect of the seawater temperature (Gestoso *et al.*, 2016) tested a maximum temperature of 21°C, the mortality risk seemed to increase above a value of this factor of ≈24°C (Anestis *et al.*, 2007; Dowd & Somero, 2013; Gazeau *et al.*, 2018). In *M. edulis*, the mortality risk was associated with a thermal threshold of ≈20°C (Incze *et al.*, 1980; Jones *et al.*, 2010; Hiebenthal *et al.*, 2013; Cottrell *et al.*, 2016; Hutchison *et al.*, 2016; Clements *et al.*, 2018; Lenz *et al.*, 2018; Wang *et al.*, 2018; Bernard *et al.*, 2018a). The two studies showing no association between an elevated temperature and mussel mortality risk explored the effect of this factor in combination with other simultaneous exposures: to zinc or cadmium (Ali & Taylor, 2010) or to a decreased pH and decreased oxygen concentration in water (Stevens & Gobler, 2018). The interactions with other stressors may have compensated the effect of the elevated seawater temperature on the mortality risk. Moreover, Ali and Taylor (2010) used lower values of the seawater temperature than the other studies (6 and 12°C). Exposure to a cold temperature of 4°C also increased the mortality risk of *M. edulis* (Wang *et al.*, 2018). Opposite results were reported for the effect of an increasing number of thermal stresses on the mortality risk of *M. edulis* (Jones *et al.*, 2009; Lenz *et al.*, 2018), whereas no effect was observed in *M. galloprovincialis* (Lenz *et al.*, 2018).

In both mussel species, an increased mortality risk was reported with low salinity values (20 and 28 practical salinity units, psu) in laboratory conditions (Hamer *et al.*, 2008; Ali & Taylor, 2010), which may sometimes be observed in field conditions in a wide desalination context.

Among seawater characteristics, the effect of acidification of seawater shows conflicting results in both mussel species, probably because of the broad variation in laboratory conditions (levels of pH tested, exposure duration or acute vs. gradual exposure). Low levels of seawater pH increased the mortality risk of *M. edulis* (Sun *et al.*, 2016; Stevens & Gobler, 2018), whereas one study reported no effect of elevated CO<sub>2</sub> concentrations (Clements *et al.*, 2018). However, no effect was observed when this factor was combined with a low level of dissolved oxygen or with an elevated temperature, suggesting antagonist interactions between these stressors (Stevens & Gobler, 2018). In *M. galloprovincialis*, extended exposure (6 months) of mussels to a low level of pH was associated with an increased mortality risk, whereas shorter exposure (3 months) did not show any effect (Bressan *et al.*, 2014). Acute exposure to acidification was associated with an increased mortality risk (Gestoso *et al.*, 2016), whereas gradual acclimation to similar lowered pH over a few weeks did not show any effect (Gazeau *et al.*, 2018).

Low levels of dissolved oxygen in seawater did not show any effect on the mortality risk of *M. edulis* (Stevens & Gobler, 2018). In *M. galloprovincialis*, hypoxia-induced stress, reproduced in laboratory conditions using an 8 h emersion treatment, increased the risk of mortality when mussels were also simultaneously exposed to pathogens and to an elevated seawater temperature of 25°C (Romero *et al.*, 2014).

Concerning seawater characteristics, the effect of food availability (quantity and quality) was also explored in *M. edulis*. A rapid decrease in the quantity of phytoplankton preceded mortality onset (Incze *et al.*, 1980), leading the authors to suggest that the mortalities may be triggered by reduced ration and starvation. A decline in indicators of phytoplankton species richness (Shannon index and total abundance) was also reported before mussel mortality onset (Travers *et al.*, 2016).

#### *Factors related to characteristics of the farming or fishing site*

The effect of characteristics of the farming or fishing site on the mortality risk was more commonly studied in *M. edulis* (10 factors by 25 studies, Table 5) than in *M. galloprovincialis* (8 factors by 14 studies, Table 4).

In both mussel species, broad spatial variation in the mortality risk between different farming or fishing sites was reported in several studies (Fuentes *et al.*, 1994; Penney *et al.*, 2006; Bownes & McQuaid, 2010; Gardner, 2013; Travers *et al.*, 2016; Glize *et al.*, 2017; Moschino *et al.*, 2017; Pépin *et al.*, 2017; Glize & Gourmelen, 2018; Pépin *et al.*, 2018; Bernard *et al.*, 2018b), whereas other studies did not observe a mortality risk variation across locations (Mallet *et al.*, 1987; Mallet *et al.*, 1990; Fuentes *et al.*, 1992; Stirling & Okumus, 1994; Myrand & Gaudreault, 1995; Lauzon-

Guay *et al.*, 2005). However, except in one study which explored mussel position on the shore (Bownes & McQuaid, 2010), the characteristics of the geographical sites potentially explaining this variation were never detailed.

Some site characteristics have been studied, specifically to understand species invasion or habitat segregation of several mussel species. In *M. galloprovincialis*, characteristics of mussel wild beds have been explored to evaluate the effects of hydrodynamic stress and sand stress, by comparing bay and open coast habitats. An increased mortality risk was reported in open coast conditions (Nicastro *et al.*, 2008; Nicastro *et al.*, 2010) and when the shore was exposed to waves (O'Connor, 2010). No effect of the position of mussels in the bed, either at the edge or in the centre, was observed (Nicastro *et al.*, 2008). Wave height was found to be a risk factor of mortality in a bay habitat (Zardi *et al.*, 2008; Nicastro *et al.*, 2010), whereas it had no effect in open coast conditions (Nicastro *et al.*, 2010). Sand accumulation on mussel beds, either because of sand burial or suspended sand in the seawater, was associated with an increased mortality risk in two studies (Zardi *et al.*, 2006; Nicastro *et al.*, 2010). However, one study showed no effect of this factor (Zardi *et al.*, 2008). In *M. edulis*, sediment parameters were investigated in particular. Mortality increased with increasing duration of burial (Hutchison *et al.*, 2016; Cottrell *et al.*, 2016), but conflicting results were reported for the effect of the depth of burial (Hutchison *et al.*, 2016). Fine sediment fractions (Hutchison *et al.*, 2016; Cottrell *et al.*, 2016) and high concentrations of organic matter in the sediment (Cottrell *et al.*, 2016) were associated with an increased mortality risk.

Emersion stress has also been explored in various studies. No effect of the mussel bed position on the shore was reported for *M. galloprovincialis* (Bownes & McQuaid, 2010; Marquet *et al.*, 2013), whereas mortality risk increased in *M. edulis* on higher tidal height in the context of snail predator activity (Petraitis, 1998) or of heatwave exposure (Tsuchiya, 1983).

The presence of predators on the farming or fishing site was studied either to explain mussel mortalities (e.g. crabs (Christensen *et al.*, 2012; Brousscau *et al.*, 2014) and diving ducks (Dionne *et al.*, 2006) for *M. edulis*; flatworm (Gammoudi *et al.*, 2017) and benthic and pelagic predators (Plass-Johnson *et al.*, 2010 for *M. galloprovincialis*) or to understand the absence of mussels at a certain level of rocky shore, for example hypothetically due to the activity of the snail *Nucella lapillus* (Petraitis, 1998).

The mortality risk due to predation was reduced in reefs with small interstructural spaces (Bertolini *et al.*, 2018). One study showed that the presence of the Pacific oyster (*Crassostrea gigas*) deterred predator attacks from mussels and reduced their mortality risk (Waser *et al.*, 2015).

*Factors related to farming or harvesting practices*

The effect of farming or harvesting practices on the mortality risk was more closely studied in *M. edulis* (15 factors by 22 studies, Table 5) than in *M. galloprovincialis* (8 factors by 13 studies, Table 4).

Concerning farming practices, the geographical origin of the seed was mainly investigated. Several studies reported an effect of this factor on the mortality risk of *M. edulis* (Mallet *et al.*, 1987; Mallet *et al.*, 1990; Myrand & Gaudreault, 1995; Bernard *et al.*, 2018a), whereas other studies showed no effect (SMIDAP 2016–2017; Glize *et al.*, 2017; Glize & Gourmelen, 2018). In particular, the effect of seed translocation on the mortality risk was explored. This farming practice, widely spread across the world in aquaculture, consists of transplanting mussel spat to areas with favourable conditions for growth (Aypa, 1990). In *M. edulis*, most of the studies reported no effect of this practice on the mortality risk (Mallet *et al.*, 1987; Mallet *et al.*, 1990; Myrand & Gaudreault, 1995; Fuentes *et al.*, 2002; Penney *et al.*, 2006; SMIDAP 2016; Glize *et al.*, 2017) although one study reported reduced mortality in mussel spat collected on-site compared to translocated spat (SMIDAP 2016–2017). In *M. galloprovincialis*, almost all the studies reported translocated spat having a higher mortality risk than local spat (Fuentes *et al.*, 1992; Fuentes *et al.*, 1994; Ramon *et al.*, 2007; Gardner, 2013; Kovacic *et al.*, 2017; Ajjabi *et al.*, 2018; Bernard *et al.*, 2018a). Only one study, conducted in the context of understanding the spatial distribution of native, introduced and hybrid *Mytilus* sp. (Shields *et al.*, 2008), observed a different result. The authors suggested that translocation to a site with cooler water temperatures decreased the mortality risk by reducing thermal stress.

A protective effect of a thermal challenge, either using elevated water temperature or air exposure before their deployment to the farming sites, was reported on *M. edulis* spat (LeBlanc *et al.*, 2008). The authors suggested a selective effect of this treatment by selecting mussels with higher levels of heterozygosity, providing them more physiological flexibility.

The effect of the initial farming density on the mortality risk of *M. edulis* was controversial, with one study reporting no short-term effect (3 months), but a long-term effect (10 months) (Lauzon-Guay *et al.*, 2005). Interestingly, another study reported no effect of this factor after 15 months (Lowen, 2008).

Regarding other farming practices, the effect of different suspended farming structures on the mussel mortality risk was investigated. In *M. edulis*, no effect of the depth of the lantern nets in a suspended raft was reported (Karayucel & Karayucel, 2000), whereas mussel mortality risk was higher in suspended mesh plastic cages maintained deeper in the open sea (14 m depth) than in the lagoon (4 m depth) (Myrand *et al.*, 2000). Conflicting results about the effect of

the position of the mussels within a suspended raft on their mortality risk were reported, with studies showing no effect of this factor for both species (Fuentes *et al.*, 1992; Karayucel & Karayucel, 2000) or a higher mortality risk in the fore part than the aft part of the suspended raft in *M. galloprovincialis* (Fuentes *et al.*, 1994).

A few studies focused on the effects of certain commercial husbandry practices regarding mussel transportation to the market. In *M. galloprovincialis*, no effect of the stocking density during re-immersion into seawater after harvesting and grading and before transport was reported (Theodorou *et al.*, 2017). Re-immersion beyond 11 days increased the mortality risk (Theodorou *et al.*, 2017). In *M. edulis*, re-immersion before transport did not have a significant effect on the mussel mortality risk, whether they were stored with ice or at a chilled ambient temperature of 5°C during transport, at any stage of the supply chain (pretransportation or post-transportation) (Barrento & Powell, 2016). Mussels being re-immersed before transport and stored on ice showed reduced mortalities compared to mussels being not re-immersed before transport and stored at ambient temperature (Barrento & Powell, 2016).

All aspects of mussel culture are impacted by tunicate fouling, and the effect of anti-biofouling chemical treatments to mitigate their consequences on the mussel mortality risk was also studied. Results showed that the potassium monopersulphate triple salt-based disinfectant (Virkon<sup>®</sup> Aquatic) has no significant effect on mussel mortality until 3 weeks post-treatment (Paetzold & Davidson, 2011). Vinegar, brime or lime could also be applied either before transportation, followed or not by a seawater rinse, or after transportation without provoking an increased mussel mortality risk (Vickerson, 2009).

When predation was the acknowledged mortality cause in *M. edulis*, some studies tested solutions to limit its impact on mussel production, for example use of mussels collected in suspended culture versus mussels collected from natural bottom mussel beds for bottom culture production, despite the presence of crabs (Christensen *et al.*, 2012), or protective socking material to protect mussels from diving ducks (Dionne *et al.*, 2006).

Farming mixed mussel species, that is *M. edulis* and *M. trossulus* (Lowen, 2008) or *M. galloprovincialis* and *Xenostrobus securis* (Gestoso *et al.*, 2016; Olabarriar *et al.*, 2016), was found to lower the mortality risk. Integrated multitrophic aquaculture (IMTA) showed a lower mortality risk for *M. galloprovincialis* when mussels were cultivated with algae (Ajjabi *et al.*, 2018), but did not show any effect when mussels were farmed with fish (Gvozdenovic *et al.*, 2017).

On wild beds, the intensive human trampling during harvesting of *M. galloprovincialis* increased mussel

mortality, particularly when mussels were infested with parasitic endoliths (Nicastro *et al.*, 2018).

#### *Factors related to contaminants from the terrestrial and marine environments*

The effect of terrestrial or marine pollutants on the mortality risk was studied more frequently in *M. galloprovincialis* (24 factors by 7 studies, Table 4) than in *M. edulis* (4 factors by 3 studies, Table 5).

All chemical compounds tested in laboratory conditions showed a lethal effect on mussels (*M. edulis*: (Suni *et al.*, 2007; Akaishi *et al.*, 2007; Ali & Taylor, 2010); *M. galloprovincialis*: (Rosen & Lotufo, 2007; Danellakis *et al.*, 2011; Tsarpali & Dailianis, 2012; Tsarpali *et al.*, 2015; Oliveira *et al.*, 2017; Li *et al.*, 2018)), except for two explosive compounds in *M. galloprovincialis* (Rosen & Lotufo, 2007). Most of these studies mimicked pollution events. Only one study investigated the effect of several chemical compounds on the mortality risk of *M. galloprovincialis* in field conditions, in Italy (Moschino *et al.*, 2016). This may be explained because it is easier to control these parameters in laboratory conditions. Results showed that concentrations in mussel soft tissues of aluminium, iron, lead and polycyclic aromatic hydrocarbons (PAHs) were correlated with the mussel mortality rate. The other 11 metals and micro-organic pollutants detected in mussel samples showed no association with mussel mortality (Moschino *et al.*, 2016).

#### *Factors related to climate characteristics*

The effect of climate characteristics on the mortality risk was studied equally in both mussel species (4 factors by 8 studies, Tables 4 and 5).

In both mussel species, wide seasonal variations in the mortality risk were reported in several studies (Myrand *et al.*, 2000; Nicastro *et al.*, 2008; Nicastro *et al.*, 2010; Bernard *et al.*, 2018a) except for one (Mallet *et al.*, 1987). Risky seasons varied across the hemispheres and were not necessarily the warmest ones, particularly in South Africa where mortality peaks were reported during winter (Nicastro *et al.*, 2010).

Aerial temperature was the main seasonal factor investigated, often in the context of stress responses and exploration of physiological capacities to explain species invasion or habitat segregation of several mussel species. In *M. edulis*, the mortality risk increased with increasing air temperature in the context of heatwave exposure (Tsuchiya, 1983), rising high summer temperatures (Jones *et al.*, 2010) or in laboratory conditions (Jones *et al.*, 2009). Only one study showed no effect of elevated air temperatures on the mussel mortality risk (Travers *et al.*, 2016), but the seasonal temperature variation reported was much less contrasted than in the other studies. In *M. galloprovincialis*, heatwave exposure above 27°C was also reported to be associated

with an increased mortality risk (Olabarriall *et al.*, 2016). Conflicting results were reported for the effect of an increased number of aerial thermal stresses, with studies showing an increased mortality risk in *M. edulis* (Jones *et al.*, 2009; Jones *et al.*, 2010), a decreased mortality risk when the mussels had previously been exposed to chronic chemical contamination (Peden *et al.*, 2018) or no effect in *M. galloprovincialis* (Dowd & Somero, 2013). In *M. galloprovincialis*, the thermal range between air and water temperature exposures showed inconsistent effects on the mortality risk between the laboratory studies (Schneider, 2008; Anestis *et al.*, 2010; Dowd & Somero, 2013), probably because of the heterogeneity of the ranges investigated, varying from 2 to 20°C.

#### *Interactions between factors*

Among the 114 studies, only one-quarter (28/114; 25%) investigated the effect of interactions between exposure factors on the mussel mortality risk. This represented 30% of the studies (20/66) on *M. edulis* and 17% of the corpus (8/48) on *M. galloprovincialis*. In both species, these studies were conducted to the same extent in observation or in laboratory conditions. Almost two thirds of these studies (17/28) explored the combined effect of three factors, while another third (11/28) investigated interactions between two factors. In *M. galloprovincialis*, the most frequently studied interactions, fell under site characteristics, while in *M. edulis*, interactions were explored for exposures pertaining mainly to mussel and site characteristics, and husbandry or fishery practices (Fig. 5).

Synergistic effects, that is a combined effect greater than the sum of the individual effects of the exposure factors, were reported on mussel mortality risk. In *M. galloprovincialis*, a synergistic effect was reported between exposure of mussels to high concentrations of bacteria *Vibrio aestuarianus* or *Vibrio* belonging to the *Splendidus* clade in seawater, an elevated seawater temperature (25°C), and to 8 h emersion to mimic hypoxia-induced stress (Romero *et al.*, 2014). Trampling and endolith infestation were reported to act together to increase the mortality risk in large *M. galloprovincialis* mussels (Nicastro *et al.*, 2018). In *M. edulis*, a synergistic joint effect was observed with exposure to heavy metals (cadmium or zinc) in combination with low salinity and high temperature of seawater (Ali & Taylor, 2010). In this species, the negative impact of enrichment of sediment with organic matter on mussel mortality was exacerbated in conditions of burial in fine sediments (Cottrell *et al.*, 2016).

Antagonistic effects, that is combined effects lower than the sum of the individual effects of the exposure factors, were also reported, particularly among seawater characteristics. In *M. edulis*, antagonistic effects were observed between low levels of pH and dissolved oxygen (Stevens &

Gobler, 2018), low levels of pH, low levels of dissolved oxygen and elevated seawater temperature (Stevens & Gobler, 2018), and between elevated seawater temperature and elevated seawater CO<sub>2</sub> concentrations (Clements *et al.*, 2018). In *M. galloprovincialis*, such antagonistic effects were reported between a lowered pH and an elevated seawater temperature (Gazeau *et al.*, 2018).

Other nonspecific interactions were reported, with exposure factors modulating the individual effect on the mussel mortality risk of another factor, without a straightforward overall interpretation when multiple factor interactions were reported. In both mussel species, interactions were reported between the presence of algal epibionts and the wave exposure of the shore, showing a negative effect of epibiotic algae on mussel survival on sheltered shores (O'Connor, 2010). In *M. galloprovincialis*, a decreased effect of a lowered pH of the seawater was reported on the mortality risk when animals were clumped with mussels of another species *Xenostrobus securis* (Gestoso *et al.*, 2016). Another study showed a negative effect of decreased seawater salinity on the mussel mortality risk, only if associated with an elevated temperature (Hamer *et al.*, 2008). In the context of the understanding of the success of *M. galloprovincialis* as an invasive species in South Africa, interactions were reported between the location, site or zone on the mussel mortality risk (Bownes & McQuaid, 2010; Marquet *et al.*, 2013). In *M. edulis*, three studies explored solutions to limit the impact of predation on mussel production or populations and found statistically significant interactions between mussel size and either farming material by showing that protective socking material was more efficient in large mussels against diving ducks (Dionne *et al.*, 2006), characteristics of the site by reporting that clumped habitats were more protective for small mussels against crab or starfish (Bertolini *et al.*, 2018), or the presence of oysters *Crassostrea gigas* by showing that this presence significantly reduced the mortality of small-sized mussels, but the effect varied according to crab size (Waser *et al.*, 2015). Another study reported the effect of hypoxia-induced stress on mussel mortality to be size-specific, with larger mussels having an increased mortality risk under hypoxia conditions than smaller ones (Altieri & Witman, 2006). Gradual acclimation of the mussels to warmer temperatures modulated the effect on *M. edulis* mortality of the combined exposure of mussels to chronic chemical contamination and acute heat stress (Peden *et al.*, 2018). The effect of the initial farming density on the mortality risk was modulated by mussel size, with mortality of small seed generally increasing with increasing initial density, while mortality of large seed was not affected by initial farming density (Lauzon-Guay *et al.*, 2005). Interactions between the geographical origin of the spat and mussel age were reported on the *M. edulis* mortality risk (Mallet *et al.*,

1990). Along the supply chain, interactions between non-depuration treatment before transport and ambient temperature treatment during transport were reported concerning the mortality risk of *M. edulis* mussels at the post-rewatering stage (Barrento & Powell, 2016).

Nonsignificant interactions were also observed, for example between duration of burial and the sediment fraction size, or between the duration of burial and the temperature of the seawater concerning the mortality risk of *M. edulis* (Hutchison *et al.*, 2016), in the context of sudden deposited sediment on the mussel bed.

Conflicting results were reported about the interaction effect of mussel stock origin (i.e. genotype) and site on the mortality risk of *M. edulis*, with some studies reporting a significant interaction (Mallet *et al.*, 1987; Fuentes *et al.*, 1992; Penney *et al.*, 2006) and one study reporting no interaction (Myrand & Gaudreault, 1995).

## Discussion

The aim of this systematic review was to summarise the findings from the literature that report risk factors for mortality of marine mussels *M. edulis* and *M. galloprovincialis*. The motivation for this study was to provide science-based information to inform actionable solutions to mitigate, or even prevent, mussel mortalities.

### Literature heterogeneity

The literature reviewed was highly heterogeneous. Across the corpus, there was considerable variability among studies with respect to methodological approaches used to define or estimate mussel mortality, and to define putative mortality risk factors and exposure metrics.

Although a systematic review question should be focused and explicit (European Food Safety Agency, 2010), the present review question was broad in scope due to the wide range of risk factors to be considered, as requested by the French Ministry in charge of Agriculture (Anon, 2016). Members of the Scientific and Technical Council (STC) were not aware of large volumes of literature on studies formally designed to identify risk factors of mussel mortality pertaining to different topics. The literature search strategy was thus chosen to be highly sensitive and not too specific to ensure that it captured most information regarding the factors associated with mussel mortality, even though this was not the main objective of the studies. Only 2.4% of the identified unique citations were ultimately selected as relevant. In fact, less than half of the included studies aimed to understand mussel production losses and were thus likely to identify potential risk factor that could be used to inform actionable solutions to mitigate or prevent mussel mortalities. The included studies were roughly concerned either



		<i>M. edulis</i>							
		Mussel	Site	Climate	Seawater	Pollutants	Pathogens	Practices	
<i>M. galloprovincialis</i>	Mussel	0	2	4	0	0	0	1	3
	Site	1	2	3	1	2	0	1	4
	Climate	0	0	0	1	0	0	0	1
	Seawater	0	0	0	1	3	1	0	0
	Pollutants	0	0	0	0	0	0	0	0
	Pathogens	1	1	0	1	0	0	0	0
	Practices	0	1	0	1	0	1	0	1

**Figure 5** Number of studies investigating interactions between risk factor topics of mussel mortality by mussel species. The upper part of the matrix is for *M. edulis* and the lower part is for *M. galloprovincialis*, for example interactions between mussel and site characteristics were explored by 4 studies for *M. edulis* and 1 study for *M. galloprovincialis*.

with understanding mussel species distribution and habitat segregation, or used mussels as bio-indicators to assess environment quality or climate change effects. Although these concerns are not completely separate, one does not replace the other and results cannot systematically be extrapolated to mussel mortality risk. Additionally, within the selected corpus, there were only a few studies with a high level of methodological quality in the STC assessment. Importantly, none of the identified studies applied the full set of known standards of epidemiological research (Martin *et al.*, 1987), and none explored the effect of several risk factors pertaining to different topics and their interactions on mussel mortality in field conditions. The final corpus, made of 91 publications corresponding to 114 studies and belonging to many different research disciplines, integrated the diverse streams of evidence, observational studies and experimental information. These studies were conducted in experimental or observational conditions and required different standards, norms and constraints to report mortality and to characterise exposures. Designs and endpoints were thus diverse and were subject to research objectives.

Another cause of heterogeneity between the results of the studies was the mussel species considered. This was expected because geographical range, ecology, physiology or functional traits differ between *M. edulis* and *M. galloprovincialis*. Multiple correspondence analysis showed a split of the corpus in two groups based on mussel species in particular. Thus, the results of the present review were separated by mussel species.

As a consequence, knowledge was too heterogeneous to be summarised in a quantitative manner; notably, aggregating these heterogeneous results into a meta-analysis was not possible. Therefore, the review results were interpreted and discussed narratively.

### Risk factor identification and ranking

In this systematic review, more than 100 factors related to mussel mortality were identified, which highlights the diversity of variables that researchers considered as potential risks or protective factors in mussel mortality.

However, it is interesting to note that although some factors coincided between studies, these were not repeated in a large number of studies. As detailed above, the small number of studies and the diversity of the definitions and exposure metrics captured for a given risk factor prevented any meta-analysis and quantification of effects on the mussel mortality risk. Therefore, comparisons of the strengths of association between mussel mortality and factors, and the subsequent ranking of risk factors were not possible. Moreover, the number of studies was artificially increased for some factors, when the same research group published several papers or several studies in the same paper on the same subject. This publication bias limited the relevance of an evidence interpretation strictly on a quantitative basis, that is the number of studies, and thus prevented the use of the vote-counting method (Allen, 2017) for establishing a ranking of the risk factors.

Even when looking at the studies that explored one particular factor, there was not often consistent evidence of an overall qualitative effect on the mussel mortality risk. Nevertheless, this systematic review highlighted that the mortality risk of both mussel species *M. edulis* and *M. galloprovincialis* varied across the seasons. It furthermore acknowledged the negative impact of an increased seawater temperature with a thermal threshold of 20 and 24°C, respectively. The mortality risk of *M. edulis* could also be associated with pathogens. However, these risk factors relate to the impacts of global changes in ocean and coastal ecosystems (Burge *et al.*, 2014; IPCC (Intergovernmental Panel on Climate Change), 2019) and cannot be changed. Therefore, although this systematic review was comprehensive, it offered limited evidence to define actionable control or mitigation strategies of mussel mortality either for policymaking, mussel industry, or wild bed conservation. For *M. galloprovincialis*, the preventive husbandry practices would be using mussel spat from the same area where the farming is carried out, protecting mussels from predation, or farming together with another mussel species, if possible. For *M. edulis*, they would be protecting mussels from predation, using pure crosses and particular mussel spat having a

selected genotype, that is parents that survived a previous mortality event, whether the selection was natural or anthropic. For wild bed conservation of both mussel species, the impacts of marine anthropic factors, for example the activities of the marine aggregate extraction industry (Barrio Frojan *et al.*, 2008), marine renewable energy technology (Miller *et al.*, 2013) or dredging to maintain access to harbours, should be evaluated *ex ante* before their implementation, to minimise anthropogenic sedimentation or sand accumulation on wild beds.

### Review limitations

Although the systematic review is an unbiased approach, the present study is subject to a few limitations that are mainly explained by the trade-off between limited resources and risk of error.

Only one reviewer read the full content and conducted the data extraction from the corpus considered in this systematic review, ensuring homogeneous data analysis across the whole corpus. However, to limit the risk of errors in data extraction, pilot tests and standardised extraction forms were used. In addition, the STC implemented collective study selection based on the title and abstract screening and data extraction verification based on random samples of the studies, respectively, 9.9% and 14.3% of the corpus. The agreement between the reviewers was substantial at the abstract and title screening level and almost complete at the data extraction stage, showing that selection or measurement bias was unlikely to have affected the review results.

The language restriction applied (French and English), due to the lack of resources to translate other languages, biased the study selection towards English- and French-speaking countries. It is possible that knowledge from some regions of the world has been under-represented, specifically data from Spain which is the main European producer of mussels (FAO 2019).

This review included some subjective interpretation as risk factors were rarely the main focus of the included studies. Effectively, translation of concepts across studies was subject to reviewer interpretation. We are therefore confident that our interpretation accurately reflects the data, although we agree that other interpretations are possible and may be equally valid.

Because this review covered a wide range of risk factors, the findings are at a high level of aggregation; a focus on more specific exposure topics would have allowed for more in-depth evaluation.

### Research gaps and future directions

This literature review revealed significant gaps in knowledge of marine mussel risk factors, which led the STC to

develop recommendations for future research to be undertaken on mussel mortality determinants.

### Develop standardised methodologies to estimate mortality in the field

The first recommendation involves the development of standardised methodologies to estimate mussel mortality in the field, which use shared epidemiological indicators. This literature review showed high heterogeneity to define and estimate mortality in mussels, which is not solely explained by the different standards required by the numerous research disciplines. In particular, technical constraints that challenge mortality estimation in mussel populations, notably in farming conditions, have so far precluded the standardised estimation of mortality. Similarly, the large population sizes and the difficulties in gaining access to the animals prevent robust estimation of epidemiological indicators, since accurately measuring the numbers of dead animals (numerator) and the total population size (denominator) is challenging (Peeler & Taylor, 2011; Lupo *et al.*, 2012). In addition, mortality is rarely homogeneously distributed in such large populations, which prevents simple application of representative sampling. Thus, and unfortunately, it seems that regardless of the innovative tools that could be developed, accurately counting dead and live mussels to calculate a mortality proportion would still be an issue. A shift in the paradigm to estimate mussel mortality is thus needed, and scaling of the concept may be a possible solution.

Marine bivalves share many epidemiological challenges with honeybees. In the context of the French surveillance programme of massive bee mortality, bee mortality is defined at the apiary level using a two-step approach over a 15 day period (Anon 2018). A bee operation owned or managed by one beekeeper is made of several apiaries, which consist of several bee colonies located in the same area, themselves made up of a group of individual bees. The first step consists of assessing a bee colony as 'dead' if more than one litre of dead bees is observed in front of the hive or if the colony is depopulated. The second step involves considering the apiary to be 'dead' if more than 20% of its forming colonies are dead. For medium apiaries (from 6 to 10 colonies), it is considered dead if two dead colonies are observed. For small apiaries (from 2 to 5 colonies), it is considered dead if one dead colony is reported (Anon 2018). Therefore, to obtain an accurate estimation of mortality at the population level, based on the observed mortality on the sampled colonies, calculation of the mortality proportions is related to the size of the apiaries. Honeybee colony mortality is a weighted average, by apiary size, of the colony mortality proportion of each apiary (Chauzat

*et al.*, 2016). The STC believes that the marine mussel community should consider this type of approach of (i) assessing mortality at a farming unit level, instead of the accurate individual animal scale, and (ii) combining qualitative and quantitative criteria within a defined time period (e.g. a tide cycle). It is considered that a mussel farm owned by one mussel farmer is made of several farming places, for example leasing grounds, which consist of several farming structures, that is 'bouchot' for *M. edulis* or raft for *M. galloprovincialis*, themselves made of a group of individual mussels. Thus, a multistage sampling plan may be adapted to estimate mortality at each unit of interest by accounting for the unit hierarchy. At each unit level, thresholds to assess whether the unit is affected by mussel mortality (i.e. 'dead') could be defined by using standardised semiquantitative criteria.

#### Use study designs that can address multiple interactions between risk factors

The second recommendation concerns the application of study designs adequately addressing the identification of many interacting mussel mortality risk factors pertaining to different topics, since the methodological quality assessment revealed frequent weaknesses in the reviewed corpus. More data are required on the combined effects of multiple risk factors. For this approach to succeed, there is a need for concomitant collection, that is at the same time and in the same place, of data on multiple exposures of different types. The essential concept should be to compare the exposure profiles of dead versus healthy mussel populations and, over time, to provide valuable clues about the risk factors of mortality. A preliminary approach would be the development of eco-epidemiological studies, which aim to analyse determinants and outcomes at different levels of organisation of the studied system, from the molecular to the social (Susser & Susser, 1996). These should necessarily be integrative and multidisciplinary to cover all the different risk factor topics. Guidelines to design and report epidemiological studies (STROBE-Vet) should be used (Sargeant *et al.*, 2016). A second approach would be the development of mesocosm experiments, which are used to simulate complex exposure dynamics under realistic field conditions (Culp *et al.*, 2017). Mesocosms are a hybrid of field and laboratory conditions; their advantages include increased control and replication compared to field studies and more realistic conditions than laboratory experiments. Currently, these approaches are used to study the effects of contaminants in the marine ecosystem (Alexander *et al.*, 2016). Once this screening step of potential risk factors is achieved, targeted experimental approaches could be developed further to assess their causality while controlling the other factors.

#### Integrate the concept of exposome

The third recommendation includes the integration of the concept of exposome, that is every exposure to which an individual is subjected from conception to death (Wild, 2005), in future investigations undertaken on multiple exposure–mortality associations in mussels. This literature review showed that only one third of the studies had explored the combined effects of multiple factors on the mussel mortality risk, and when they had, the effect of no more than three factors was investigated. The exposome is assessed at the individual level by characterising the specific signatures (or profiles) of the effects of previous exposures based on 'omics' technologies (Wild, 2012). The exposome complements the genome by providing a comprehensive description of the lifelong exposure history of an individual. On the one hand, the recent use of tissue and molecular biomarkers in mussels *M. galloprovincialis* has enabled us to distinguish coastal sites according to their pollution level (Carella *et al.*, 2018; Matozzo *et al.*, 2018). On the other, the application of 'omics' approaches has significantly improved knowledge about the interactions between the ostreid herpesvirus OsHV-1 and the Pacific oyster *Crassostrea gigas* (Nguyen *et al.*, 2018). Further application of 'omics' technologies should be encouraged to develop and validate sets of biomarkers relevant to multiple exposures in the context of mussel mortality events. However, exposure biomarker approaches should be coupled with refined questionnaire-based approaches to collect husbandry practices and the life history of the mussel population under study, and environmental monitoring at different temporal and geographical scales.

#### Develop tools to assess multi-exposure of mussels on a routine basis

The fourth recommendation draws attention to the need for tools for mussel exposure assessment. In particular, there is a need to develop screening tools that capture multiple pathogens and pollutants on a routine basis. Effectively, in the literature reviewed, these risk factor topics were often explored using targeted approaches and only a few pathogens or pollutants were simultaneously investigated. Generic methods such as histopathology allow for detection of multiple infections and emerging diseases, but their slowness and low sensitivity for detection of small protistan, viral or bacterial pathogens are not suitable for extensive routine use. Rapid tools such as multiplex DNA-based polymerase chain reaction (PCR) and DNA microarray-based assays have low detection limits but require that the specific target pathogens have been identified, which is not appropriate in mortality exploration without prior knowledge of the causative pathogen. Development of

microbial metagenomics should be encouraged because such approaches allow simultaneous identification of a large number of pathogen genomes (abundance and diversity) from the same sample at the same time, without prior knowledge of their genomic sequences (Gilbert & Dupont, 2011). This type of overall approach has the ability to identify co-infections within the host (Yang *et al.*, 2011) and is also applicable to environmental samples (Munang'andu, 2016). The development of high-throughput sequencing (HTS) technologies and bioinformatics tools for nucleic acid sequence assembly and annotation has made it possible to use these approaches in a cost-effective manner and thus at a large scale. Although microbial metagenomics is still underused in aquaculture (Martinez-Porchas & Vargas-Albores, 2017), studying mussel mortalities through the metagenomics perspective should be favoured to help understand the involvement of pathogens in mortality outbreaks by comparing the microbial profiles of animals and seawater in sites in which mortality occurs vs. sites with a nonmortality context, or before vs. during the course of mortality events. To go further, as positive results provided by DNA-based methodology are not clearly indicative of actual infection, metatranscriptomics approaches should be preferentially developed, in agreement with the exposome concept detailed above, to identify only active pathogens in a replication state. This would facilitate the biological interpretation of the results and discard environmental DNA or traces that are not relevant to the mortality occurrence. First milestones in that direction have been laid by combining microbiome characterisation (16S rRNA HTS) and host gene expression profiles (RNA-Seq) to decipher the factors underlying mass mortality in the striped venus clam, *Chamelea gallina*, which suggested potential chemical pollutant–pathogen interactions (Milan *et al.* 2019).

Similarly, further work is needed on long-term monitoring of multiple relevant pollutants in marine environments. Data are required to assess the effects of long-term and low-level exposure to multiple contaminants on the mortality risk of mussels. However, progress in *in situ* sensor technologies is still needed to enable cost-effective and continuous monitoring of contaminants in seawater (Justino *et al.*, 2015). In particular, passive sampling technologies (Schintu *et al.*, 2014) that capture a wide range of environmental pollutants should enable us to assess the effects of multiple exposures (i.e. a cocktail effect) and of chronic exposure to contaminants on the mortality risk of mussels.

In addition to these previous recommendations, the STC highlights the need to cautiously define the epidemiological units and their appropriate related exposures, as the hierarchical organisation of the system under study should be considered. Future investigators should be warned against the ecological fallacy, that is inferring causation at the individual level from population-level comparisons, as well as

the atomistic fallacy, that is inferring causation at the population level from individual-level comparisons (Susser, 1973; Schwartz, 1994).

#### **Assess the impact of husbandry and fishery practices on the mortality risk**

The fifth recommendation pertains to the need for assessment of the impact of husbandry and fishery practices on mussel mortality risk. Although one third of the corpus reviewed investigated the effect of husbandry practices on mussel mortality, these were always controlled field trial studies, that is studies in which the investigator controls the allocation of the mussels to the study groups, with or without application of the practice under study. Future research should include long-term monitoring of mussel populations and the multiple exposures, and importantly practices occurring in usual farming or harvesting conditions. Observation studies of this kind would involve engaging mussel farmers and fishermen in the study.

#### **Coconstruct studies with stakeholders**

The last recommendation is the need for coconstruction of future large-scale prospective studies on mussel mortality risk factors with stakeholders, specifically mussel farmers and fishermen, to guarantee sustainability and utility of the results. Stakeholders should be engaged as early as possible and throughout the process, in as many of the following phases as possible: knowledge provision, data collection and integration, interpretation of results and development of mitigating solutions (Reed, 2008).

Addressing the STC recommendations implies the need for interdisciplinary research. Conducting large-scale eco-epidemiological analyses of multiple exposures associated with mussel mortality, including the different organisation levels of the system under study, would require increased collaboration between epidemiologists, biostatisticians and experts in bioinformatics and biotechnologies, as well as laboratory, environmental and social scientists. Processing and analysing large data sets generated and collected at different scales would also require adapted capabilities for the management and analysis of large data flows. The STC panel, by gathering scientists from different research disciplines, the shellfish industry and government authorities, represents a first step in this interdisciplinary process. This configuration made it possible to build overarching recommendations that highlight multidisciplinary research needs.

The STC also recognised that, although assessing all risk factors of mussel mortality within a large-scale survey would be ideal, it is not realistically achievable at this time. By their nature, prospective cohort studies take time as well as funding. The cost of equipment and technologies needed

may be high, and therefore, their application to population-based studies may also be costly. This type of project would require an enormous effort for general coordination, for the supervision of the participating mussel farmers and fishermen, and for the maintenance of a central database. These recommendations also involve a significant financial contribution and may not always be immediately feasible as innovative tools and developments are needed, for example, for improved measurement of multiple exposures at different time points of the production cycle of mussels. Thus, given the very high costs of such studies and the complexity of putative risk factors in mussel mortality, even a partial understanding of a subset of exposures could provide substantial advances in understanding mussel mortality determinants. There could be further efforts to coordinate a major national prospective cohort study, supported by coordinated national investment with regional funders, able to target their contribution to exposures of regional priority. Data generated should be shared in a common and publicly available database among stakeholders, to facilitate cooperation. Overall, standardising the efforts and developing cooperative initiatives would facilitate comparisons between studies to increase the robustness of data if meta-analyses are required.

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## Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Appendix S1.** Search equation used for searches in the Web of Science database.

**Appendix S2.** Citations excluded at the full-text examination step and reasons for their exclusion (N=117 citations).

**Appendix S3.** Table synthesising key results of the 114 studies included in the narrative synthesis.

**Appendix S4.** Graphical solution of the MCA on the first and second factorial axis, which explained, respectively, 15.5% and 12.5% of the total inertia of the 14 variables, for descriptive characteristics of 114 studies related to risk factors of mussel mortality. Each variable is plotted on the graph according to the coordinates on factorial axes 1 (horizontal) and 2 (vertical).