Harmful Algae 98 (2020) 101901

Contents lists available at ScienceDirect

Harmful Algae

journal homepage: www.elsevier.com/locate/hal

Marine harmful algal blooms and human health: A systematic scoping review

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ARTICLE INFO

Keywords:
Shellfish poisoning
Harmful algal bloom
Population health
Marine toxins
Ciguatera Poisoning

ABSTRACT

Exposure to harmful algal blooms (HABs) can lead to well recognised acute patterns of illness in humans. The objective of this scoping review was to use an established methodology and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) reporting framework to map the evidence for associations between marine HABs and observed both acute and chronic human health effects. A systematic and reproducible search of publications from 1985 until May 2019 was conducted using diverse electronic databases. Following de-duplication, 5301 records were identified, of which 380 were included in the final qualitative synthesis. The majority of studies (220; 57.9%) related to Ciguatera Poisoning. Anecdotal and case reports made up the vast majority of study types (242; 63.7%), whereas there were fewer formal epidemiological studies (35; 9.2%). Only four studies related to chronic exposure to HABs. A low proportion of studies reported the use of human specimens for confirmation of the cause of illness (32; 8.4%). This study highlighted gaps in the evidence base including a lack of formal surveillance and epidemiological studies, limited use of toxin measurements in human samples, and a scarcity of studies of chronic exposure. Future research and policy should provide a baseline understanding of the burden of human disease to inform the evaluation of the current and future impacts of climate change and HABs on human health.

1. Introduction

The adverse effects on human health of harmful algal blooms (HABs) occur primarily through the impacts of natural phycotoxins via various exposure routes including the ingestion of contaminated seafood, inhalation or direct skin contact (Berdalet et al., 2016). Numerous species of microalgae are known to produce these toxins, with well recognised acute patterns of illness. A significant disease burden is seen worldwide, for example, with the incidence of Ciguatera Poisoning (CP) reported at 251 cases per 10,000 persons per year in certain Pacific populations; similar levels are also reported in the Caribbean (Chateau-Degat et al., 2007; Radke et al., 2013). Human fatalities are not infrequent, e.g. with outbreaks of Amnesic Shellfish Poisoning (ASP) (Perl et al., 1990), CP (Hamilton et al., 2010), Palytoxicosis (Wu et al., 2014) and Paralytic Shellfish Poisoning (Suleiman et al., 2017). However, precise estimates of the human health impacts of HABs on population health, and associated trends, are lacking in the absence of robust surveillance systems. Furthermore, there is a reported lack of evidence describing the potential long-term sequelae of both acute illness and particularly chronic exposure (Backer and Fleming, 2008).

With climate and other environmental changes, the geographical context of the disease burden is anticipated to change, with effects

Abbreviations: ASP, Amnesic Shellfish Poisoning; AZP, Azaspiracid Shellfish Poisoning; CP, Ciguatera Poisoning; DSP, Diarrhetic (Diarrheic) Shellfish Poisoning; HAB(s), Harmful Algal Bloom(s); NSP, Neurotoxic Shellfish Poisoning; PSP, Paralytic Shellfish Poisoning

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https://doi.org/10.1016/j.hal.2020.101901
Received 5 April 2020; Received in revised form 29 August 2020; Accepted 30 August 2020
Available online 17 September 2020

likely to be seen outside of currently known areas of risk. Variations in sea-surface temperature resulting from climate change are predicted to affect the distribution and intensity of HABs in a highly species-specific manner (Backer and Moore, 2010; Berdalet et al., 2016; Hallegraeff, 2010; Moore et al., 2008; Van Dolah, 2000; Wells et al., 2020). Considering these changing risks, and the current growing breadth and quantity of HAB research describing the association with human health impacts, a review of the current evidence base is vital to identify research gaps and to drive future research and public health policy (Wells et al., 2020; Wells et al., 2015). Whilst many of the mechanisms of algal toxins and their impacts on human health are known, a limited number of studies have attempted to methodically identify the evidence base for an association between a single HAB exposure type and subsequent human health and wellbeing effects (Arnich and Thébault, 2018; Friedman et al., 2017; Friedman et al., 2008; Tubaro et al., 2011) or for a single route of exposure (Nicolas et al., 2017). A comprehensive review of the topic is required to inform the future research agenda, in order to address the current and future impacts of HABs on human health.

Whilst systematic reviews, with or without meta-analyses, are a well-established method, particularly in health research (Higgins et al., 2011), scoping reviews are needed to establish the extent of the evidence base and inform research questions to be addressed by a subsequent systematic review or original research. This means that scoping reviews can be used to address a broader question across a diverse evidence base incorporating varied study types, methods and scientific disciplines (Arksey and O'Malley, 2005; Pham et al., 2014). Consequently, these are frequently used to inform the research agenda for a particular topic. Like systematic reviews, scoping reviews also adopt a comprehensive, rigorous, systematic and reproducible methodology (Arksey and O'Malley, 2005).

This scoping review aimed to map the existing evidence for the associations between exposure to marine toxic HABs and subsequent observed acute and chronic human health effects. A secondary aim is to identify existing gaps in the available evidence base, thereby highlighting future research and policy directions and priorities.

2. Materials and methods

This scoping review adopted an established approach to map out the breadth and depth of existing evidence (Arksey and O'Malley, 2005) and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) reporting framework (Liberati et al., 2009).

A formal five-step method was used as follows.

2.1. Stage 1. Identifying the research question

The research question was defined as: what is the existing evidence for the associations between exposure to marine toxic HABs and subsequent acute and chronic human health effects? A comprehensive broad approach was taken, to map the extent and scope of published evidence. The identification of the research question was used to produce inclusion and exclusion criteria (Table 1). Review studies were not included because comprehensive search methods were used to identify the original relevant papers.

The study focused on marine HABs only, and thus harmful blooms in freshwater environments were not included. Exposure to marine cyanobacteria was not included given current uncertainties regarding associations with human health (Golubic et al., 2010; Laurent et al., 2008) and technical challenges in the feasibility of safely excluding only freshwater sources. Additionally, it was considered that the evidence of exposure to a bloom event was not required; evidence of exposure to HAB toxins per se was included.

Table 1
Inclusion and exclusion criteria.

Criteria	Include	Exclude
Population	Human	Human Cell lines In vitro
Exposure	Direct or indirect exposure to microalgae or micro-algal derived toxins Bloom event not-required Exposure routes include: ingestion; inhalation; skin contact; sexual transmission; eye contact; other Routes include consumption through a vector such as seafood	Tetrodotoxin, cyanobacteria Chelonitoxin Scombroid Exposure via desalinated water Experimental exposure Food supplements *Lyngbya* *Pfiesteria* Exposure to palytoxin via coral/cnidarians/ zoanthids
Context	Marine/Estuarine/Coastal Worldwide	Freshwater including lakes
Outcomes	Adverse health effects including but not exclusively: Death, ASP, NSP, PSP, DSP, CP, AZP, Palytoxicosis, *Ostreopsis spp. algal syndrome*, gastrointestinal illness, respiratory illness, neurological illness, hospital admissions Wellbeing impact – if estimates of adverse wellbeing Treatment if cases reported	Economic impacts Wider societal impacts – tourism/beach closure. Haff disease Exposure data only
Study type	English language 1985 – search date Case reports Epidemiological studies Surveys Published surveillance data Incidence studies Modelling studies estimating incidence	Non-English language Pre-1985 Editorials Review papers "No illness reported" × Conference abstracts

2.2. Stage 2. Identifying relevant studies

A search strategy was developed in consultation with subject matter experts and an evidence synthesis specialist, detailing the population (human), exposure (i.e. HABs), context (i.e. marine) and health outcomes (e.g. DSP) as outlined in Table 1. The full search strategy is described in the supplementary materials.

To identify relevant literature, a systematic search of the following electronic databases was conducted on 12th May 2019: MEDLINE; PubMed; Global Health; SCOPUS; Environment Complete; and Web of Science. Searches were restricted to English language studies from 1st January 1985 onwards because of the relative lack of publications prior to this date available online. The full search strategy is presented in supplementary materials. All results were managed in EndNote (version X8). Duplicate studies were identified, and removed, in Endnote using the Bramer method that allows for variations in page number format across electronic databases (Bramer et al., 2016).

To identify further studies, backwards and forwards citation

searching was used. The reference lists for any papers included in the final synthesis were hand searched (backwards searches); and Web of Science used to identify any relevant studies that had cited included papers (forward searches).

2.3. Study selection

To identify relevant articles, the titles and abstracts of the search results were reviewed against the inclusion and exclusion criteria (Table 1). The full text of any articles included at the title and abstract screening stage were then obtained and assessed for inclusion by two reviewers (NY and LEF or RS); any conflicts between reviewers were discussed (NY, LEF, RS, EB) and a final decision regarding article inclusion made.

2.4. Stage 4. Charting the data

Standard data was extracted from each study including: year, author, study type, country of outcome, syndrome/toxin involved, and study outcomes. These data were then used to sort the studies for reporting and synthesis.

HAB clinical syndromes were classified as described in Table 2.

Exposure was classified as “acute” for an identified single HAB exposure event – for example the ingestion of a meal or beach visit - and “chronic” for studies where an assessment of exposure over time was made. In the absence of an accepted temporal distinction between acute and chronic outcomes from toxic events in HAB and wider scientific literature, a pragmatic decision was taken to classify outcomes occurring with 28 days of exposure as “acute”, and “chronic” thereafter - This was based on the likelihood that acute effects from a HAB poisoning episode resolve within days or sometimes weeks, and symptoms beyond 28 days are more likely to reflect long-term sequelae. The clinical syndrome or HAB biotoxin implicated in reported illness was classified as described in table 2 (Berdalet et al., 2016; Tubaro et al., 2011).

Study types were defined as follows: *anecdotal mention of cases*, where cases were mentioned without significant detail; *case reports*, including clinical data such as detailed symptoms and incubation period; *routine surveillance data*, including publication of routine surveillance data and/or ecological studies of environmental variables with pooled case data; *formal epidemiological studies*, including case definitions, formal epidemiologic study designs and measures of effect sizes (e.g. case-control and cohort studies); *auxiliary studies* describing cases but primarily reporting toxin results in implicated food vector or other exposure route; *trials of treatment*; and *biological marker/genomic studies* of cases.

Confirmation of cause of illness was recorded as follows (adapted from definitions of Tubaro et al. 2011):

1 Toxin detected in remnants of food consumed.
2 Toxin detected in same batch of food to that consumed.
3 Toxin detected in same area of food production/exposure within one week either side of harvesting/exposure.
4 Harmful algal species detected in same area of food production/exposure within one week either side of harvesting/exposure.
5 Toxin detected in same area of food production/exposure outside of one week either side of harvesting/exposure.
6 Harmful algal species detected in same area of food production/exposure outside of one week either side of harvesting/exposure.
7 Direct measure of exposure – for example personal or ambient air monitoring.
8 Based on clinical symptoms only.
9 Toxin or metabolites detected in human specimens.
10 Human samples negative for toxin or metabolites.

2.5. Stage 5. Collating, summarising and reporting the results

A summary of key study information, such as the year of publication and the syndrome/toxin type, was produced. Following this, studies were presented as a summary organised by HAB-related toxic syndromes in humans and their associated toxins. Consistent with established scoping review methods, study results were not aggregated nor quality assessed, but rather the results are presented as a narrative synthesis, describing the range of research and identifying research gaps (Arksey and O'Malley, 2005).

3. Results

After the removal of duplicates and screening, 380 studies meeting the eligibility criteria were included. The PRISMA diagram in Fig. 1 presents the flow of information through the stages of the review.

Tables 3 summarises the general characteristics of these 380 studies. There is a trend of increasing frequency of studies over time, with 35 studies published in the five years from 1985–1989, compared to 136 for the longer time-period from January 2010 to May 2019. CP was reported in the greatest number of studies (220 or 57.9% all studies), followed by PSP (80; 20.8%); and AZP in the fewest studies (3; 0.8%). Studies were predominately case reports (53.9%), surveillance data and ecological studies (23.2%) and anecdotal reports of illness (9.8%); only 35 (9.2%) reports were classified as formal epidemiological studies. Eight auxiliary studies provided later confirmation of the cause of outbreaks but reported cases; and there were six biological marker/genomic studies and a single trial of treatment. The most commonly reported continent of clinical outcome was North America (44.2%), followed by Australasia/Oceania (21.8%) and Asia (17.1%).

The most commonly reported route of exposure (Table 3) was ingestion through a food vector (93.7% of studies). Other routes of transmission were inhalation and direct contact with seawater. In addition, a small number of studies, all describing CP, reported possible transmission through breastfeeding, sexual contact and placental transfer.

Exposure to toxins was classified as an acute event for the majority of studies (89.5%), with only four studies reporting chronic exposure.

Table 2
Classification of HAB clinical syndromes and associated toxins considered in the review (Adapted from Berdalet, 2015, Tubaro 2011).

Clinical Syndrome	HAB toxin*	Notes
Amnesic Shellfish Poisoning (ASP)	Domoic acid	
Azaspiracid Shellfish Poisoning (AZP)	Azaspiracid	
Ciguatera Poisoning (CP)	Ciguatoxin	
Diarrhetic (Diarrheic) Shellfish Poisoning (DSP)	Okadaic acid (dinophysistoxins)	
Neurotoxic Shellfish Poisoning (NSP) and brevetoxin associated respiratory irritation	Brevetoxins	
Palytoxicosis	Palytoxin	Refers to seafood intoxication only
Effects of Palytoxin-like toxins or "*Ostreopsis* spp. algal syndrome"	Attributed to Palytoxin-analogues.	Respiratory and cutaneous irritation after postulated exposure to seawater and/or aerosol during *Ostreopsis* spp. blooms
Paralytic Shellfish Poisoning (PSP)	Saxitoxin	

* Including toxin-derivatives

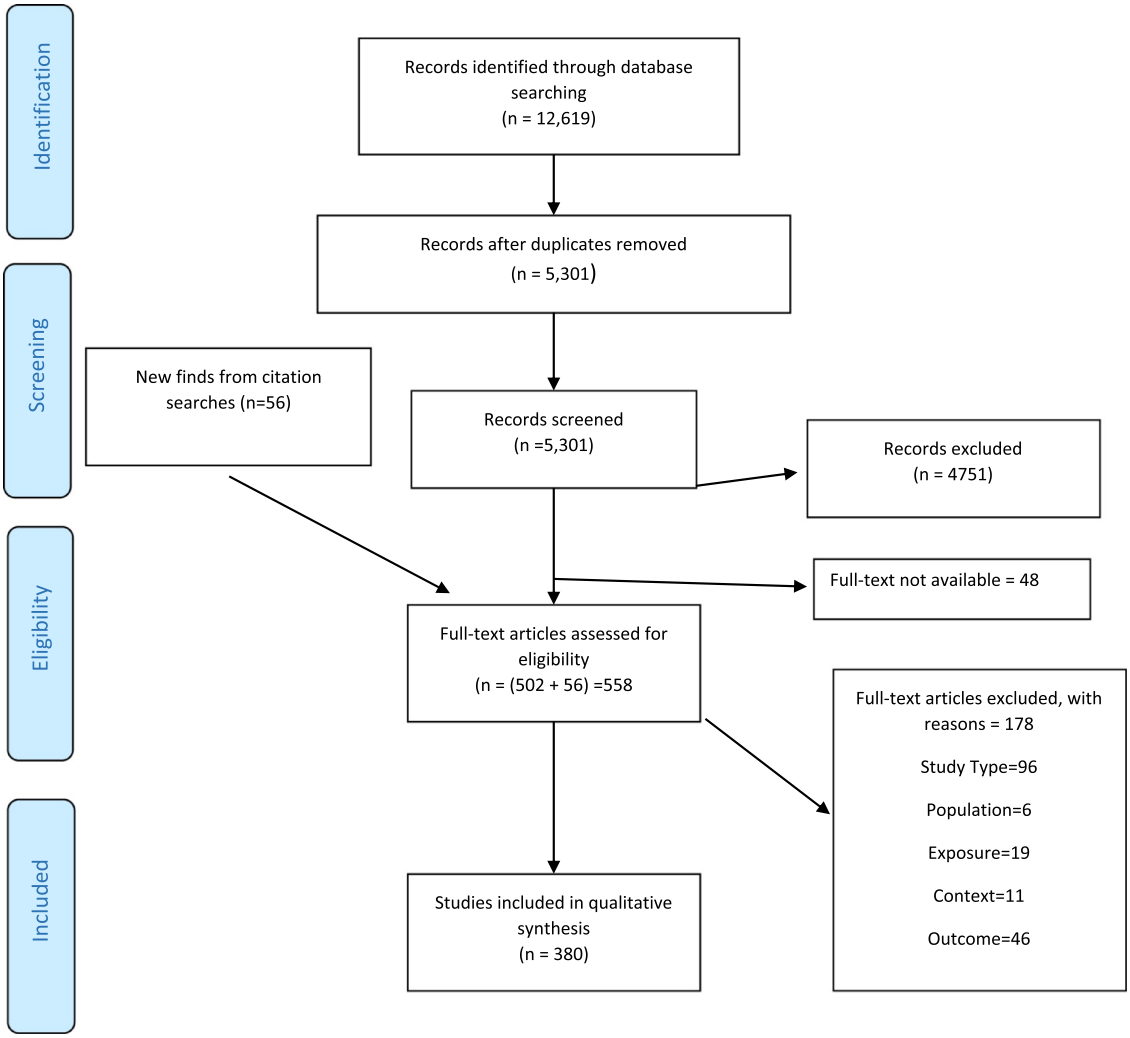

Fig. 1. PRISMA diagram – flow of identified studies through to final inclusion.

Acute outcomes only were reported in 233 (61.3%) studies, with 69 (18.2%) reporting both acute and chronic outcomes; 18 (4.7%) studies focussed solely on chronic outcomes.

The highest number of surveillance studies were related to CP (73 studies), of which 16 provided incidence estimates; incidence estimates were not reported for other clinical syndromes. Surveillance studies were predominately generic studies of notified foodborne disease, rather than HAB-specific, with the exception of two studies: a bespoke active surveillance system in the US reporting cases of ASP, NSP and PSP (Backer et al., 2015); and a study of the respiratory and cutaneous effects of palytoxin-like toxins related to *Ostreopsis spp. algal syndrome* in a limited number of exposed persons in Spain (Vila et al., 2016). There were no surveillance studies for AZP or foodborne palytoxicosis.

Three surveillance reports were identified for ASP – of which one did not report this specific outcome rather the ecological level association of diarrheal disease with the relevant toxin and the association with DSP and NSP toxins (Zhang et al., 2015); an additional three surveillance studies reported DSP cases, all from generic foodborne disease reporting. Twenty-one surveillance reports were identified relating to PSP, including routine notifications and generic foodborne outbreak data from the USA (12 studies) and Asia (three studies), in addition to US poison centre data (five studies) and the aforementioned US bespoke reporting system. Two generic foodborne surveillance reports reported cases of NSP.

A total of 35 formal epidemiological studies were included, of which 15 studied outcomes associated with exposure – predominately inhalational – to brevotoxins in the USA. Eight of the 220 CP reports were formal epidemiology studies, describing measures of association with species of fish consumed, consumption of fish organs, alcohol, pre-existing conditions, and clinical associations with chronic disease. Ecological level estimates of chronic exposure to DSP toxins associated with digestive tract cancer were evaluated in two studies. Additionally, there were two case-control studies estimating the association between mussel consumption and the risk of illness in acute DSP poisoning events. Chronic exposure to domoic acid and measures of memory were involved in two studies in the Pacific North-West of the USA, but there were no further formal epidemiological studies of ASP. Six case-control studies measured the association between variables including specific food consumption, eating viscera and drinking alcohol, and the risk of PSP in acute events. No formal epidemiological studies related to AZP, foodborne palytoxicosis or the respiratory and cutaneous effects of palytoxin-like toxins/*Ostreopsis spp. algal syndrome*.

Confirmation of the cause of illness (Table 3) was through clinical signs and symptoms for 120 studies (31.6%), and not reported in 73 (19.2%) studies. A low proportion (32; 8.4%) of studies attempted to measure toxins or their metabolites in human specimens, of which 27 (7.1%) reported their detection.

The key characteristics for each paper are described in online supplementary materials; Table 4 below contains the narrative summary for papers by HAB clinical syndrome.

Table 3
General characteristics of 380 included studies.

Study characteristic (number of studies = 380)		Count* (% of all studies)
Year of Publication	1985–1989	35 (9.8)
	1990–1999	88 (23.2)
	2000–2009	121 (31.8)
	2010–2019	136 (35.8)
Outcome syndrome	ASP	18 (4.7)
	AZP	3 (0.8)
	CP	220 (57.9)
	DSP	29 (7.6)
	NSP	30 (7.9)
	Palytoxicosis	9 (2.4)
	"Ostreopsis spp. algal syndrome"	8 (2.1)
	PSP	80 (20.8)
	Non-specific	3 (0.8)
Study Type	Anecdotal reports	37 (9.8)
	Case reports	205 (53.9)
	Surveillance data/ecological	88 (23.2)
	Epidemiological study	35 (9.2)
	Auxiliary studies	8 (2.1)
	Trials of treatment	1 (0.3)
	Biological/genomic studies	6 (1.6)
Outcome continent	Africa	15 (3.9)
	Asia	65 (17.1)
	Australasia/Oceania	83 (21.8)
	Europe	37 (9.7)
	North America including Caribbean	168 (44.2)
	South America	9 (2.4)
	Missing/other	7 (1.8)
Exposure continent location	Africa	13 (3.4)
	Asia	57 (15.0)
	Australasia/Oceania	67 (17.6)
	Europe	31 (8.2)
	North America including Caribbean	143 (37.6)
	South America	10 (2.6)
	Missing/other	63 (16.6)
Exposure route	Ingestion of vector	356 (93.7)
	Inhalation	29 (7.6)
	Direct water contact	4 (1.1)
	Sexual transmission	3 (0.8)
	Breast-feeding	2 (0.5)
	Placental transfer	2 (0.5)

Table 3. General characteristics of included studies -continued.

Study characteristic (number of studies)		Count* (%)
Exposure	Acute	340 (89.5)
	Chronic	4 (1.1)
	Not-specified	36 (9.5)
Health Outcome	Acute	233 (61.3)
	Both acute and chronic	69 (18.2)
	Chronic	18 (4.7)
	Not-specified	60 (15.8)
Confirmation**	Toxin detected in food consumed	97 (25.5)
	Toxin detected in same batch	13 (3.4)
	Toxin detected same area within ± one week	68 (17.9)
	HAB species detected same area within ± one week	50 (13.2)
	Toxin detected same area > one week	7 (1.8)
	HAB species detected same area > one week	5 (1.3)
	Direct measure of exposure	7 (1.8)
	Clinical signs/symptoms only	120 (31.6)
	Toxin/metabolites in human specimens	27 (7.1)
	Human samples negative for Toxin/metabolites	5 (1.3)
	Not reported	73 (19.2)

* Totals may exceed total number of studies as multiple characteristics described in some manuscripts

** Described in detail in section 2.4.

4. Discussion

This scoping review systematically maps the extent of published evidence for the associations between marine HABs and observed human health effects. This study demonstrates an evidence base dominated by reactive case reports of illness following acute poisoning episodes. Studies describing chronic exposure to HABs are lacking, and there are few studies that use human biomarkers for the confirmation of the cause of illness. Furthermore, there is insufficient application of formal epidemiological studies to address disease associations and burden.

Despite the increasing number of publications seen over time (which may reflect bias in online availability), it is outside the stated aims and scope of this review to address trends in HAB human disease incidence. Furthermore, in the highlighted absence of robust systematic surveillance in human populations, detection of any changes in incidence will remain elusive. Illness is reported globally, however outcomes are most commonly reported from North America, Asia and Australasia/Oceania. The low number of studies reporting illness in Africa and South America may suggest possible neglected disease and/or under-reporting in the English language literature from these continents. The relatively low number of studies describing outcomes in Europe may reflect the success of monitoring programs in areas where commercial (e.g. aquaculture) rather than wild harvesting predominates.

Case reports and anecdotal reports dominate the literature (almost two-thirds of studies) whereas there are few formal epidemiological studies – nearly half of which relate to brevotoxin exposure in North America. Only four studies, restricted to ASP and DSP, addressed the potential human health effects of chronic exposure to HABs, with the literature dominated by acute poisoning episodes; the evidence presented is thereby largely reactive to sporadic outbreak events. The current literature is dominated by CP and, to a lesser extent by PSP, which by default represents the known burden of disease. However, as previously described, formal epidemiological studies suggest that the disease burden from HABs should include other HAB organisms/toxin exposures.

Exposure assessment, including proxy measures, was used to confirm the diagnosis across a large proportion of studies. This included both, direct measures of toxin levels in food-consumed in one-quarter of the papers, and levels of toxins and HAB species linked geographically and temporally to harvesting/direct exposure areas in around one-third of the literature. This present study found that only a small number of formal epidemiological studies – all related to airborne exposure to brevotoxins – used direct personal measures of exposure. However, some attempts have been made to calculate the levels of toxin ingested from biotoxin levels in produce and estimated portion size (Hossen et al., 2011; Young et al., 2019).

Further confirmation of the cause of illness in reporting HAB poisoning episodes was based on clinical signs or symptoms in one-third of the studies, with a further 19% not reporting any relevant information. A few studies reported measurements of biotoxin levels in human specimens; sampling included: faeces, serum, urine, and post-mortem gastric contents and internal organs. The development of biomarkers for exposure to HABs has been previously reported to be insufficient and the findings of this present review support the lack and inconsistency of the use of these methods as diagnostic tools (Backer and Fleming, 2008; Berdalet et al., 2016).

4.1. Strengths and limitations

This study provides the most comprehensive review to date of the evidence of the link between marine HABs and observed human health effects. Previous studies have been limited to single clinical syndromes/toxins (Arnich and Thébault, 2018; Friedman et al., 2008; Tubaro et al., 2011) or exposure routes (Nicolas et al., 2017). The use of rigorous,

Table 4
Narrative summary of 380 studies by HAB clinical syndrome.

Clinical Syndrome	Number of studies	Narrative summary
ASP	18	12 studies describing clinical or environmental elements of an outbreak of ASP from the consumption of mussels in Canada in 1987. One case report from 1992 mentions possible domoic acid intoxication among 25 US residents following razor clam consumption from US waters. One case of ASP is reported between from 2007-11 in a US surveillance paper; a USA surveillance paper 2009-2015 reported a single case. A 2013 paper from China reported the ecological association between multiple HAB toxins including ASP in aquatic products and diarrhoea. A cohort study and cross-sectional study from US Pacific NW described the possible associations between razor clam consumption - a chronic exposure - and memory loss.
AZP	3	Anecdotal and case reports describe small numbers of azaspiracid poisoning following ingestion of mussels produced in Ireland, with outcomes locally, in the US and the Netherlands.
CP	220	131 case/anecdotal reports 73 surveillance/ecological papers including 16 papers with incidence estimates (for North America and Australia/Oceania only). 8 epidemiological studies, one axillary study and one randomised control trial of treatment with mannitol. 6 studies describing biological or genomic markers. Studies by outcome continent predominately from North America (92) Australia/Oceania (69) and Asia (35) but also 12 African and 7 European; no studies with outcomes in South America.
DSP	29	20 anecdotal/case reports, across 5 continents mostly following exposure in Europe. Cases reported in 5 surveillance reports. 4 epidemiological studies including 2 case-control studies following acute exposure and 2 ecological level studies describing possible associations between seafood consumption, or a proxy measure of exposure to DSP toxins, and digestive cancer.
NSP and respiratory irritation	30	7 anecdotal/case reports describing illness following inhalation or ingestion of toxin; six from USA and one describing large 1993 outbreak of NSP in New Zealand. 5 auxiliary studies describe subsequent biotoxin identification related to this event. 3 studies of surveillance/ecological data, 2 from the USA and a study from China describing ecological level associations between toxin levels in aquatic products and diarrhoeal illness. 15 formal epidemiological studies from the USA describing the association between predominately airborne exposure to brevetoxins and outcomes including respiratory function and emergency room admissions for respiratory, gastrointestinal and neurological illness.
Palytoxicosis	9	8 case reports and one anecdotal report detailing 1-4 cases per study; 6 studies report fatalities. All cases followed ingestion with various vectors implicated; 6 studies from Asia, in addition to individual reports from Hawaii, Madagascar and Vanuatu.
Ostreopsis spp. algal syndrome	8	2 anecdotal/case reports and 1 auxiliary study focussing on toxin analysis included describing cases of illness in 2005 (~200) and 2006 (~20) associated with *Ostreopsis ovata* blooms near Genoa, Italy. Two studies described cases of similar illness in other parts of Italy in 2003/4 and 2009. 2 additional anecdotal/case reports from France (2006–9) and Croatia (2010). A single ecological study explored the association between the physiological aspects of *Ostreopsis* spp. blooms and associated illness in Spain.
PSP	80	53 anecdotal/case reports across five continents describing a total of 1431* cases – all with acute exposure and outcomes – including nineteen studies reporting fatalities. 21 surveillance reports, predominately from the US and Canada ($n=17$), also reporting cases from Malaysia, Thailand, the Philippines and South Africa; a total of over 6000 cases and 227 fatalities are recorded from multiple overlapping data sources including surveillance systems and poison centre data. 6 case-control studies are reported, reporting factors associated with illness following acute episodes in North America and Asia.
Other	3	3 studies were not able to be coded under a specific clinical outcome. One case series from India reported 67 cases of "panic-attack" following airborne red tide exposure. One UK study of surveillance data reported cases of "toxic effects" from seafood between 1998-2009 using health records. Furthermore, a 2009 study described the ecological level association between the level of various phytoplankton groups and a range of symptoms in Puerto Rico.

* Some double counting likely overestimating at least 19 cases – duplicated cases in multiple papers.

systematic and reproducible scoping review methods have previously been applied to environmental sciences, including environmental factors and human health, but has not been previously used to address this subject area (Haddaway et al., 2018; Ng et al., 2017; Pullin et al., 2018; Sun and Zhu, 2019).The use of strict and transparent search, inclusion criteria and more than one reviewer, were intended to reduce bias in study selection. A further strength of this approach is that it maps the existing evidence to inform the focus of future original research and/or systematic reviews that provide a structured approach to synthesising the health impacts.

A number of limitations exist. We excluded grey-literature, such as conference abstracts, and other reports that could provide further insights and could be included in future research. While we adopted a valid and comprehensive extensive search strategy, wider consultation might have led to further reports of illness but were beyond the scope of this review.

As a method of knowledge synthesis, scoping reviews have been used predominantly in health research to provide an inventory of available evidence for researchers and policy-makers (Armstrong et al., 2011), with similar methods increasingly employed in environmental sciences (Haddaway et al., 2018). Despite a rapid increase in the use of scoping review methodology over recent years, there remains some inconsistency in their methods and reporting, with a lack of a common definition and clear guidance (Peters et al., 2015; Pham et al., 2014). The most widely established method is based on that described by Arksey and O'Malley (2005) as applied in this study, with recent attempts to establish consistency through newer guidance (Peters et al., 2015).

Consistent with an accepted approach, this study used scoping review methods to purely map the existing literature (Arksey and O'Malley, 2005). A limitation of this approach means that the quality of studies was not assessed. Furthermore, this study does not attempt to estimate the baseline burden of disease or make definitive statements as to temporal trends (Arksey and O'Malley, 2005).

The review was focussed predominantly on individual adverse health impacts of HABs, and did not search for evidence of wider societal impacts, such as economic loss that can affect community wellbeing. From this review we found that HAB and human health research has been focussed on disease not the impacts on wellbeing; this is therefore an important area for future HAB research.

4.2. Gaps in the evidence base and research priorities

Significant gaps in the evidence base for the association between marine HABs and human health have been demonstrated in this review. Notably, there is a lack of studies of chronic exposure, infrequent use of human biomarkers to confirm or refute the cause of disease, and very little application of formal epidemiological methods – outside of the brevotoxin studies – to estimate the baseline disease burden and associations. Research should now focus on improving techniques for the confirmation of the cause of illness, applying formal epidemiological methods to estimate the baseline disease burden and associations with outcomes, and formally investigating the effects of chronic low-dose exposure to HAB toxins. Improvements in exposure assessment, including at low levels, are required to address the need for a better understanding of dose-response relationships. Formal reporting and surveillance programs, to document and analyse HAB impacts on human health, are also needed and are in general lacking, with few notable exceptions (e.g. US CDC One Health Harmful Algal Bloom System (OHHABS) https://www.cdc.gov/habs/ohhabs.html).

Understanding the burden of disease, through acute and chronic exposure and effects, requires transdisciplinary collaborative work across the environmental/marine sciences, toxicology, and public health with the use of more advanced epidemiological methods and mathematical modelling. The toxic effects of HABs can resemble those of infectious disease, including norovirus, or other chemical exposures, and so are often underdiagnosed (Berdalet et al., 2016). Similarly, as these illnesses can be mild and self-limiting and many healthcare providers are unaware of their existence, there is significant under-reporting to public health authorities; therefore, the evidence presented in this review is likely to represent a small proportion of all actual illness. Estimating the current burden of disease in humans from HABs is vital to understanding and addressing the changes in disease incidence likely to occur as a result of climate and other environmental changes (Backer and Moore, 2010; Gobler et al., 2017; Hallegraeff, 2010; Moore et al., 2008; Van Dolah, 2000).

4.3. Conclusions

This scoping review comprehensively maps the current breadth of evidence describing the association between HABs and observed human health effects. Notable gaps in the evidence base include a lack of formal surveillance and epidemiological studies, inadequate methods of exposure assessment and diagnosis, and lack of studies of chronic exposure. An interdisciplinary focus on determining the true burden disease, following acute and chronic exposures, and including impacts on wellbeing, is required to provide a baseline to facilitate the measurement and the understanding of variations in response to current and predicted climate and other environmental change.

Funding

The research was funded in part by the UK Natural Environment Research Council (NERC) Case PhD in Climate Change, Harmful Algal Blooms and Human Health; the UK National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Environmental Change and Health at the London School of Hygiene and Tropical Medicine in partnership with Public Health England (PHE), and in collaboration with the University of Exeter, University College London, and the Met Office; the UK Medical Research Council (MRC) and UK Natural Environment Research Council (NERC) for the MEDMI Project (https://www.data-mashup.org.uk); and the European Union's Horizon 2020, Grant/ Award Number: 774567 (SOPHIE Projecthttps://sophie2020.eu) and 666773 (BlueHealth Projecthttps://bluehealth2020.eu); UK Global Challenges Research Fund (GCRF) via the United Kingdom Research and Innovation (UKRI) under grant agreement reference NE/P021107/1 to the Blue Communities project; and the UKRI grants OFF-Aqua BB/S004246/, CAMPUS NE/R00675X/11 and the Atlantic Area Interreg project PRIMROSE. This paper contributes to the implementation of the objectives of the IOC-SCOR GlobalHAB international programme (www.globalhab.info) concerning HABs and Human Health.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Alison Bethel provided guidance on scoping review methods and search strategy.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.hal.2020.101901.

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