10 Diseases and Disorders in Fish due to Harmful Algal Blooms

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10.1 Introduction

Sustaining clean and healthy waters for aquaculture and fisheries to meet the growing demand for aquatic foods is a great challenge of the 21st century (Brown *et al*., 2020). Presently, approximately 820 million people (one in nine people in the world) are malnourished (FAO, IFAD, UNICEF, WFP and WHO, 2018) and the human population is projected to rise from 7.6 to 11.2 billion by 2100 (UN, 2017; Brown *et al*., 2020). Aquaculture and fisheries have emerged as a sustainable protein source to improve future food security (FAO, 2018; Gephart *et al*., 2020) providing more than half of the world's seafood (FAO, 2018; Lenzen *et al*., 2021). This additional production will come from the expansion of aquaculture, both into marine and freshwater environments. However, this expansion is under threat by harmful algal blooms (HABs), which are increasing in frequency, severity and toxicity worldwide (Huisman *et al*., 2018; IPCC, 2022; Parmesan *et al*., 2022) and pose health risks to humans and wildlife (Carmichael, 2001; Shahmohamadloo *et al*., 2022b, 2023). The total economic loss due to HABs in aquaculture is estimated at US$8 billion/year globally (Brown *et al*., 2020), which represents 3.2% of the US$250 billion/year revenue (FAO, 2020a).

HABs are the excessive growth of phytoplankton (e.g. microalgae, cyanobacteria) or biomagnification of their toxins in marine, estuarine and freshwater systems (Huisman *et al*., 2018). Several factors induce the formation of HABs. First, eutrophication from anthropogenic activity (e.g. agriculture, aquaculture, wastewater disposal) has dramatically increased nitrogen and phosphorus inputs into aquatic systems dating from the 1960s and remains a global management challenge (Schindler, 1974). Second, rising carbon dioxide (CO_2) concentrations in the atmosphere result in the acidification of marine and freshwater systems (Gobler, 2020). Third, rising temperature (IPCC, 2022) is a keystone parameter of climate change that influences phytoplankton growth rates, photosynthesis, stratification through the water column and nutrient uptake rates, as well as the seasonal window of growth and geographical distribution of HABs (Huisman *et al*., 2018; Trainer *et al*., 2020; Wells *et al*., 2020). Fourth, key functional traits enable the competitive

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 Climate Change on Diseases and Disorders of Finfish in Cage Culture, 3rd Edition (eds P.T.K. Woo and R.P. Subasinghe)
DOI: 10.1079/9781800621640.0010

advantage of some species of phytoplankton, including nitrogen-fixation abilities (Stal, 2009), CO_2-concentrating mechanisms (Verspagen *et al*., 2014), buoyancy (Walsby, 1994), rapid generation times and short life cycles (Govaert *et al*., 2021), and the ability to produce toxic secondary metabolites (Huisman *et al*., 2018).

HABs remain a long-standing concern to aquaculture and fisheries, mainly because their toxins and other indirect effects can kill aquatic organisms (Díaz *et al*., 2019; Brown *et al*., 2020; Lenzen *et al*., 2021; IPCC, 2022; Parmesan *et al*., 2022). These toxins may also have sublethal effects on fish (e.g. non-lethal impacts on phenotype through the release of toxins into water after the lysis of a HAB event), of which associated acute and chronic impacts on fish are still largely unknown. Aquaculture is particularly threatened by HABs compared with wild capture fisheries (Trainer *et al*., 2020) because movement of cultured fish is restricted and they cannot evade HABs (Lenzen *et al*., 2021). Fish-farm operational procedure options for managing HABs are limited and additionally these options are expensive or sacrifice a major part of the yield (Shumway, 1990). For example, a HAB event in the Patagonian fjords of Chile in 2016 led to 40,000 tonnes of fish mortalities estimated at US$800 million in economic losses (Díaz *et al*., 2019) and major social unrest (Trainer *et al*., 2020). The numerous and widespread HAB-driven fish kills, like the event in Chile, demonstrate the need for new insights, management actions and policies that are informed by a mechanistic understanding of the adverse health effects in fish from exposure to HABs.

This chapter focuses on the sublethal (or non-lethal) impacts in fish from exposure to commonly occurring toxins produced by HABs. Although mass-mortality events such as the one described in Chile gained prominent attention worldwide, repeated exposure of animals to sublethal levels may become more common (Huisman *et al*., 2018; Shahmohamadloo *et al*., 2020a). Food recalls connected to tissue accumulation of HAB toxins in fish and poisoning cases in humans and animals are also rising (Svirčev *et al*., 2019; IPCC, 2022; Parmesan *et al*., 2022). Climate change is further projected to increase the mean number of days of a HAB event from 7 days presently to 16–23 days in 2050 and 18–39 days in 2090 (Chapra *et al*., 2017), posing greater health and economic risks to aquaculture and fisheries. For these reasons, the Food and Agriculture Organization of the United Nations (FAO) stressed fish consumption as a primary route of exposure to HAB toxins in humans and called for a deeper understanding of the gene–environment interconnections in HAB species that continue to damage aquatic systems and the global blue economy (FAO, 2020b).

10.2 Diseases and Disorders

This section describes diseases and disorders in finfish resulting from sublethal (or non-lethal) exposure to marine and freshwater toxins produced by HABs, explaining the mechanisms of toxicity, non-clinical effects and clinical signs (with pathological lesions) on fish. The goal of this section is to provide an account of the detection, fate, occurrence and toxicity of HABs in fish, with particular attention on the acute (or short-term) and chronic (or long-term) effects on fish physiology and health.

10.2.1 Microcystins

Microcystins (MCs) are a class of cyclic peptides that are produced by several freshwater cyanobacteria including *Microcystis*, *Dolichospermum*, *Oscillatoria* and *Planktothrix* (Huisman *et al*., 2018) (Fig. 10.1). More than 250 structural variants of MCs have been identified (Bouaïcha *et al*., 2019) and have been detected in every continent worldwide (Harke *et al*., 2016). Most MCs are hydrophilic, resistant to boiling and typically occur at high concentrations in fresh waters (WHO, 2020a), although their fate, occurrence and toxicity depend on a variety of factors including their molecular structure as well as pH, temperature, light intensity and nutrient concentrations (Wicks and Thiel, 1990; Pineda-Mendoza *et al*., 2016; Puddick *et al*., 2016). MCs are also seasonally present in temperate regions although year-round exposure is rare; however, greater risks of year-round exposure to MCs are possible in areas that have high seasonal temperatures favouring HAB persistence (WHO, 2020a).

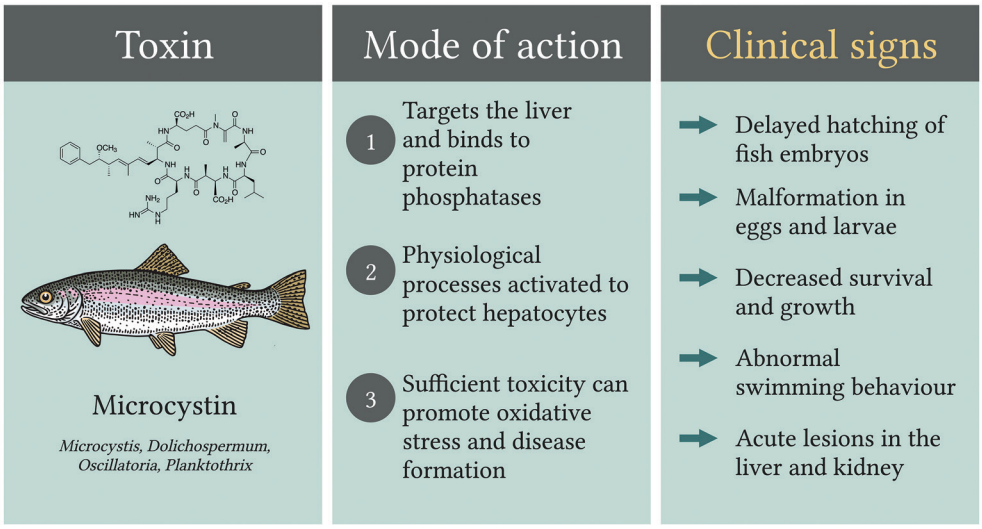

Fig. 10.1. Microcystin mode of action and clinical signs of toxicity in fish species.

Fish encounter MCs through direct contact with contaminated water, feeding, or by accumulation in aquatic food webs. The main route by which MCs are taken up by fish is thought to be through the gastrointestinal (GI) tract via dietary intake (Ibelings and Havens, 2008); however, it is also hypothesized that MCs can pass through fish gills when cells are lysing and releasing their toxins (Tencalla *et al.*, 1994; Xie *et al.*, 2005; Dyble *et al.*, 2011). Recent evidence suggests MCs inside healthy cyanobacterial cells can also affect fish populations, even in the early stages of a bloom's development when biomass is low and the bloom is not yet visible to humans (Shahmohamadloo *et al.*, 2021). Mortality in fish from MC exposure has been experimentally demonstrated by intraperitoneal injection and oral gavage (Tencalla *et al.*, 1994; Kotak *et al.*, 1996; Malbrouck and Kestemont, 2006). However, these routes of MC administration are not realistic and it is more common for fish to experience sublethal effects from balneation (Shahmohamadloo *et al.*, 2022a) and dietary intake (Ibelings and Havens, 2008).

Impact on fish production

The global occurrence of HABs has raised widespread concerns that MCs can have serious economic consequences to aquaculture and fisheries (Zimba *et al.*, 2001). For decades it has been postulated that MCs are one among several stress factors involved in fish kills during HAB events (Ibelings *et al.*, 2005). Harmful, sublethal impacts from MCs are evident in various aquatic organisms (Gene *et al.*, 2019; Shahmohamadloo *et al.*, 2020a,b, 2021, 2022a, 2023) and MC-producing HABs have occurred at record levels in some of the world's largest sources of fresh water (e.g. the Great Lakes, USA, see Michalak *et al.*, 2013; Hellweger *et al.*, 2022). Waterborne MCs can degrade within days to weeks (Edwards *et al.*, 2008), and climate change is projected to increase the mean number of days of a HAB event (Chapra *et al.*, 2017). Consequently, aquaculture and fisheries may be at greater health and economic risks since fish can be exposed to MCs for longer periods of time (Shahmohamadloo *et al.*, 2022a,b, 2023).

Mechanism of toxicity

MC toxicity in fish frequently starts in the liver through irreversible binding with high affinity to protein phosphatases (PP1, PP2A), which are connected to regulatory pathways that are responsible for cell replication, cytoskeletal structure, stress responses and DNA repair (Buratti *et al.*, 2017; WHO, 2020a). Several physiological processes are activated at the cellular level to protect hepatocytes from disease and death including detoxification as well as preventing

cellular apoptosis, cellular proliferation, and possibly cancer (Pearson *et al.*, 2010). Depending on the length of exposure and severity of the HAB, MC toxicity can promote tumour formation, haemorrhage and organ failure (Chorus and Welker, 2021). It is important to note that MCs can also accumulate in other areas including the kidney (Kotak *et al.*, 1996; Shahmohamadloo *et al.*, 2021), which serves an important role of removing toxic compounds, and the edible muscle tissues (Xie *et al.*, 2005; Dyble *et al.*, 2011; Shahmohamadloo *et al.*, 2021, 2022a).

Clinical signs

In early life stages, MC exposure at sublethal concentrations can cause dose-dependent delays in hatching of fish embryos (Oberemm *et al.*, 1999), decreases in survival and growth rate (Oberemm *et al.*, 1999; Palikova *et al.*, 2003), abnormal swimming behaviour (Råbergh *et al.*, 1991), disturbances in reproductive success by causing malformations in eggs and larvae (Ernst *et al.*, 2001), mutagenic effects (Vasconcelos *et al.*, 2013), and histopathological effects including an enlarged and opaque yolk sac, small head, and curved body and tail (Oberemm *et al.*, 1999; Best *et al.*, 2002; Malbrouck and Kestemont, 2006). Liver disease signs of MC toxicity (or hepatotoxicity) typically involve acute lesions including necrosis, apoptosis and haemorrhage in juvenile and adult life stages (Tencalla *et al.*, 1994; Shahmohamadloo *et al.*, 2021; Shartau *et al.*, 2022). Lesions can be either predominantly peribiliary or perivenular (or around the vein). The character of the lesions may also vary depending on the severity of toxicity exposure, ranging from individualized hepatocytes to more basophilic shrunken hepatocytes. Kidney toxicity (or nephrotoxicity) also follows a similar pattern of histopathological alterations including dilatations of Bowman's capsule, vacuolization, necrosis and pyknosis of tubular cells, and oedema (Kotak *et al.*, 1996; Svirčev *et al.*, 2015; Wang *et al.*, 2019). Myopathy has also been found in muscle tissues that may be caused by an indirect downstream effect from MC toxicity in the liver and kidney (Shahmohamadloo *et al.*, 2021).

10.2.2 Nodularins

Nodularins (NODs) are hepatotoxic, cyclic, non-ribosomal pentapeptides that are structurally very similar to MCs and so far have been found mainly to be produced by *Nodularia* (Wiegand and Pflugmacher, 2005; Chorus and Welker, 2021) (Fig. 10.2). These toxins are relatively stable and occur in freshwater, brackish and marine systems (Codd *et al.*, 1999; Pearson *et al.*, 2010). NOD degradation is stimulated by

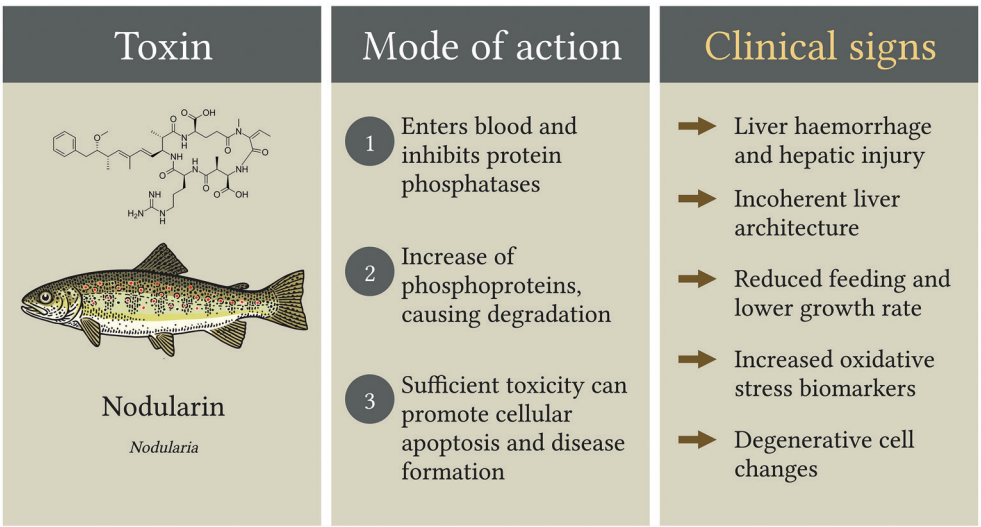

Fig. 10.2. Nodularin mode of action and clinical signs of toxicity in fish species.

ultraviolet (UV) radiation, microbial activity and by binding to copper sulfate (Heresztyn and Nicholson, 1997; Mazur-Marzec *et al.*, 2006; Edwards *et al.*, 2008; Toruńska *et al.*, 2008). NODs are primarily bound to proteins in viable cyanobacterial cells, and less than 20% is generally released into the surrounding water (Chorus and Welker, 2021). Both NODs from within cyanobacteria and in the surrounding water can bioaccumulate in fish (i.e. the gradual accumulation of the toxins in fish from consuming lower trophic-level organisms), thus posing a risk to humans from seafood consumption (Van Buynder *et al.*, 2001; Kankaanpää *et al.*, 2002; Chen *et al.*, 2013), although NODs are not classifiable as carcinogens due to a lack of exposure data in humans (Chen *et al.*, 2013).

Impact on fish production

Massive fish kills of greasy rockcod (*Epinephelus tauvina*), longfin eel (*Anguilla reinhardtii*), yellowfin bream (*Acanthopagrus australis*) and sea mullet (*Mugil cephalus*) have been linked to *Nodularia* blooms in Queensland, Australia (Stewart *et al.*, 2012). Sea mullet in particular contained high concentrations of NODs in livers, with high hepatic levels maintained in fish at 10 months after the HAB event. NODs were also detected in muscles, although concentrations were below human consumption guideline values for adults and children. However, no abnormal behaviours were observed in the sea mullets, raising concerns that NOD exposure can go undetected and toxin exposure via fish consumption can occur if fish are consumed whole.

Mechanism of toxicity

NODs enter the blood via bile acid carriers and are transported preferentially to hepatocytes (Van Apeldoorn *et al.*, 2007). Here, NODs inhibit protein phosphatase (PP1 and PP2A) activity that results in an increase of phosphoproteins, which causes cytoskeleton degradation, loss of cell junctions, disturbances of cell metabolism and cell-cycle control, and oxidative stress (Gulledge *et al.*, 2002; Pearson *et al.*, 2010). NODs are also considered a tumour promoter (Van Apeldoorn *et al.*, 2007). *In vitro* studies further revealed a dose-dependent apoptotic reaction of lymphocytes to NOD exposure, which can cause condensed cytoplasm, DNA fragmentation, and increased reactive oxygen species followed by programmed cell death (Sotton *et al.*, 2015). This suggests NOD exposure can rapidly and strongly affect mitochondrial-mediated pathways in fish cell apoptosis (Sotton *et al.*, 2015).

Clinical signs

In animals NODs can induce lethal liver haemorrhage, hepatic insufficiency, and oxidative stress in the tissues where they accumulate (Eriksson *et al.*, 1988; Van Apeldoorn *et al.*, 2007; Pearson *et al.*, 2010). Information on the effects of NODs on fish is still relatively scarce (Sotton *et al.*, 2015). NOD exposure has been shown to cause slightly incoherent liver architecture, degenerative cell changes and increased liver glutathione *S*-transferase (GST) activity (Vuorinen *et al.*, 2009). Comparing repeated exposure of fish to a single exposure has shown that NODs remain absent in the bile, indicating that they can be rapidly detoxified, and that by-products are quickly disintegrated and excreted (Vuorinen *et al.*, 2009). In early life stages, fish larvae exposed to NODs show reduced feeding and lower growth rates, likely as a result of the metabolic cost of detoxification (Karjalainen *et al.*, 2007). In adult life stages, dietary exposure to NODs does not appear to cause adverse effects on fish swimming activity and behaviour (Kankaanpää *et al.*, 2002); however, complete loss of liver architecture was observed after 1 to 2 days of oral exposure to NODs, although 4 to 8 days later there was partial recovery of hepatocytes (Kankaanpää *et al.*, 2002).

10.2.3 Cylindrospermopsins

Cylindrospermopsins (CYNs) are a class of cyclic guanidine alkaloids that are produced by several freshwater cyanobacteria including *Raphidiopsis* (formerly *Cylindrospermopsis*), *Aphanizomenon*, *Dolichospermum* and *Umezakia* (WHO, 2020b; Chorus and Welker, 2021) (Fig. 10.3). Four different structural variants of CYNs have been identified (Wimmer *et al.*, 2014) and have been detected in surface waters worldwide (Armah *et al.*, 2013), although the organisms producing cyanotoxins can vary with geography (WHO, 2020b). CYNs are chemically stable (Sotton

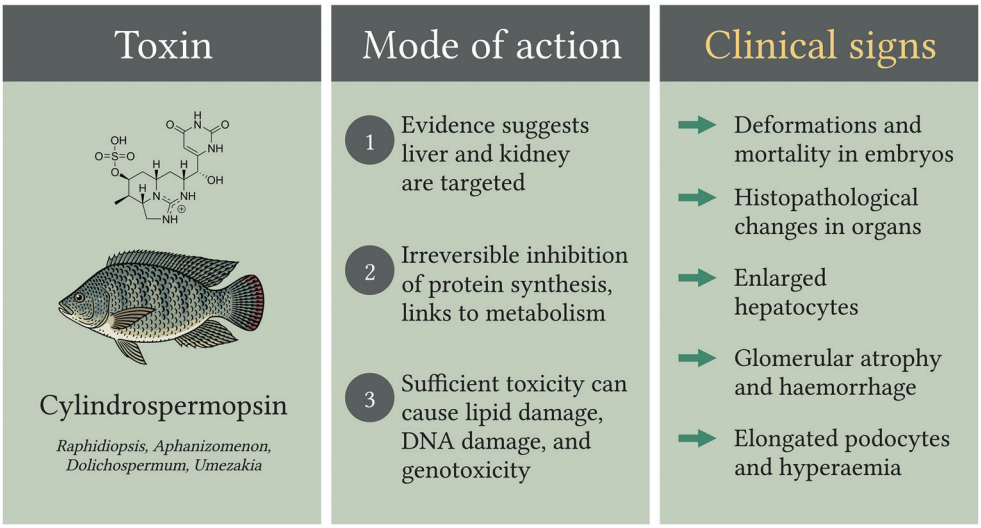

Fig. 10.3. Cylindrospermopsin mode of action and clinical signs of toxicity in fish species.

et al., 2015), hydrophilic, and resistant to boiling and variable pH (Chiswell *et al*., 1999), although temperatures >50°C in combination with alkaline conditions can cause degradation (Chiswell *et al*., 1999; Adamski *et al*., 2016). CYNs typically occur at lower concentrations in fresh water because the cyanobacterial producers rarely form scums with high cell densities (WHO, 2020b; Chorus and Welker, 2021). CYNs also seem to occur more frequently in tropical and subtropical regions; communities that rely on local fish as a primary source of protein, in particular those who consume the entire fish, are at increased risk of exposure to CYNs given the mounting evidence of higher concentrations in fish liver and kidney (WHO, 2020b).

Fish encounter CYNs through direct contact with contaminated water, feeding, uptake through the gills or skin, or by accumulation in aquatic food webs (Guzmán-Guillén *et al*., 2014; WHO, 2020b). Approximately 90% of CYNs in natural surface waters are released from cyanobacteria in the dissolved fraction (Rücker *et al*., 2007) and are available for accumulation by fish via the intestine and gills (Guzmán-Guillén *et al*., 2014).

Impact on fish production

Fish kills to cyprinids (Cyprinidae) have been linked to *Raphidiopsis* blooms recurring in a lake in Aleksandrovac, Serbia (Đorđević *et al*., 2015). Fish kills occurred within 24 h when CYNs reached maximum concentrations of 24 µg/l in the lake, although it is postulated that other factors including uncharacterized toxic metabolites in *Raphidiopsis* may have also contributed to fish mortality (Svirčev *et al*., 2016). Nevertheless, there are increasing concerns that CYN exposure to humans can occur through fish consumption.

Mechanism of toxicity

CYN toxicity in fish is rare and the mechanism has not been elucidated. Preliminary evidence suggests that CYNs target the liver (hepatotoxicity) and kidney (nephrotoxicity) and can reveal magnitude differences in mode of action depending on the length of exposure and concentration of the dose (Guzmán-Guillén *et al*., 2013, 2014; Chorus and Welker, 2021). At low concentrations CYNs cause irreversible inhibition of protein synthesis (Terao *et al*., 1994; Froscio *et al*., 2003), whereas at higher concentrations CYNs interact with metabolites and mechanisms linked to cytochrome P450 which serve an important role in the detoxification of xenobiotics (Froscio *et al*., 2003; Falconer and Humpage, 2006). A concentration-dependent increase in reactive oxygen species, lipid peroxidation and stress responses have also been observed from exposure to CYNs, causing damage to lipids, proteins and DNA (Gutiérrez-Praena *et al*., 2011;

Liebel *et al.*, 2011; Guzmán-Guillén *et al.*, 2013). Evidence further suggests CYNs can cause genotoxicity that is linked to pronounced and prolonged oxidative stress (Guzmán-Guillén *et al.*, 2014). Cellular mechanisms to maintain cell viability and prevent DNA damage are activated to counteract these toxic effects (Liebel *et al.*, 2011). It is important to note that CYNs can also accumulate in other areas including the edible muscle tissues in various fish species (Berry *et al.*, 2012), although this work utilized the enzyme-linked immunoassay (ELISA) which can overestimate toxin concentrations and undermine the confidence in the data on toxin levels in seafood (Testai *et al.*, 2016).

Clinical signs

CYN exposure at sublethal concentrations can cause deformations and rapid mortality in fish embryos after injection of pure toxins (Berry *et al.*, 2009). However, it is suggested that CYNs cannot readily permeate cellular membranes of embryos, and companion studies exposing embryos to waterborne toxins demonstrated no developmental toxicity or mortality (Berry *et al.*, 2009; Sotton *et al.*, 2015). In juvenile and adult life stages, histopathological damages are dose-dependent and primarily occur in the liver and kidney. The liver can show enlarged hepatocytes with central nuclei and cytoplasmic vacuolization and hyalinization, increased hepatocyte nuclear diameter, steatosis and scarce cytoplasmic organelles (Gutiérrez-Praena *et al.*, 2012; Puerto *et al.*, 2012), and the kidney can show glomerular atrophy, dilations of Bowman's capsule, haemorrhage, elongated podocytes and hyperaemia (Gutiérrez-Praena *et al.*, 2012; Puerto *et al.*, 2012). Histopathological damages have also been shown in the heart, gills and intestines as well (Gutiérrez-Praena *et al.*, 2012; Puerto *et al.*, 2012). The clinical signs investigated here are all considered acute (short-term) exposure, and further work is needed to assess chronic (long-term) exposure from CYNs (Sotton *et al.*, 2015).

10.2.4 Anatoxin-a

Anatoxin-a (ATX) is a secondary amine alkaloid produced by a number of cyanobacteria, including *Dolichospermum*, *Aphanizomenon*, *Raphidiopsis*, *Cylindrospermum*, *Oscillatoria*, *Planktothrix* and *Phormidium* (Van Apeldoorn *et al.*, 2007; WHO, 2020c) (Fig. 10.4). It has a worldwide distribution and occurs in freshwater and brackish environments, as well as temperate, tropical and cold climatic regions (WHO, 2020c). ATX is relatively stable in low-light or acidic environments (Stevens and Krieger, 1991; Kaminski *et al.*,

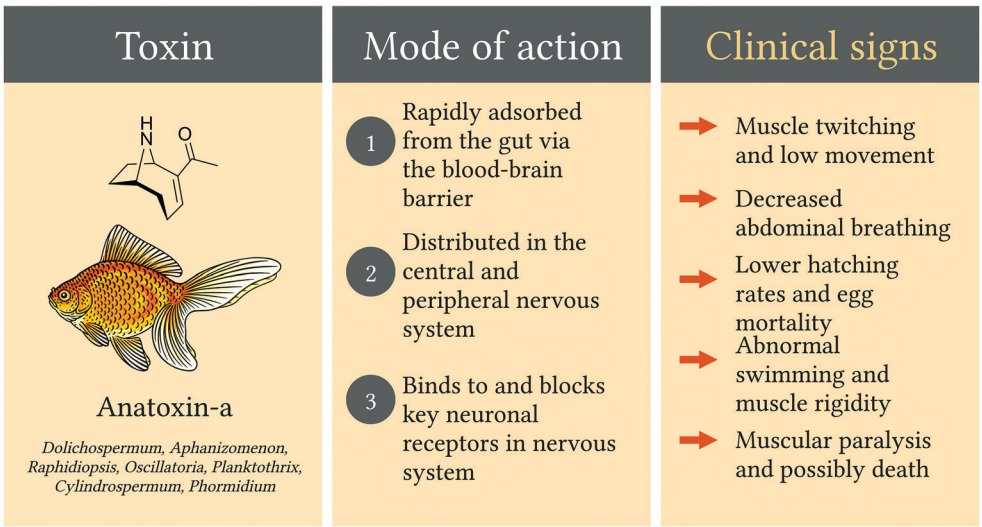

Fig. 10.4. Anatoxin-a mode of action and clinical signs of toxicity in fish species.

2013). However, ATX degradation is promoted by high pH, high temperature, increased light availability, UV-B irradiation and by bacterial activity (Stevens and Krieger, 1991; Rapala *et al*., 1994; Van Apeldoorn *et al*., 2007; Kaminski *et al*., 2013). Under normal conditions, the half-life of ATX ranges roughly between 4 and 14 days (WHO, 2020c). However, during HAB conditions, when phytoplankton growth often causes increases in water pH, half-life may be as short as a few hours (Stevens and Krieger, 1991). ATX is highly soluble in water and is not susceptible to enzymatic hydrolysis (Van Apeldoorn *et al*., 2007; Chorus and Welker, 2021). There is no clear evidence that ATX is released in large amounts from healthy cyanobacterial cells; exposure can thus be mainly expected during bloom lysis (Chorus and Welker, 2021). Limited data suggest that ATX bioaccumulation, and thus risk of human exposure via seafood consumption, is low (Testai *et al*., 2016).

Impact on fish production

Although no known examples of socio-economic impacts on aquaculture and fisheries have been implicated with ATX, the risks of fish kills and animal poisonings are concerning in lakes that form shore scums with high concentrations of ATX (Viaggiu *et al*., 2004).

Mechanism of toxicity

Acute toxicity studies in animals (i.e. mice, trout) show that ATX is rapidly adsorbed from the gut across the blood–brain barrier following oral exposure and is most likely distributed widely in the central and peripheral nervous systems, binding to receptors that play a key role in neuronal communication (Wonnacott and Gallagher, 2006; WHO, 2020c). It is likely that as a result ATX exposure leads to neuromuscular blocking (Carmichael *et al*., 1975; Wonnacott and Gallagher, 2006; Van Apeldoorn *et al*., 2007).

Clinical signs

As a result of neuromuscular blocking, depending on species and dose, ATX can cause death in animals within minutes to hours after exposure as a result of muscular paralysis and consecutive respiratory arrest (Carmichael *et al*., 1975; Van Apeldoorn *et al*., 2007; Chorus and Welker, 2021). Clinical signs of poisoning progress from muscle twitching, decreased movement, abdominal breathing and cyanosis, to convulsions and eventually death (Van Apeldoorn *et al*., 2007). ATX had no acute toxic effect on zebrafish (*Danio rerio*) embryos, although at very high concentrations temporal changes in heart rate could be observed (Oberemm *et al*., 1999). Similarly, exposure to pure ATX was almost harmless to fish in early stages of development, except that larval length was reduced at very high, but ecologically relevant, concentrations of the toxin (Osswald *et al*., 2009). Interestingly, effects of cyanobacterial cell extracts containing ATX were more harmful than when ATX was administered as a pure toxin, but this may also be a result of other toxic substances or bacteria (Osswald *et al*., 2009). The toxic effects of ATX depend on the life stage of fish. Cyanobacterial extracts containing ATX caused higher mortality of common carp (*Cyprinus carpio*) eggs and a lower hatching rate, and the larvae that hatched were smaller in size and had a higher incidence of skeletal malformations (Osswald *et al*., 2009). In juvenile common carp, mortality occurred within 26–29 h, but morphological effects and lesions could not be identified (Osswald *et al*., 2007). Juvenile common carp also showed rapid opercular movement and abnormal swimming compared with controls (Osswald *et al*., 2007). Goldfish (*Carassius auratus*) given oral or intraperitoneal doses of cyanobacterial cell extracts containing ATX showed a latent period of 2 to 4 mins followed by muscle rigidity and death after 12 to 14 mins due to respiratory arrest (Carmichael *et al*., 1975). However, goldfish were not affected when placed directly into algal culture, lyophilized culture or an aqueous medium containing the cell extracts, indicating that the toxin is not readily absorbed across the gill membranes (Carmichael *et al*., 1975).

10.2.5 β-Methylamino-L-alanine

β-Methylamino-L-alanine (BMAA) is a polar and non-lipophilic neurotoxin produced by *Microcystis*, *Nostoc* and other cyanobacteria (Huisman *et al*., 2018) (Fig. 10.5). There are also indications that it may be produced by diatoms and dinoflagellates (Metcalf *et al*., 2021). BMAA has been reported in a variety of aquatic and

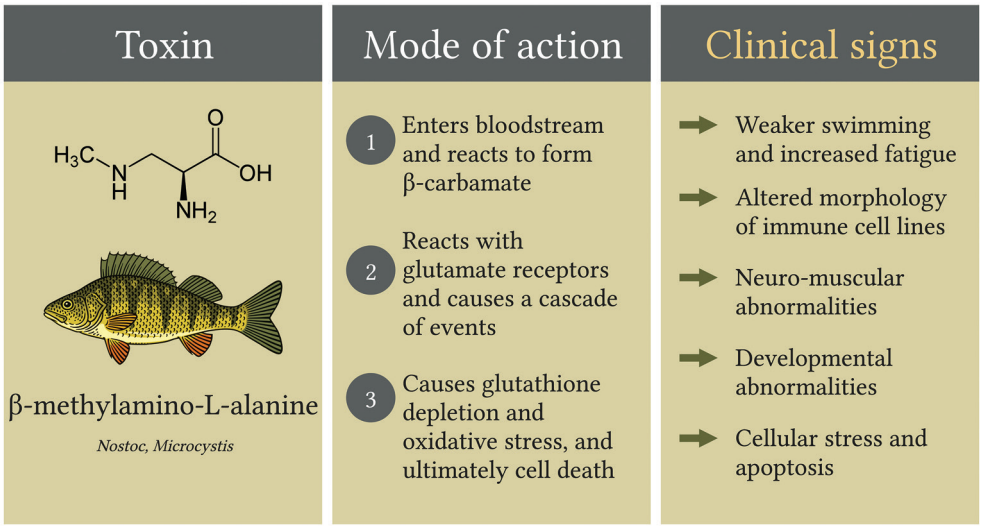

Fig. 10.5. β-Methylamino-L-alanine mode of action and clinical signs of toxicity in fish species.

terrestrial environments worldwide, suggesting that it is ubiquitous (Chiu *et al.*, 2011). In natural environments BMAA concentrations are generally low, but can vary by several orders of magnitude, and there are indications that it may bioaccumulate (Jonasson *et al.*, 2010; Lürling *et al.*, 2011; Metcalf *et al.*, 2021). Since it is also often found in seafood, this may be a pathway to human exposure (Jonasson *et al.*, 2010; Jiang *et al.*, 2014; Salomonsson *et al.*, 2015). Also inhalation of aerosolized BMAA is becoming of increasing concern (Metcalf *et al.*, 2021). However, methodological limitations, reporting and prolific analytical errors limit the conclusions that can be drawn from many existing BMAA studies (Faassen, 2014).

Since BMAA is hydrophilic, fish may be exposed to BMAA in the dissolved fraction, but also when feeding on phytoplankton or zooplankton containing protein-bound BMAA (Jonasson *et al.*, 2010; Lürling *et al.*, 2011; Lance *et al.*, 2018). Although BMAA has been found in fish, they seem to be considerably less contaminated compared with shellfish and aquatic invertebrates (Lance *et al.*, 2018; Metcalf *et al.*, 2021).

Impact on fish production

Although no known examples of socio-economic impacts on aquaculture and fisheries have been implicated with BMAA, exposure is expected to be minimal as BMAA's acute toxicity to fish is relatively low (Lance *et al.*, 2018).

Mechanism of toxicity

BMAA toxicity mechanisms are mainly based on animal models (i.e. rodents, birds and primates). When BMAA is consumed orally it enters the bloodstream and passes the blood–brain barrier where it reacts with bicarbonate (HCO_3^-) to form β-carbamate (Weiss and Choi, 1988; Duncan *et al.*, 1991). There, it can react with several glutamate receptors and cause a cascade of events beginning with: (i) changes in cellular ion concentrations; (ii) depolarization of cells; (iii) permeabilization of cell membranes; and eventually (iv) release of noradrenaline (Chiu *et al.*, 2011 and references therein). BMAA inhibits the cystine/glutamate antiporter (system Xc^-)-mediated cystine uptake, which in turn leads to glutathione depletion, increased oxidative stress and ultimately cell death (Liu *et al.*, 2009; Metcalf *et al.*, 2021). Additionally, BMAA disrupts calcium and mitochondrial homeostasis and can propagate neurotoxic effects between adjacent cells (Metcalf *et al.*, 2021).

Clinical signs

Acute toxic effects on fish are not described, and it is expected that BMAA mainly affects fish via

prolonged or chronic exposure. Behavioural effects of BMAA on fish have been observed, in line with its neurotoxic potential (Purdie *et al.*, 2009). Zebrafish have shorter embryonic nerves, weaker swimming performance and increased fatigue (Powers *et al.*, 2017). Cytotoxic effects of BMAA on fish immune cell lines are known, leading to a reduction in their total count, altered morphology and decreased integrity (Sieroslawska and Rymuszka, 2019). BMAA exposure induces a range of neuromuscular and developmental abnormalities in zebrafish which can be directly related to disruptions to glutamatergic signalling pathways (Purdie *et al.*, 2009). Increased misfolding in proteins leads to protein aggregation, which may lead to cellular stress and increased apoptosis (Sieroslawska and Rymuszka, 2019).

10.2.6 Lipopolysaccharides

Lipopolysaccharides (LPSs) are large, complex molecules first discovered in membranes of Gram-negative bacteria. Also, many marine and freshwater cyanobacterial species are able to produce LPSs including *Anabaena*, *Microcystis*, *Planktothrix*, *Synechococcus*, *Agmenellum* and *Schizothrix* (Codd *et al.*, 1999; Durai *et al.*, 2015) (Fig. 10.6). Generally, LPSs consist of three structural components: (i) a glycan with an *O*-specific polysaccharide that is attached to (ii) a glycolipid anchor lipid A through (iii) a connecting polysaccharide core region (Caroff and Karibian, 2003). The function of LPSs is considered structural, thereby acting as a permeability barrier against antimicrobials but also as an active immune modulator (at low concentrations) inducing resistance to other invading microbes (Bertani and Ruiz, 2018). The structure of LPSs in water can be quite variable (i.e. it is not species and/or strain specific) but this also depends on abiotic factors such as temperature and osmolarity (Moosová *et al.*, 2019).

LPSs are normally excreted in low amounts when bacterial cells divide or are lysed (Caroff and Karibian, 2003). Phytoplanktivorous fish are expected to be exposed to LPSs while feeding, although no earlier studies can confirm this. As a result, fish may mainly encounter LPSs during the senescence of a HAB. Consequently, LPSs are degraded enzymatically by various organisms including mammals, molluscs, moulds and bacteria (Jamieson and Wardlaw, 1989). LPSs also easily form aggregates and complex molecules with a number of other natural products (Nowotny, 1969).

Impact on fish production

Bacterial disease is common and causes large economic losses in aquaculture (Toranzo *et al.*, 2005); however, it remains unclear to what

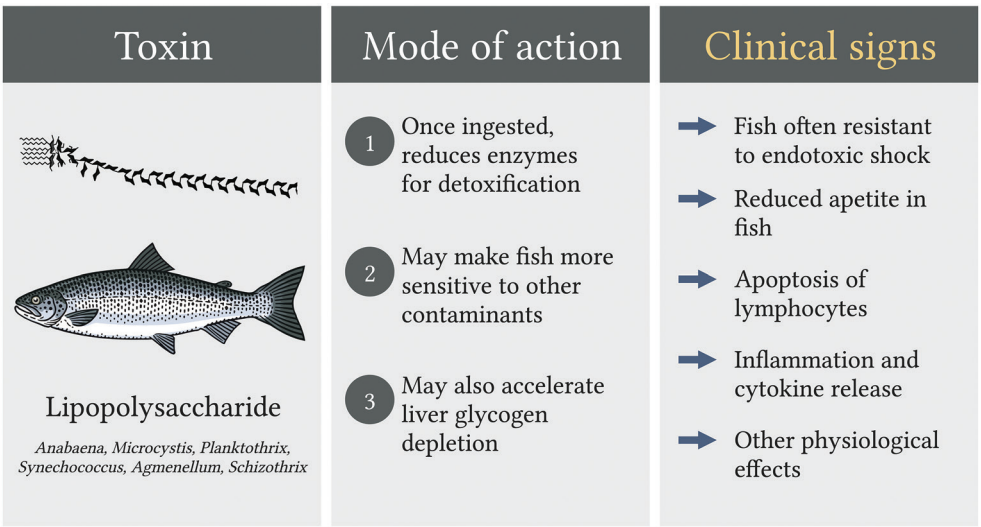

Fig. 10.6. Lipopolysaccharide mode of action and clinical signs of toxicity in fish species.

extent LPSs themselves cause direct fish mortality in aquaculture. Indirectly, there are indications that naturally occurring, low concentrations of LPSs may stimulate the immune response of fish, thus making them more resistant against bacterial infections and resulting in higher survival (Nya and Austin, 2010; Ispir and Dorucu, 2014). LPSs may also potentiate the toxic effects of heavy metals, representing a significant risk to organisms exposed to combinations of LPSs and metals in the environment (Notch *et al.*, 2011).

Mechanism of toxicity

No other natural product is known to elicit such a variety of reactions as endotoxins do when injected into the proper host (Nowotny, 1969). It is, however, well known that the lipid A part of the LPS structure is responsible for both the toxicity and the immune response of fish to LPS (Iliev *et al.*, 2005). At higher doses exposure may be lethal to animals. Fish are relatively resistant to LPSs compared with other animals (Wedemeyer *et al.*, 1969; Sepulcre *et al.*, 2009; Bi *et al.*, 2018). In zebrafish embryos, exposure to purified cyanobacterial LPS can significantly reduce the activity of microsomal and soluble GST, a group of enzymes that are important in detoxification (Best *et al.*, 2002; Jaja-Chimedza *et al.*, 2012). This reduction, however, only occurs in an *in vivo* experiment, whereas *in vitro* preparations of GST show no significant change in GST activity in response to LPS (Best *et al.*, 2002), which may suggest that LPS may modulate *de novo* synthesis of GST (Wang *et al.*, 2006). This reduced detoxification capacity induced by LPS exposure may make organisms more sensitive to co-exposure with other contaminants such as MCs. LPS exposure may also accelerate liver glycogen depletion in salmonids (Wedemeyer *et al.*, 1969).

Clinical signs

The properties of cyanobacterial LPSs are poorly characterized in comparison with those of other heterotrophic bacteria (Durai *et al.*, 2015). Adverse effects from LPS exposure in animals include pyrogenicity, hypotension, neutropenia, intravascular coagulation, hypoferraemia, leucocytosis, leucopenia, sepsis, abortion and shock (Swain *et al.*, 2008). Fish, however, are often resistant to endotoxic shock (Iliev *et al.*, 2005; Swain *et al.*, 2008). At high-dose exposures to fish no clinical signs (i.e. changes in body coloration, abnormalities, behavioural changes) were observed (Wedemeyer *et al.*, 1969; Nayak *et al.*, 2008). Other work indicates that LPSs may reduce the appetite of goldfish and may induce apoptosis of lymphocytes (Volkoff and Peter, 2004; Xiang *et al.*, 2008). Fish may also show pronounced inflammation, cytokine release and other physiological effects in response to LPSs (Swain *et al.*, 2008).

10.2.7 Saxitoxins

Saxitoxins (STXs), also known as paralytic shellfish poisons, are a class of natural alkaloids that are produced in both marine and freshwater systems (Fig. 10.7). In marine waters, STXs are produced by dinoflagellates including *Alexandrium*, *Gymnodinium* and *Pyrodinium*; in fresh water, STXs are produced by cyanobacteria including *Dolichospermum*, *Raphidiopsis*, *Cylindrospermum*, *Aphanizomenon*, *Scytonema*, *Lyngbya*, *Oxynema* and *Planktothrix* (WHO, 2020d; Chorus and Welker, 2021). More than 50 analogues of STXs have been identified (Wiese *et al.*, 2010) and detected in marine waters worldwide (Kleinteich *et al.*, 2013; Murray *et al.*, 2015; Chorus and Welker, 2021), although production of STXs depends on the HAB species (WHO, 2020d). Nearly all STXs are hydrophilic, except those produced by *Lyngbya* in freshwater systems (Chorus and Welker, 2021). Evidence suggests STXs persist in surface waters for 1–2 months (Batoréu *et al.*, 2005) and can remain stable at alkaline pH (>8.5) (Castro *et al.*, 2004) and high temperature (Jellett *et al.*, 1995). STX production is also influenced by several environmental factors including pH, temperature, light intensity, nutrient concentrations and high conductivity (Sivonen and Jones, 1999; Neilan *et al.*, 2008). STXs seem to occur more frequently in warm temperate regions (Laabir *et al.*, 2011; Murray *et al.*, 2015). Consequently, communities should take caution when consuming fish that may have encountered STX producers (Galvão *et al.*, 2009; de Morais Calado *et al.*, 2019; WHO, 2020d).

Fish encounter STXs through direct contact with contaminated water, feeding, uptake after the lysis of a HAB via epithelial absorption, or by accumulation in aquatic food webs (Lefebvre

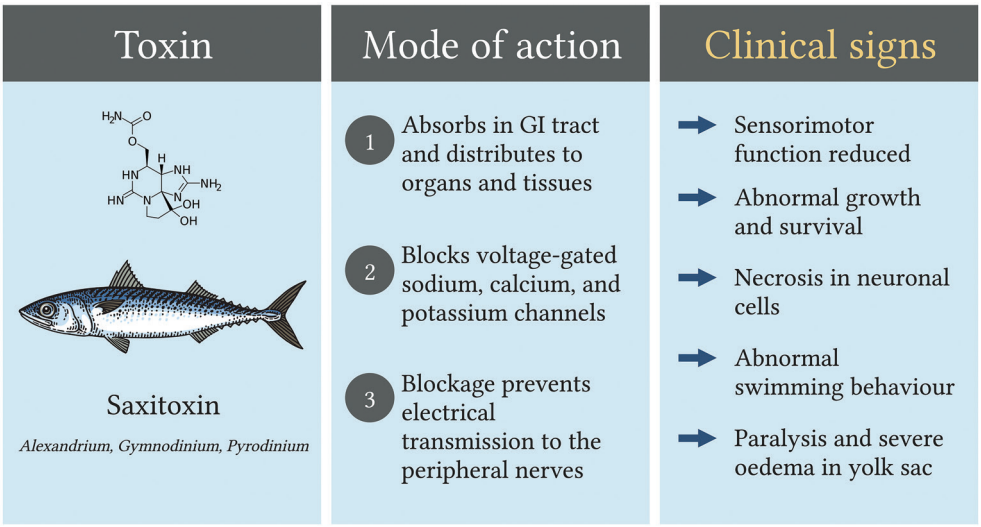

Fig. 10.7. Saxitoxin mode of action and clinical signs of toxicity in fish species.

et al., 2004; Galvão *et al.*, 2009). There is increasing interest to understand the sublethal effects in fish from exposure to STXs at naturally occurring concentrations, in particular for finfish populations that are endangered (Lefebvre *et al.*, 2004; Galvão *et al.*, 2009; Berry *et al.*, 2012; Fire *et al.*, 2012).

Impact on fish production

Fish kills are well documented and coincide with direct consumption of STX-producing dinoflagellates and cyanobacteria or by dietary intake of zooplankton that accumulated STXs (White, 1981; Fire *et al.*, 2012; Moustaka-Gouni *et al.*, 2016; Barrientos *et al.*, 2019). Recent examples include large-scale and multi-year sharp-nose puffer (*Canthigaster rostrata*) mortality events on the southern Caribbean coast of Costa Rica (Barrientos *et al.*, 2019).

Mechanism of toxicity

STX toxicity is well documented in humans from shellfish consumption. However, information for fish is scarce. As highly potent neurotoxins, STXs are readily absorbed in the GI tract and distributed to various organs and tissues including the central nervous system (Pearson *et al.*, 2010; WHO, 2020d; Chorus and Welker, 2021). Once inside the body, STXs are potent blockers of voltage-gated sodium channels in neuronal cells and calcium and potassium channel blockers in cardiac cells (Wang *et al.*, 2003; Su *et al.*, 2004; Testai *et al.*, 2016). Blockage of these channels prevents electrical transmission to the peripheral nerves including skeletal and cardiac muscles (Chorus and Welker, 2021). Neurological symptoms and mortality can occur, in some cases within minutes, depending on the length and severity of STX exposure (FAO, 2004). STXs can also produce free radicals in fish and induce cytotoxicity, genotoxicity and apoptosis in neuronal cells (Banerjee *et al.*, 2021). Generation of reactive oxygen species can further disrupt cellular antioxidants and cause lipid peroxidation and DNA damage in neuronal cells (da Silva *et al.*, 2014). In response, cellular detoxification mechanisms are activated in fish to chelate free radicals and prevent cellular damage (Banerjee *et al.*, 2021). STXs are further metabolized as glucuronides then rapidly excreted in the urine, suggesting glucuronidation as a metabolic pathway of detoxification in humans and animals (Munday *et al.*, 2013; Testai *et al.*, 2016; de Morais Calado *et al.*, 2019). However, glucuronidation can, in some instances, form more potent STX analogues. It is important to note that STXs can also accumulate in the liver of fish and induce oxidative stress and membrane damage (de Assis *et al.*, 2013). STXs can remain in fish muscles for 90 days after exposure, raising concerns

for higher trophic-level species including humans (Galvão *et al.*, 2009; de Morais Calado *et al.*, 2019).

Clinical signs

In early life stages of fish, STX exposure at sublethal concentrations can cause reductions in sensorimotor function and paralysis by 96 h post-fertilization, severe oedema in the yolk sac, eye and pericardium, reduced yolk sac size, and abnormal growth and survival during larval development (Lefebvre *et al.*, 2004; Tian *et al.*, 2014). Morphological and sensorimotor effects in fish can be reversible if transferred into clean water (Lefebvre *et al.*, 2004). In juvenile and adult life stages, necrosis can form in neuronal cells from increased lipid peroxidation levels (da Silva *et al.*, 2014; Banerjee *et al.*, 2021). STX exposure can also alter locomotor activities (i.e. swimming behaviours) in fish at sublethal concentrations (Lopes *et al.*, 2017). Consequently, changes in behaviour can alter the reproductive fitness and predator–prey relationships in fish populations (Banerjee *et al.*, 2021).

10.2.8 Domoic acid

Domoic acid (DA) is a naturally occurring excitotoxin produced by diatoms *Nitzschia*, *Pseudo-nitzschia*, *Amphora*, and the red macro-alga *Chondria* in the bays and coastal areas of marine systems worldwide (Trainer *et al.*, 2012), although recently it has been detected in estuaries as well (Peacock *et al.*, 2018) (Fig. 10.8). Monitoring of DA has intensified globally since its discovery in 1987 after 145 people experienced amnesic shellfish poisoning in Prince Edward Island, Canada (Bates *et al.*, 1989). Since then, numerous incidences of extreme neurodegenerative disorders and lethality have been reported in birds and mammals (Scholin *et al.*, 2000; Bejarano *et al.*, 2008; Trainer *et al.*, 2012). DA is a cyclic amino acid with three carboxylic acid groups that give it high hydrophilicity and polarity (Quilliam *et al.*, 1989). It is known that DA acts as a glutamate agonist (Hampson and Manalo, 1998), mimicking glutamate, the principal neurotransmitter in the central nervous system that sends signals in the brain and throughout the nerves in the body (Landsberg, 2002). DA only has one major analogue and an epimer (epi-DA) that is of toxicological relevance (Ramsdell, 2007). It is also heat stable and not typically destroyed after cooking, but evidence suggests it is light-sensitive and can undergo epimerization with warming (Quilliam, 2003).

Fish encounter DA through direct contact with contaminated water, feeding, or by accumulation in aquatic food webs (Scholin *et al.*, 2000; Lefebvre *et al.*, 2012; Lewitus *et al.*, 2012). Although behavioural toxicity and mortality

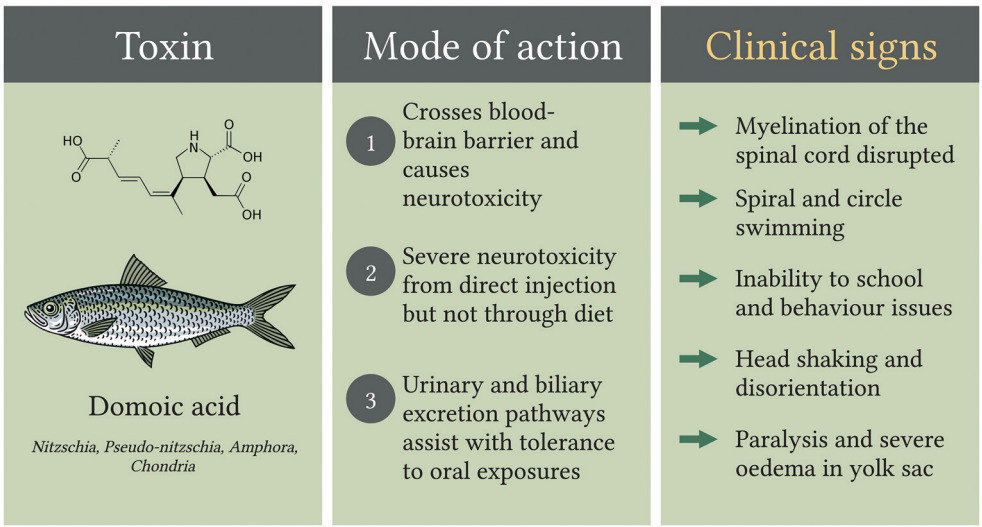

Fig. 10.8. Domoic acid mode of action and clinical signs of toxicity in fish species.

have been observed in seabirds and marine mammals, evidence suggests fish may be tolerant to DA under natural exposure conditions (Lefebvre *et al*., 2012), resulting in high DA content, particularly in planktivorous fish such as sardines and anchovies (Trainer *et al*., 2020). This information is important because under natural conditions DA-producing HABs may not necessarily cause diseases and disorders in fish. However, its sublethal accumulation at high concentrations in fish and subsequent consumption by higher trophic-level species raises concerns for its toxicity at higher levels of the food chain.

Impact on fish production

The global occurrence of HABs has raised widespread concerns that DA can have serious economic consequences to aquaculture and fisheries. DA can poison planktivorous finfish (e.g. anchovies and sardines) and serve as a vector for toxicity and mass mortality to higher trophic-level species including birds, sea mammals and humans (Scholin *et al*., 2000; Lewitus *et al*., 2012; Trainer *et al*., 2012).

Mechanism of toxicity

DA toxicity in fish has been described in detail but its ecologically relevant route of exposure is debated. Toxicological studies administering sublethal concentrations of DA by direct injection resulted in severe neurotoxicity in various fish species (e.g. spinning, head shaking, disorientation, inability to school) and proof DA could cross the blood–brain barrier (Lefebvre *et al*., 2001; Nogueira *et al*., 2010; Panlilio *et al*., 2020, 2021). This raised serious concerns because disoriented and intoxicated fish could be easily preyed upon by higher trophic species. However, other work indicated that direct injection is not an ecologically relevant route of exposure (Lefebvre *et al*., 2012). In fact, a follow-up study found that dietary exposure to DA at naturally occurring concentrations is unlikely to cause behavioural defects in fish or significant impacts on fish populations (Lefebvre *et al*., 2012). This conclusion was reached after recognizing DA shows remarkably similar lethal concentration values and impacts on the central nervous system in fish, birds and mammals that received the toxin by intracoelomic or intraperitoneal injection (Lefebvre *et al*., 2001) yet starkly different responses after oral exposure (Lefebvre *et al*., 2012). A similar study was performed in coho salmon to confirm whether a maximum ecologically relevant dose of DA would accumulate in relevant organs and tissues and cause behavioural changes (Lefebvre *et al*., 2007). No behavioural symptoms were observed, and it was suggested that urinary and biliary excretion pathways assist with fish tolerance to DA oral exposures (Lefebvre *et al*., 2007). These findings highlight the importance of the route of administration of DA in fish, which has implications for its absorption, distribution, metabolism and excretion pathways throughout the body.

Clinical signs

Although developmental defects (e.g. disruption in myelination of the spinal cord) and behavioural signs of excitotoxicity or neurotoxicity (e.g. spiral swimming, circle swimming, upside-down swimming, inability to school) have been found in fish that received direct injection of DA in laboratory studies (Lefebvre *et al*., 2001; Nogueira *et al*., 2010; Panlilio *et al*., 2020, 2021), other work suggests oral exposure of DA in the field will not cause clinical signs in fish (Lefebvre *et al*., 2012). Thus, it is difficult to describe clinical signs for DA since the relevant route of exposure from HABs must be considered.

10.2.9 Ciguatoxins

Ciguatoxins (CTXs) are a class of large polyether compounds that contain 13 to 14 fused rings giving them ladder-like structures (Nicolaou *et al*., 2008; FAO and WHO, 2020) (Fig. 10.9). They are potent neurotoxins that are produced by the epiphytic benthic dinoflagellates *Gambierdiscus* and *Fukuyoa*, which have pantropical distribution (Yong *et al*., 2018; FAO and WHO, 2020). CTXs cause the tropical disease ciguatera fish poisoning in humans, regarded as the most common fish poisoning resulting in >50,000 global cases annually (Traylor and Singhal, 2018). Ciguatera poisoning stems from small herbivorous reef fish grazing on toxic algae and detritus found on the dead corals, which are then preyed upon by larger carnivorous fish (Lehane, 2000;

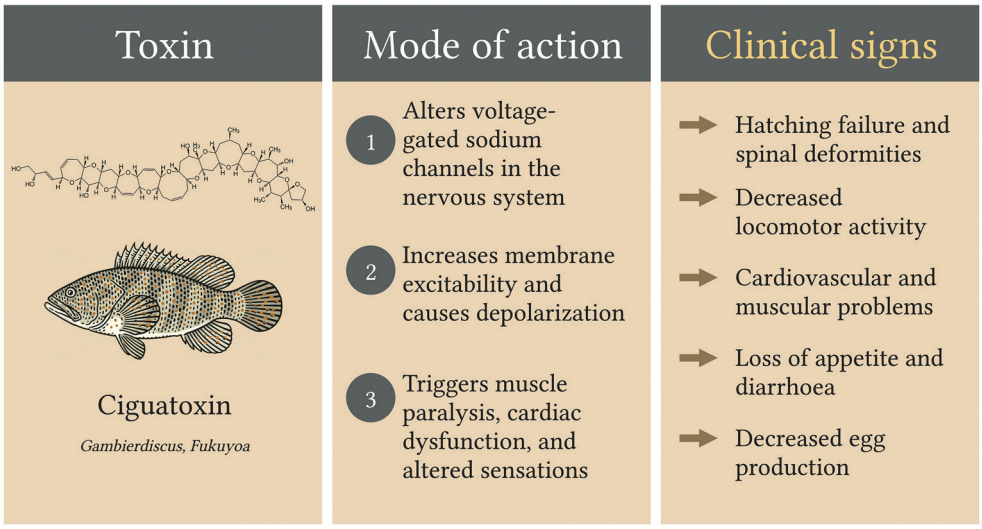

Fig. 10.9. Ciguatoxin mode of action and clinical signs of toxicity in fish species.

FAO, 2004; Ledreux *et al.*, 2014). From here CTXs can accumulate in these predatory reef fish (Lehane and Lewis, 2000) and biomagnify up the food chain, with levels reaching 50–100 times more concentrated in the viscera, liver and gonads (De Fouw *et al.*, 2001).

Ciguatera fish poisoning is of ongoing concern for aquaculture and fisheries because CTXs are odourless, tasteless, lipid-soluble, heat stable and resistant to mild pH fluctuations (Guzmán-Pérez and Park, 2000; FAO and WHO, 2020). CTXs are often present at very low concentrations in seafood (<ppb) and are not destroyed by cooking or freezing, making them difficult to detect in the absence of advanced detection methods (FAO and WHO, 2020). Intoxicated fish taste and smell normal (Lehane, 2000; FAO, 2004), which further complicates human perceptions of seafood safety and HABs toxicity. The impacts of global warming on sea-level rises, precipitation and nutrient inputs into aquatic systems support the growth and expansion of CTX-producing HABs, raising additional concerns for fish populations in marine waters (Gingold *et al.*, 2014; Yong *et al.*, 2018; FAO and WHO, 2020).

Impact on fish production

Over 425 fish species from the pantropics have been impacted by CTXs (Pérez-Arellano *et al.*, 2005). Coral reef fishes are an important seafood for the global market yet frequently contribute to the worldwide occurrence of ciguatera poisoning (FAO and WHO, 2020). Reef fish affected by CTXs include amberjack (*Seriola*), barracuda (Sphyraenidae), grouper (Serranidae), jack (Carangidae spp.), moray eel (Muraenidae spp.), parrotfish (Scaridae spp.), po'ou (Labridae spp.), roi (*Cephalopholis* spp.), snapper (Lutjanidae), surgeonfish (Lutjanidae spp.), trevally (*Caranx* spp.) and wrasse (Labridae spp.) (FDA, 2011).

Mechanism of toxicity

CTX toxicity is thoroughly documented in human poisoning cases from fish consumption. As highly potent neurotoxins, CTXs bind with high affinity and decrease the threshold for opening voltage-gated sodium channels in synapses of the nervous system (Bidard *et al.*, 1984). Open sodium channels increase membrane excitability and cause depolarization, which can trigger muscle paralysis, cardiac dysfunction, and altered sensations from heat and cold (FAO, 2004; Zimmermann *et al.*, 2013; Traylor and Singhal, 2018; FAO and WHO, 2020).

CTX toxicity in fish continues to be elucidated, in part because several congeners of CTXs exist that vary in oxygenation (i.e. oxocene and oxopene CTXs) and may metabolize differently depending on the trophic level of the species (Yogi *et al.*, 2011). For instance, in response to

controlled dietary exposure to toxic *Gambierdiscus polynesiensis* cells, the planktivorous fish mullet (*M. cephalus*) showed rapid accumulation of CTXs in the GI tract and in the bloodstream, followed by rapid distribution into the somatic tissues, with the flesh and intestine carrying the highest proportion of CTXs (Ledreux *et al.*, 2014). High levels of CTXs were also measured in the gills, suggesting the respiratory route may be an important route for accumulation and elimination of CTXs (Ledreux *et al.*, 2014). However, rapid elimination of the oxocene congeners was observed in the blood, bile and liver, while oxopene congeners were retained (Ledreux *et al.*, 2014). Since it is known that carnivorous fish can accumulate oxopene CTXs in their tissues and cause ciguatera poisoning in humans (Yogi *et al.*, 2011), these findings suggest herbivorous fish metabolize oxopene CTXs in a time-dependent manner and these toxins will biomagnify through higher trophic-level species (Ledreux *et al.*, 2014).

Clinical signs

CTX exposure at sublethal concentrations can cause severe embryonic defects including hatching failure, spinal deformities and caudal fin malformation, haemorrhaging and discoloration of the gallbladder, immune dysfunction, decreased locomotor activity and altered muscle physiology (Colman *et al.*, 2004; Mak *et al.*, 2017; Yan *et al.*, 2017). CTXs can also cause cardiovascular, muscular and skeletal abnormalities and significantly reduce the hatching success of finfish (Edmunds *et al.*, 1999). In adults, CTX can cause abnormal behaviours including loss of appetite, diarrhoea, abnormal swimming, decreased egg production, gender-specific differences in reproductive performance and decreased hatching rate of offspring (Yan *et al.*, 2020).

10.2.10 Prymnesins

Prymnesins (PRMs) are potent phycotoxins produced by the haptophyte *Prymnesium parvum*, widely regarded as 'golden or golden-brown alga', which causes surface waters to appear golden and foamy (Manning and La Claire, 2010; Taylor *et al.*, 2021) (Fig. 10.10). This mixotrophic HAB-forming alga recurs in brackish estuarine waters and in mainland freshwater reservoirs across six continents in the northern and southern hemisphere (Guo *et al.*, 1996; Manning and La Claire, 2010; Taylor *et al.*, 2021). Three different PRMs have been identified (Manning and La Claire, 2010; Rasmussen *et al.*, 2016; Binzer *et al.*, 2019), and little is known about their molecular mechanisms of synthesis, mode of transport and biological relevance beyond the

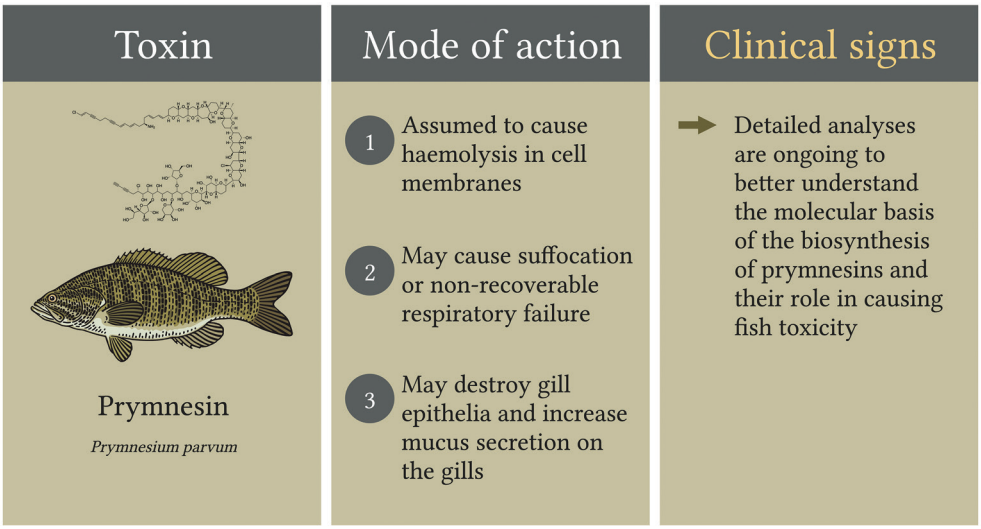

Fig. 10.10. Prymnesin mode of action and clinical signs of toxicity in fish species.

suggestion that they play an important role in the physiology of *P. parvum* (Binzer *et al.*, 2019; Medić *et al.*, 2022). PRMs are remarkably complex molecules with ladder-like, polycyclic ethers that make them potent polyketides with ichthyotic and haemolytic activities (Igarashi *et al.*, 1999). These toxins can have deleterious effects on co-occurring plankton by influencing trophic interactions and altering community structure (Tillmann, 2003; Blossom *et al.*, 2014). The production of PRMs is largely dictated by abiotic factors including moderate-to-low light, temperature ranging between 2 and 30°C, alkaline pH > 8.0, nutrient availability and low salinity (Guo *et al.*, 1996; Larsen *et al.*, 1998; Baker *et al.*, 2007; Manning and La Claire, 2010; Roelke *et al.*, 2016). Recent evidence suggests high irradiance can cause photodegradation of PRMs (Medić *et al.*, 2022), which corresponds with reduced toxicity to aquatic organisms including fish (Taylor *et al.*, 2021).

Fish encounter PRMs through direct contact with contaminated water by uptake through the gills (Baker *et al.*, 2007; Manning and La Claire, 2010; Taylor *et al.*, 2021). It is postulated that PRMs are excreted into surrounding waters during the senescent stages of a HAB and are positively correlated with acute toxicity in fish (Taylor *et al.*, 2020).

Impact on fish production

HABs of *P. parvum* continue to have devastating effects on aquaculture and fisheries around the world by causing fish kills (Brooks *et al.*, 2011; Roelke *et al.*, 2016) hypothesized to be caused by PRMs (Taylor *et al.*, 2021). A profiled example comes from Texas, USA, that reported a fish kill of over 34 million fish, valued at US$13 million and representing important smallmouth bass (*Micropterus dolomieu*), striped bass (*Morone saxatilis*), channel catfish (*Ictalurus punctatus*) and blue catfish (*Ictalurus furcatus*) sport fisheries (Southard *et al.*, 2010).

Mechanism of toxicity

Despite decades of research, it remains debated how *P. parvum* and PRMs affect fish. It is assumed that toxins released by *P. parvum* cause haemolysis (Kozakai *et al.*, 1982), destroy fish gill epithelia (Ulitzur and Shilo, 1966) and increase mucus secretion on the gills (Otterstrøm and Nielsen, 1939), acting as a barrier for oxygen transport (Bergsson *et al.*, 2019). It is believed massive fish kills result from suffocation, or non-recoverable respiratory failure, due to severe internal oxygen deficiency from exposure to *P. parvum* and its toxins (Ulitzur and Shilo, 1966; Svendsen *et al.*, 2018; Bergsson *et al.*, 2019; Medić *et al.*, 2022). Recent evidence of PRMs in the gill tissues of dead fish that encountered a *P. parvum* HAB suggests that PRMs caused toxicity (Wagstaff *et al.*, 2021).

Clinical signs

Detailed analyses of *P. parvum* are ongoing to better understand the molecular basis of the biosynthesis of PRMs and their role in causing fish toxicity. Clinical impacts from direct exposure to PRMs are at best hypothesized until analytical standards can be developed to explain their effects. Advancing our understanding of PRM toxicity in fish is of high interest given the massive socio-economic and ecological damage *P. parvum* HABs cause globally.

10.2.11 Blooms coinciding with fish kills but cannot be pinpointed to a toxin

Other HAB species with an uncharacterized toxin or combinations of toxins are associated with recurring fish kills worldwide. The mechanism of mortality may involve direct physical damage to fish gills. Alternatively, a suite of toxins or toxins acting in combination with environmental stressors, such as elevated temperature, low oxygen, high pH and ammonium, and co-occurrence with pathogens may play a role. Two commonly occurring species – the dinoflagellate, *Karenia* spp., and the raphidophyte, *Chattonella* spp. – have been selected and are discussed below to represent organisms that can cause fish mortalities through mechanisms that are not yet fully elucidated. Other fish-killing raphidophytes that are discussed include members of the genera *Pseudochattonella* (Eckford-Soper and Daugbjerg, 2016), *Chrysochromulina* (Simonsen and Moestrup, 1997), *Cochlodinium* (Tang and Gobler, 2009) and *Heterosigma* (Chang *et al.*, 1990).

Karenia *spp.*

Karenia is a genus of at least 12 species of marine dinoflagellates found in both oceanic and coastal waters worldwide (Glibert *et al*., 2002; Haywood *et al*., 2004; Brand *et al*., 2012). This bloom-forming genus causes mortality of marine life (Oda, 1935; Gunter *et al*., 1948) and huge financial losses for aquaculture (e.g. loss of US$330 million, Fujian Province, China, 2012) (Li *et al*., 2017, 2019). *Karenia brevis* receives the most attention because it plagues coastal waters and releases toxins including brevetoxin, a potent ichthyotoxic neurotoxin that readily absorbs across the gill membranes in fish (Naar *et al*., 2007) and shellfish (Landsberg *et al*., 2009), the latter of which can cause acute neurotoxic shellfish poisoning in humans and mammals. However, the trophic transfer of brevetoxins makes it difficult to pinpoint this toxin as the cause of fish kills observed during *K. brevis* HABs. For instance, evidence suggests fish can safely accumulate brevetoxins by dietary transfer, yet when fish mortality from *K. brevis* occurs, brevetoxins are not detected in their tissues and viscera (Tester *et al*., 2000; Naar *et al*., 2007; Landsberg *et al*., 2009).

The elusive toxicity of *Karenia* can also be due to *Karenia mikimotoi*, a species that does not produce brevetoxins, yet it is implicated in fish kills across Europe and Asia (Li *et al*., 2019). Reason(s) for its toxicity are unclear because its HABs cause fish mortality well before the senescent stages, ruling out hypoxia as the culprit and supporting the possibility that healthy, intact cells are the cause (Li *et al*., 2019). Some hypotheses for the toxicity of *Karenia* include: (i) toxins other than haemolysins and cytotoxins are involved which may break down rapidly once released by *K. mikimotoi*, therefore making it difficult to isolate and study them; (ii) these unknown toxins may reside predominantly near the cell membrane of *K. mikimotoi* at lethal concentrations; or (iii) the toxicity of *K. mikimotoi* might increase due to environmental or grazing pressures (Li *et al*., 2017).

Histopathological changes from *Karenia* toxicity are scarce but have been observed in Atlantic salmon (*Salmo salar*) and rainbow trout (*Oncorhynchus mykiss*). Changes include gill disorders such as acute necrosis, sloughing of epithelial cells, severe oedematous separation of the epithelium from the lamellar branchial vessels, and swelling and pyknosis of branchial vessels (Mitchell and Rodger, 2007; Rodger *et al*., 2011). Additional pathologies include pyknosis of the outer epithelium and sloughing of cells into the lumen of the intestine, and liver necrosis (Mitchell and Rodger, 2007).

Chattonella *spp.*

Chattonella is a genus of five species of marine raphidophytes found in tropical, subtropical and temperate regions worldwide (Edvardsen and Imai, 2006; Imai and Yamaguchi, 2012; Lum *et al*., 2021). *Chattonella* spp. produce 'red tides' and perform diel vertical migration in coastal embayments between 10 and 20 m, which under favourable environmental conditions allows them to take up nutrients, expand and eventually cause massive fish kills (Watanabe *et al*., 1995; Imai and Yamaguchi, 2012). However, mechanisms of toxicity remain unclear beyond the general understanding that suffocation is the ultimate cause of fish mortality.

Chattonella physically clog fish gills and cause mucus excretion (Matsusato and Kobayashi, 1974). Previous theories suggest gill damage is caused by polyunsaturated fatty acids (Shimada *et al*., 1983) or brevetoxins (Endo *et al*., 1992). Other evidence suggests the generation of reactive oxygen species (e.g. superoxides) and their synergistic role with free fatty acids could be responsible for gill tissue injury and mucus production causing fish mortalities (Marshall *et al*., 2003; Shikata *et al*., 2021). More recently, light was reported to be responsible for the haemolytic activity in *Chattonella*, demonstrating a significant relationship between haemolytic activity and chlorophyll c2 biosynthesis, suggesting that haemolytic toxins may be generated during electron/energy transfer through the chlorophyll c2 biosynthesis pathway (Wu *et al*., 2021).

Histopathological changes from *Chattonella* toxicity are scarce but have been observed in northern bluefin tuna (García-Mendoza *et al*., 2018). During a mass-mortality event in 2016 (from May to August), tuna were disoriented, gasping and swimming erratically prior to death that occurred hours after these symptoms manifested (García-Mendoza *et al*., 2018). Histopathology in dead fish revealed abundant mucus and congestion in the gills, characterized by hyperplasia,

fusion of gill filaments and lamellae, telangiectasia, oedemas, increased mucus cells and severe haemorrhage (García-Mendoza *et al.*, 2018).

10.3 Future Implications

10.3.1 Climate change

One obvious impact of climate change will be increasing lake and ocean temperatures which favour stratification and shallowing of mixed-layer depth in many locations, enhanced by greater precipitation and runoff in others (Hays *et al.*, 2005; IPCC, 2022). Increased stratification is expected to worsen the impacts of HABs in coastal seas as rapid depletion of surface nutrients may favour phytoplankton, including harmful algae, with unique nutrient acquisition strategies, including swimming towards nutrient-rich areas and mixotrophy (Smayda, 2010). Many dinoflagellate and raphidophyte HAB species have competitive physiological advantages for survival under stratified conditions, such as the ability to migrate vertically towards nutrients or sunlight required for their photosynthesis using flagella or gas vacuoles (Smayda and Reynolds, 2001). In particular, the raphidophyte HABs have caused massive economic damage to fish farms around the world, and it is believed that their competitive advantage and potentially also their impacts on fish farms will increase under warming conditions (Wells *et al.*, 2020).

Bloom-forming cyanobacteria are believed to benefit from anthropogenically driven changes in lakes (Hellweger *et al.*, 2022). However, cyanobacteria are a very diverse group, consisting of taxa that are morphologically, physiologically and ecologically radically different. Whereas *Microcystis* spp. may indeed benefit from climate-induced changes (Wilhelm *et al.*, 2020), the dominant cyanobacterium that forms blooms in alpine lakes, *Planktothrix rubescens*, actually does less well in warm summers because it is a cold-adapted species (Anneville *et al.*, 2015). 'Blooms like it hot' (Paerl and Huisman, 2008) has been interpreted to mean that cyanobacteria have higher optimal growth temperatures than their eukaryotic competitors, something that was, however, disproved in experiments (Lürling *et al.*, 2013). Still, cyanobacterial growth rate tends to increase with increasing temperature (Huisman *et al.*, 2018). Climate warming, furthermore, has already enhanced stability in the water column, and will select for buoyant cyanobacteria that can use intracellular gas vesicles to float (Walsby, 1994). In particular, colony-forming taxa like *Microcystis* translate their buoyancy into effective diurnal migration through the water column (Ibelings *et al.*, 1991). Additionally, in the absence of mixing, buoyant cyanobacteria float to the lake surface where they may produce thick scums, resulting in extremely high toxin concentrations (Chorus and Welker, 2021). Scum formation, however, should not be seen as adaptive, given the extreme conditions (e.g. high irradiance, strongly elevated temperatures, desiccation) leading to population losses in the scum. A second environmental driver is increasing atmospheric CO_2 concentrations; they are relevant as a result of a long-standing reputation that cyanobacteria do well at high pH and low CO_2, given their capacity to use HCO_3^- (Miller *et al.*, 1990). Again, studies show that the reality is more complex. Cyanobacteria possess a range of carbon-concentrating mechanisms (CCMs), some of which make species like *Microcystis* well adapted to increased CO_2 availability, with the additional consequence of changes in the genetic composition of HABs since different strains possess different CCMs (Sandrini *et al.*, 2016).

10.3.2 Socio-economic impacts

The largest known losses to the marine fish aquaculture industry worldwide have been due to the raphidophytes, including the genera *Chattonella*, *Pseudochattonella*, *Chrysochromulina*, *Heterosigma* and *Cochlodinium*. Together, Norway, Chile, Scotland and Canada generate more than 90% of the global farmed Atlantic salmon, and each of these countries has faced US$ millions in losses due to HABs, primarily because of raphidophyte blooms (Trainer, 2020). This section highlights the major economic losses to marine fish aquaculture worldwide due to HABs while discussing considerations for impacts of HABs to inland aquaculture.

A fish-kill event in Chile occurred in 2016 following a *Pseudochattonella* bloom, resulting in the mortality of more than 39 million salmon,

approximately 15% of Chile's annual production, and an estimated US$800 million loss (Trainer *et al*., 2020; Mardones *et al*., 2021). In 2019, a bloom of *Chrysochromulina leadbeateri* in northern Norway killed ~8 million salmon with a direct value of ~US$93.5 million. A bloom of the raphidophyte, *Cochlodinium*, caused massive losses to aquaculture along the coast of south-east Korea in 1995, resulting in US$60 million loss, with losses occurring almost annually thereafter (Trainer, 2020). Similar impacts on fish aquaculture have been documented in other Asian countries such as Japan and China (Guo *et al*., 2014; Itakura and Imai, 2014), where *Chattonella* causes fish mortality (e.g. 14.2 million fish worth US$90 million were lost in Harima-Nada Sea, Japan in 1972) (Imai and Yamaguchi, 2012). Mass mortalities of farmed fish include Atlantic salmon (*S. salar*), northern bluefin tuna (*Thunnus orientalis*), bluefin tuna (*Thunnus maccoyii*) and yellowtail (*Seriola quinqueradiata*) (Hallegraeff *et al*., 1998; García-Mendoza *et al*., 2018; Lum *et al*., 2021). Recurring threats from the raphidophyte, *Heterosigma akashiwo*, caused extensive devastation (US$2 million to US$6 million per episode) to net-penned salmon in Washington State, USA (Trainer *et al*., 2015). The total direct losses due to lost fish sales have been compounded by the loss of future sales, clean-up costs, losses of tax income and unemployment benefits. Total direct and indirect gross costs of up to US$300 million were estimated for the kill event in Norway (Marthinussen *et al*., 2020). Other costs of HABs arise due to mitigation measures, including aeration, oxygenation, increased monitoring (including artificial intelligence methods), fish treatment, movement of fish to waters with reduced HAB concentrations, and clay dispersal. Consumer price of farmed fish can also decrease due to public perception of risk after a HAB event (Adams *et al*., 2018).

The potential impacts of HABs to inland aquaculture are substantial (Brown *et al*., 2020) but not yet fully described. Inland fisheries provide valuable sources of food for billions of people and jobs for millions of workers around the world (FAO, 2014). Approximately 80% of inland fisheries, including aquaculture operations, are found in the developing world (FAO, 2020a) and are important for reducing poverty in communities including minorities, rural impoverished people and women (Weeratunge *et al*., 2004). However, as both the interest in land-based aquaculture and the occurrence of freshwater HABs are expected to increase around the world, due to anthropogenic activities and climate change, sources of water for inland aquaculture must be carefully considered. Cyanotoxins have been detected in freshwater fish worldwide but rarely at levels that would seriously impact the health of human consumers if guidelines for fish preparation, above all removal of viscera, are followed (Ibelings *et al*., 2021). Because microbes or their toxins have been known to pass through some filtration systems used for aquaculture (King *et al*., 2021), there is a likelihood that HAB toxins pose a threat to inland aquaculture operations through toxin incorporation into fish flesh (Hardy *et al*., 2015) or via fish mortalities.

The global insurance industry has documented an increase over the last decade in HAB-related claims for aquaculture losses, constituting approximately 32% of all claims and totalling US$225 million in 2021 (G. Myer, AXA XL Global Commercial Insurance and Reinsurance, 2022, personal communication), in large part due to expansion of marine fish aquaculture into new locations, entry of new countries into the aquaculture industry and changing environmental conditions due to global warming that promote the occurrence of some HABs. Many insurers are not willing to support aquaculture operations unless plans for effective mitigation of HABs, government involvement in monitoring and warning of HABs, and development of new technologies for HAB prevention are demonstrated by the industry.

Mitigation measures should be planned by establishment of early warning systems that include autonomous underwater vehicle sampling (Free *et al*., 2022) and other automated tools that can be used to identify HABs and their toxins, such as the environmental sample processor (ESP) and imaging flow cytobot (IFCB) (Jochens *et al*., 2010; Anderson *et al*., 2019). The cost–benefits of different mitigation or early warning measures should be assessed in each region as one approach may not be cost-effective in all locations and for all species (Wells *et al*., 2020).

10.3.3 Management and monitoring

When monitoring of HABs, performing risk assessment and management, or deciding on the

management and control of blooms, it is important to consider that HABs respond to different environmental drivers, with nutrient inputs a major contributing factor for freshwater HABs. The control of nutrient loading should be at the basis of freshwater HAB management (Ibelings *et al.*, 2016) with a focus at the level of the catchment. For instance, lakes with a watershed dominated by natural forest, rather than agriculture, rarely suffer from blooms of toxic cyanobacteria (Hamilton *et al.*, 2016). If nutrient control fails to result in preventing HAB formation, lake managers have several methods they can choose from to control the blooms, ranging from artificial lake mixing (Visser *et al.*, 2016) to biomanipulation (Triest *et al.*, 2016) or even use of hydrogen peroxide (Matthijs *et al.*, 2016). However, these measures can support but not replace control of nutrients, tackling both external and internal (resulting from the fish-farming operation itself) eutrophication. In order to prevent the impacts of nutrients on the development of freshwater HABs, there are initiatives exploring the use of artificial ponds using manufactured seawater and recirculating water systems (Timmons and Ebeling, 2013).

For monitoring and management of HABs affecting fish farms in natural lakes or ponds or associated with net-penned fish in nearshore marine systems, not all countries have policies in place to ensure regular monitoring using advanced automated technologies nor have access to the highly sophisticated analytical equipment that is needed, for instance, to do a full survey of the suite of toxins – and their multiple variants – present in HABs. Analysis of toxins in complex matrices of animal tissues is even more complicated (Anaraki *et al.*, 2020) and the scientific literature is full of studies that report unreliable data (see Testai *et al.*, 2016). For the majority of countries, it seems wise to base HABs monitoring on simpler, yet robust and reliable parameters based upon detection of cells, especially when analysis of toxins is not automated or when toxins produced by the HABs of concern have not been characterized. The second edition of the World Health Organization's (WHO) handbook *Toxic Cyanobacteria in Water* (Chorus and Welker, 2021) shows how this may be achieved for freshwater HABs. For instance, when alert levels for chlorophyll a or cyanobacterial biovolume are exceeded, it is likely that guideline values for cyanotoxins in drinking-water or food will be exceeded (see updated guideline values in Chorus and Welker, 2021), confirming that general chlorophyll- or cell-based monitoring can be effective. Even this being the case, the monitoring challenge is to provide sufficient temporal and spatial coverage. While these simpler, cell-based methods are broadly applicable in many parts of the world, progress is also being made using automated, high-frequency monitoring of lakes and oceans, even for phytoplankton (Marcé *et al.*, 2016; Wüest *et al.*, 2021), that allows data to be acquired and reported in real time. Likewise, algorithm development using the latest generation of satellites like Sentinel-2 is promising HAB detection with wide spatial coverage (Sòria-Perpinyà *et al.*, 2020). To safeguard consumers against toxin exposure, the FAO's Hazard Analysis and Critical Control Points (HCAPPs) for food or the WHO's Water Safety Plans (WSPs) for drinking-water provides optimal guidance. HACCPs and WSPs are tools to assess hazards and establish control systems that focus on prevention rather than relying mainly on end-product testing. They systematically assess hazards, risks and control measures at multiple stages (from catchment to consumer).

Similarly, comparable monitoring systems are being developed for live, *in situ* monitoring of HABs upstream of marine fish net-pen aquaculture systems. These use artificial intelligence tools such as the IFCB, an advanced flow cytometry system that is trained through classifier development to detect phytoplankton cells of concern (Jochens *et al.*, 2010; Anderson *et al.*, 2019). In Scotland, RS Aqua salmon farmers are developing early warning systems that use a suite of autonomous sensors developed by the manufacturer Innovasea and deployed upstream from the farm. These sensors detect environmental factors known to be indicative of HABs, such as chlorophyll and oxygen, or physical and chemical conditions potentially conducive to HAB development in the area, such as currents, turbidity and salinity. Data are sent via wireless networks to the cloud where they are analysed by algorithms to establish a HAB risk index which is then relayed to fish farmers in real time. This enables them to take action to minimize the impact of HABs. Another company, OTAQ, is developing an automated deep

learning-based microscopic image analysis system called LPAS (live plankton and algae sensor), which will process live HAB images, in real time, and provide a digital output of the HAB species present in the farm and measure their abundance. Similarly, Grieg Seafoods in Canada, one of the world's largest salmon producers, is using a data collection system integrating collection of environmental data with phytoplankton data in conjunction with machine learning to provide early warning of HABs and prediction of risk. This information is used to determine when additional samples need to be collected or when mitigation strategies need to be triggered, such as platform diffusers used to upwell deep water and push surface water away (Brown, 2021). Fish aquaculture operations without proven monitoring and HABs mitigation strategies will have difficulty finding insurance, resulting in unsustainable losses (Trainer, 2020).

10.3.4 Pathogens

Pathogens infecting HAB species have been known for some time; however, only relatively recently have pathogens been acknowledged for their ecological roles in aquatic ecosystems and for the ecosystem services they provide to humans (Suttle, 2005; Frenken *et al.*, 2017; Paseka *et al.*, 2020). For instance, pathogens may be very effective top-down control agents of HABs (Wilhelm and Suttle, 1999; Frenken *et al.*, 2017) and as such may drive phytoplankton community succession, population subdivision, and even increases in within-species genetic diversity (Sønstebø and Rohrlack, 2011; Gsell *et al.*, 2013). Pathogens may also infect very selectively within host subpopulations and are able to adapt quickly to new or novel host strains (De Bruin *et al.*, 2008; Laundon *et al.*, 2021), thus showing potential for co-evolution.

Although HABs are often considered trophic dead ends, from a pathogen's perspective they are certainly not (Haraldsson *et al.*, 2018). Pathogens may kill a set of cells within a phytoplankton filament or colony, reducing filament length or colony size, and can thus make HABs more edible to herbivores (Frenken *et al.*, 2020; Park *et al.*, 2021). Possibly, subsequent shifts in HAB cell size distribution as a result of these pathogens (Šulčius *et al.*, 2017; Frenken *et al.*, 2020) may negate their physical impact on fish. Fungal parasites infecting inedible HABs nutritionally upgrade HABs into fungal zoospores that are edible to zooplankton (Frenken *et al.*, 2018; Gerphagnon *et al.*, 2019) and support high fitness levels (Kagami *et al.*, 2007). Similarly, viruses released after lysis of phytoplankton hosts may also serve as food to non-host organisms (Welsh *et al.*, 2020). Pathogens thus produce edible free-living stages that may fuel aquatic food webs and ultimately be beneficial to fish populations.

Many HABs can produce toxic metabolites, and the quantity and identity of toxin produced may be affected by pathogens (Rohrlack *et al.*, 2013; Šulčius *et al.*, 2018). When HABs are terminated by pathogens, toxins may be suddenly released into the surrounding water, as may have happened in Lake Erie, where viral infection of HABs contributed to the shutdown of Toledo's water supply when toxin concentrations were too high to be removed by conventional water treatment (Steffen *et al.*, 2017; McKindles *et al.*, 2020). Still, it is important to remember that although the maximum levels of MCs in Toledo's drinking-water (1.2 μg/l for a few days) exceeded the WHO's guideline value for lifetime exposure (1 μg/l), MCs remained well below the guideline value for short-term exposure (12 μg/l for up to 2 weeks). Consequently, these mass-release HAB events of toxins may also affect fish in aquaculture and should be considered when designing HAB control strategies to be used at finfish production sites. In fact, in the derivation of lifetime exposure guideline values, the WHO allocates 80% to drinking-water and 20% to food, although in certain situations this allocation may be incorrect (Ibelings and Chorus, 2007).

Parasites and bacteria may be used to biologically control HABs; however, testing and application have mostly been limited to laboratory studies (Sigee *et al.*, 1999; Pal *et al.*, 2020). Scaling up these approaches will pose a formidable challenge. Moreover, the potential for host–parasite antagonistic co-evolution presumably means that periods of host resistance will occur during which a selected parasite strain may not be effective until a further round of co-evolution restores that parasite (Brockhurst *et al.*, 2007).

10.3.5 The role of the microbiome

The holobiont concept posits that to understand the ecology and evolution of a particular species, its associated microbiota must also be studied (Zilber-Rosenberg and Rosenberg, 2008). While there has been debate about the holobiont concept (Doolittle and Booth, 2017), there is strong evidence across a range of taxa that the associated microbiome strongly influences host physiology (Bäckhed *et al.*, 2005), ecology (Rennison *et al.*, 2019) and evolution (Rudman *et al.*, 2019a; Lim and Bordenstein, 2020). There are two separate, but potentially critical, ways in which microbiomes may shape fish responses to HABs: (i) the effect of algae–microbe symbiosis on the formation and toxicity of blooms; and (ii) the effect of exposure to HABs on the fish microbiome.

The effect of algae–microbe symbiosis on the formation and toxicity of HABs

There is considerable evidence that the microbiome is a critical component in the growth and toxicity of *Microcystis*. Metagenomic sequencing of *Microcystis* colonies has been used to investigate the functional genomics of both cyanobacteria and associated microbes. These data suggest mutualistic interactions and functional complementation that influence a range of characteristics, including nitrogen cycling (Li *et al.*, 2018). Direct study of host-associated microbiomes of *Microcystis aeruginosa* has uncovered patterns of convergence in microbiome function associated with a trade-off between host fitness in low- and high-phosphorus conditions (Jackrel *et al.*, 2019), providing a potential mechanism by which *M. aeruginosa* maintains abundance across a range of phosphorus conditions. Microbiome composition can also influence the outcome of competitive dynamics between toxigenic strains of *Microcystis* and green algae, with microbiome presence an important component of *Microcystis* growth in establishing green algal cultures (Schmidt *et al.*, 2020). This suggests that host–microbiome associations may be a key part of the domination of cyanobacteria over green algae. Finally, a survey across 12 lakes demonstrated that the environmental microbiome in lakes where *M. aeruginosa* is present is remarkably consistent across populations spanning considerable geographical variation (Cook *et al.*, 2020). This pattern is similar to that observed in the genetic diversity of *M. aeruginosa*, suggesting that associations with components of the microbiome may not be geographically limited and could play out similarly across the globe.

The importance of microbiomes in the formation of blooms is best studied in *M. aeruginosa*, however work on other species of harmful algae has also demonstrated an important role of host–microbiome association in the formation of HABs. Both *Alexandrium fundyense* and *Dinophysis acuminata* are associated with unique prokaryotic and eukaryotic microbes that are likely to influence the formation and severity of HABs (Hattenrath-Lehmann and Gobler, 2017). The microbiome composition of *Alexandrium tamarense* and *Cochlodinium polykrikoides* shows substantial variation, even when held across generations in laboratory media, leading authors to suggest that the microbiome may be critical to formation of blooms (Shin *et al.*, 2018). Overall, it is clear that host–microbiome interactions are part of the ecology of many species of harmful algae. Moving forward, larger comparative data sets over space and time, in areas where HABs form and where they do not, are needed to determine whether there are particular host–microbiome associations that underlie the formation and severity of blooms in nature. This information could be critical to understanding why particular algae species become dominant, what causes temporal fluctuations in their abundance and the environmental mechanisms underpinning the production of toxins.

Effect of exposure to HABs on fish microbiomes

Several researchers have examined the effects of HAB exposure on fish microbiomes as a way of understanding the toxic effects of HABs on fish. One such study of the microbiome of Asian sea bass (*Lateolabrax maculatus*) exposed to *Microcystis* bloom and control conditions found no significant effects in microbiome composition or diversity but did uncover some family-level effects in bacterial abundance (Duan *et al.*, 2020). In contrast, zebrafish exposed for short durations to various concentrations of *M. aeruginosa* showed marked shifts in microbiome composition, including increases in the abundance of pathogenic members of the microbiome. The putative

mechanism suggested by the authors was a host inflammatory response in the gut driven by *Microcystis* exposure that resulted in an increase in the proportion of pathogenic bacteria present (Qian *et al*., 2019). Duperron *et al*. (2019) investigated the effects of pure MC and crude metabolite extracts from *M. aeruginosa* to determine whether exposure to either could drive shifts in microbiome composition in medaka (*Oryzias latipes*). They reported shifts associated only with exposures to extracts, suggesting that detrimental effects may come from secondary metabolites and not direct exposure to MCs. These represent some early examples investigating a previously unidentified way in which harmful algae can impact fish. To better integrate this work into a holistic understanding of the lethal and sublethal effects of HABs on fish health, future work that quantifies the effects of any observed shifts in microbiome composition on function and whole-organism growth or performance is key.

10.3.6 Leveraging -omics tools

Genomic tools have demonstrated utility in the study of toxicology, ecology and fisheries biology. There have been several well-cited reviews on the application of -omics data to understanding harmful algae (Anderson *et al*., 2012; McLean, 2013). Hence, the focus in this section is to provide a brief description of some of the data types and the promise of some emerging applications.

Demonstrated utility for understanding HABs and their effects on fish health

Genomic tools have been useful in identifying the species and morphospecies responsible for HAB events (Pérez-Carrascal *et al*., 2019) and in quantifying the prevalence of pathogens (McKindles *et al*., 2021). Transcriptomics can provide links between ecology and physiology in harmful algae, including how gene regulation changes with environmental conditions (Harke and Gobler, 2015) and gene regulation related to toxin production (Zhang *et al*., 2014). Proteomics approaches can provide new data types to document sublethal effects from exposure to harmful algae or toxins (Shahmohamadloo *et al*., 2020b, 2022a). A meta-analysis of the proteomic effects from MC found 39 proteins that showed altered abundances in multiple toxicity studies including evidence that exposure may often induce oxidative stress (Welten *et al*., 2020). Similar non-targeted proteomic approaches have been used to investigate the sublethal effects of several other harmful algae (Rodrigues *et al*., 2016). Metabolomics has been demonstrated to have similar utility as a way of quantifying the effects of exposure on fish (Le Manach *et al*., 2018). Determining the predictability of proteomic and metabolomic responses across disparate fish species and how strongly changes in the proteome relate to animal health and fitness are areas of future work.

Emerging technologies to enhance the study of HABs and their impact on fish health

There are numerous promising applications of -omics tools that are not yet widely used. CRISPR (clustered regularly interspaced short palindromic repeats)-based detection of algal toxins using SHERLOCK (sensitive high-efficiency reporter unLOCKing) can provide a remarkably simple and inexpensive way to test for algal toxins, and detection can greatly enhance the spatial and temporal resolution of HABs both in nature and aquaculture settings. Amplicon sequencing approaches that allow for the genotyping of thousands of individuals quickly and inexpensively (Meek and Larson, 2019) have great promise to improve understanding of the biological basis of HABs. Given the extensive intraspecific genetic variation in harmful algae (Guedes *et al*., 2019; Dick *et al*., 2021; Geffroy *et al*., 2021), information on the spatial and temporal variation in strain presence can be critical to predict the location, severity and duration of blooms. Ionomics, the measurement of the total elemental composition of an organism (Salt *et al*., 2008), has promising applications for understanding sublethal effects in fish (Jeyasingh *et al*., 2017; Rudman *et al*., 2019b) and the stoichiometric flows of nutrients that may sustain (Ipek and Jeyasingh, 2021) or reduce the severity of HABs.

10.3.7 Eco-evolutionary dynamics

The integration between ecology and evolutionary biology has grown considerably stronger in recent decades as empirical data demonstrating

that evolution often occurs over contemporary timescales have mounted (Hairston *et al*., 2005; Rudman *et al*., 2022). In addition, it has become clear that rapid evolution can be a prominent driver of ecological patterns at the population, community and ecosystem levels (Yoshida *et al*., 2003; Bassar *et al*., 2010; Rudman and Schluter, 2016). Rapid evolution is likely pervasive in algal communities, where many species are both clonal and have short generation times. Hence, changes in the relative frequency of clones could profoundly shape the characteristics of algal populations over short timescales. Genetic variation within species (i.e. intraspecific variation) is likely also a factor in the response of fish to exposure to HABs, as a number of studies have demonstrated that genetic variation and adaptation can occur in response to toxic insults (Wu *et al*., 1975; Di Giulio and Clark, 2015; Reid *et al*., 2016; Oziolor *et al*., 2019).

Rapid adaptation as a driver of HABs

Bloom-forming algae typically are rapidly reproducing species with large population sizes, hence the potential for fast evolution is considerable. This includes rapid evolution in toxin production and growth rate that can evolve within a single bloom. The extent of intraspecific genetic variation has been well studied in *Microcystis* where genomic sequencing and phylogenetic reconstruction have revealed some deeply divergent clades within this single species (Pérez-Carrascal *et al*., 2019; Dick *et al*., 2021). There are also notable examples of mutants that complicate some algal control methods, such as copper-tolerant *Microcystis* mutants (García-Villada *et al*., 2004). Considerable intraspecific diversity is present in some other HAB-forming genera, including *Alexandrium*, which exhibits variation in genome size and copy number variation in genes related to toxin production (Geffroy *et al*., 2021). A comparative analysis of interspecific and intraspecific variation across five strains each of *M. aeruginosa* and *Raphidiopsis raciborskii* showed a greater degree of intraspecific variation (Guedes *et al*., 2019). Considerable differences in key functional traits between strains suggest a trade-off between suites of traits (Wilson *et al*., 2006). This creates the potential for rapid clonal sorting that could have profound effects on the conditions over which HABs form, their severity and duration. Yet there has been little research documenting temporal clonal sorting and considerable work is needed to determine whether and how rapid evolution contributes to HABs (Dick *et al*., 2021).

Intraspecific genetic variation and adaptation in response to HABs

When genetic variation is present and selection is strong, adaptation can occur quickly (Barrett and Schluter, 2008). As such, taxa that interact strongly with HABs may undergo rapid adaptation in response. *Daphnia* are noted for their ability to consume *Microcystis* and clones of *Daphnia* vary considerably in their ability to do so (Hairston *et al*., 1999, 2001). The extent of adaptation in *Daphnia* to cyanobacterial HABs has been quantified (Sarnelle and Wilson, 2005; Chislock *et al*., 2019) and *Daphnia*'s ability to remediate the severity of HABs due to rapid evolution has also been measured (Sarnelle, 2007; Chislock *et al*., 2013). The role of intraspecific variation and rapid adaptation in response to other HAB-forming species is not well known, nor is the importance of intraspecific genetic variation in susceptibility to HAB toxins in fish responses. Future work aimed at filling in these gaps is crucial to understanding the full effects of HABs on co-occurring species and in understanding factors that control and limit HABs.

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