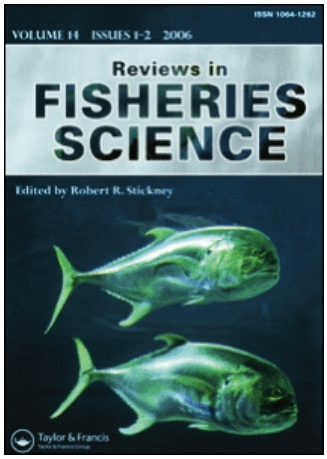

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The Effects of Harmful Algal Blooms on Aquatic Organisms

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ABSTRACT: This review provides an in-depth survey of the recorded incidences in aquatic organisms of mortality and disease events suspected or known to be caused by microalgal or ciliate blooms, their biotoxins, or their harmful mechanisms. Some 200 species of dinoflagellates, diatoms, raphidophytes, prymnesiophytes, silicoflagellates, cilliates, and cyanobacteria are currently known to be, suspected to be, or have the potential to be toxic or harmful to a wide spectrum of organisms. This review summarizes the current information on toxic or harmful microalgal species that affect aquatic organisms (and, when relevant, those that affect terrestrial organisms, including humans), provides an updated list of such species, cites pertinent case

histories, and includes relevant information on harmful or toxic species from freshwater, brackish, and marine ecosystems. It is hoped that this review will provide documentation and reference material suitable for researchers, students, managers, and resource and health professionals alike and that it will stimulate future research questions critical to our understanding of harmful algal bloom (HAB) species and the significant effects they have upon aquatic systems.

KEY WORDS: harmful algal blooms, effects, aquatic organisms, toxins.

I. INTRODUCTION

The recent increase in harmful algal blooms (HABs) in aquatic systems has begun to demonstrate the farreaching effects of these blooms on species interactions, aquatic animal health and population growth, ecology, human health, and ecosystem integrity, as well as on major industries and economies (Hallegraeff, 1993, 1995; Steidinger, 1993; Burkholder, 1998; Van Dolah, 2000). The HABs, about which most is known, tend to be planktonic, often visibly obvious, and quickly lead to acute shellfish poisonings or mass mortalities of aquatic organisms. Some 5000 species of marine microalgae have been described worldwide, and although less than 2% are now known to be harmful or toxic, that percentage appears to be increasing (Smayda, 1990; Hallegraeff, 1993, 1995; Sournia, 1995). The number of aquatic species (including freshwater species) currently considered to be toxic or harmful varies in many summary papers (Sournia, 1995; Hallegraeff, 1995), in some cases because certain groups of aquatic microalgae are ignored. Some of the apparent increase in the number of harmful species can be attributed to the recent inclusion of benthic microalgae and nonphotosynthetic harmful species that do not typically "bloom" and also to the inclusion of species that were previously described as being benign, but that have now been found to be harmful. In freshwater systems, more cases of animals being poisoned by drinking water containing toxic cyanobacteria (blue-green algae) blooms are also being reported (Carmichael, 1996). The increase in the number of species known to be harmful or toxic reflects technological improvements in our ability to accurately identify HAB species and their toxins, as well as enhancements in global monitoring and surveillance. Anthropogenic influences interacting with natural processes have helped to increase the frequency of blooms, and the frequency with which toxic species are transferred globally (Hallegraeff, 1995). These interactions have also brought about an increase in the number of formerly benign species that have become toxic because of altered environmental or genetic adaptations, or both.

Often referenced as one of the first toxic red tides reported to kill fish was that described in the Old Testament of the Bible (Exodus 7:20-21): "all the water of the river was changed into blood. The fish in the river died and the river itself became so polluted that the Egyptians could not drink the water" (Moore 1977; Hallegraeff, 1995). Although this may be a reference to red tide in the river Nile, there is little historical or fossil (?) evidence that red tides occurred often in this region, except possibly for *Alexandrium minutum* blooms in the Nile Delta, Alexandria (Halim, 1960). In addition, if the river was used for drinking this would imply that the incident occurred in freshwater farther upstream than in the Nile Delta; such

upstream areas would not be a common habitat for red tides per se. Others have theorized that the coloration and associated fish kills were perhaps caused by the volcanic discharge of red iron oxide, which is ichthyotoxic, from the Mediterranean into the Nile River (Wilson, 1985). Even this historical example illustrates how inferences are sometimes made about the co-occurrence of a "red tide" and an aquatic mortality event.

One of the earliest reports linking red tides to a fish kill may have been referring to the seasonality of Florida red tides caused by *Karenia brevis* (= *Gymnodinium breve*) Hansen and Moestrup (Daugjberg *et al.*, 2000). Cabeza de Vaca (1542) reported that the Native Americans in the Gulf of Mexico used to refer to the seasons as follows: "none of these peoples reckoned time by the sun or the moon, nor did they keep track of the month or the year. But they do understand and know about the different seasons when fruits ripen or fish die..." In Florida, red tides are most common in the fall and kill thousands of fish, many of which wash up along the beaches.

In North America, before Europeans reached the Pacific coast, Native Americans were reputed to have watched the sea for the streaks of red water during the day and luminescence at night (caused by dinoflagellates). If red streaks or luminescence were seen, the chiefs forbade the taking of mussels and posted guards to warn those not acquainted with the dangers (Carson, 1951, cited in Grindley and Sapeika, 1969). Although Native Americans knew that humans could be poisoned if they consumed toxic shellfish (Kao, 1993, and references therein), early visitors to North America obviously did not. One of the first documented cases concerned the paralytic shellfish poisoning incident involving some of Captain Vancouver's crew in British Columbia, Canada, in 1793. Several of the crew became sick and one crew member died $5^1/_2$ h after consuming toxic mussels (Vancouver, 1798, cited in Kao, 1993). Since that early report and because of threats to public health, a concerted effort has been made to improve the public's knowledge regarding shellfish poisoning events. Shellfish, which can accumulate a variety of biotoxins, continue to pose a public health risk in coastal areas where toxigenic microalgae occur. Today, a wealth of information exists about the short-term human health risks associated with the consumption of toxic shellfish and fish, but many of the potential longer-term effects are not well understood, nor are the effects of exposure to toxins through other routes, for example, via aerosols.

Before the 1980s, most HAB research concerned the species that pose a risk to human health and to other mammals, but the risks posed to aquatic organisms were largely unknown. More research was also needed on two other important subjects: many HAB species are nontoxic to humans or small mammals in bioassays, but they can significantly effect aquatic organisms, and of the microalgal species that produce multiple toxic compounds only a few of the compounds have been tested for toxicity.

Several recent reviews have provided information about particular harmful algal species or groups, and others have detailed the specific groups of organisms affected by HABs or by HABs in particular environments (e.g., Carmichael, 1988; Hallegraeff, 1993; Van Dolah, 2000). However, none of these reviews has addressed the overall current state of knowledge regarding HABs and their effects on aquatic organisms. Because so much progress has been made in this area recently, I felt that it was a good opportunity to provide readers with a summary of the information available.

This review summarizes the current information on toxic or harmful microalgal species that affect aquatic organisms (and when relevant those that affect terrestrial organisms, including humans), provides an updated list of such species, cites pertinent case histories, and includes relevant information on harmful or toxic species from freshwater, brackish, and marine ecosystems. I hope that this review provides documentation and reference material suitable for researchers, students, managers, and resource and health professionals alike, and that it will stimulate future research questions critical to our understanding of HAB species and the significant effects they have on aquatic systems.

II. HARMFUL ALGAL BLOOMS

For the purposes of this review, harmful algal blooms include all aquatic species that are known to produce toxins or to cause harm, directly or indirectly, to aquatic organisms or to terrestrial organisms associated with aquatic habitats or their products. Toxic or harmful species can affect the full spectrum of living systems — from the biochemical to the ecosystem level. For example, at the ecosystem level, high concentrations of cells may interfere with light penetration and influence subsurface communities such as submerged aquatic vegetation. At the biochemical level, secondary metabolites produced by microalgae may interfere with particular cellular processes in the organism, but may not adversely affect the organism as a whole. In this review, species that have demonstrated effects only at the cellular or microbial level will be mentioned only briefly. In terms of species interactions, many microalgae may adversely affect other organisms through, for example, predator-prey relationships, but this aspect is also outside the scope of this review.

The groups of harmful microalgae considered here include the dinoflagellates, diatoms, cyanobacteria, raphidophytes, prymnesiophytes, pelagophytes, and silicoflagellates (Table 1). These microalgae include about 200 species that are known to be, suspected to be, or have the potential to be toxic or harmful to aquatic organisms (Tables 2 to 7). Harmful effects may also extend to terrestrial organisms (including man) that are exposed to aquatic systems or to their products (e.g., shellfish). Although the ciliate *Mesodinium rubrum* is not a microalga, blooms of this species are often associated with harmful effects and thus will be included. For pertinent information on the taxonomy of these groups, numerous references are available (Skulberg *et al.*, 1993; Steidinger, 1996; Hasle and Syvertsen, 1996; Throndsen, 1993; Taylor *et al.*, 1995) and, except where relevant to this review, are not discussed further. The species names used here are those currently accepted in the literature; when it is appropriate, synonyms are provided.

III. ROUTES OF EXPOSURE

Typically, aquatic animals are exposed to toxic or harmful concentrations of algae when planktonic or epibenthic species bloom and dominate the food web, but there are also less obvious means of exposure. The chances of an organism being exposed to a toxic or harmful species depends on the basic ecology of the HAB species, the environmental conditions that are conducive to bloom formation, and the likelihood

TABLE 1. Harmful and toxic aquatic microalgae and ciliates, habitat, toxins or bioactive compound produced, text reference, and action either in the field or experimentally, ? = unknown or suspected, * = only demonstrated experimentally, ** = human toxicity or harmful event, ? = potential for event but not yet documented, *** = parasites. M = marine, B = brackish, F = freshwater. Action listed alphabetically, first by known action in the field, then experimental (as *). Species discussed in the text under toxins/harmful mechanisms (section V) are listed under bolded headings that are listed in the column text reference; NDIT = not discussed in text. Note this is just for the organization of the text, it is not a classification scheme and there are other species that may fit into these categories. Other secondary metabolites that act at the cellular level are produced by many of these species but are not included.**

Species	Habitat	Toxin/ bioactive compound	Text reference	Action	Reference
Dinoflagellates					
Akashiwo sanguinea (= *Gymnodinium sanguineum*)	M	Unknown, reactive oxygen species (ROS)	**Suspected**	?Ichthyotoxic Harmful to molluscs *Antimycotic *Toxic to mice	Cardwell et al. (1979) cited in Shumway (1990), Tindall et al. (1984), Nagai et al. (1990), Kim et al. (1999a), Daugbjerg et al. (2000)
Alexandrium acatenella	M	Saxitoxins (STX)	**Saxitoxins**	Neurotoxic, PSP**	Prakash and Taylor (1966), Schmidt and Loeblich (1979), Cembella et al. (1987)
Alexandrium andersoni	M	STX, NEO	**Saxitoxins**	*Neurotoxic, ?PSP**	Ciminiello et al. (1999, 2000)
Alexandrium angustitabulatum	M	?STX	**Saxitoxins**	?Neurotoxic, ?PSP**	Taylor et al. (1995)
Alexandrium catenella	M	STX, gonyautoxins (GTX1-4), neosaxitoxin (NEO), *N*-sulfo-carbomoyl toxins (B1-2, C1-4), uncharacterized hemolysins	**Saxitoxins** **Uncharacterized**	Neurotoxic, PSP** Toxic to marine organisms	Schantz et al. (1966), Proctor et al. (1975), Onoue et al. (1980, 1981a, 1981b), Boyer et al. (1985a), Ogata and Kodama (1986), Hallegraeff et al. (1991), Kim et al. (1993)
Alexandrium cohorticula	M	STX, GTX	**Saxitoxins**	Neurotoxic, PSP**	Kodama et al. (1988a), Fukuyo et al. (1989)
Alexandrium fundyense	M	STX, NEO, GTX1-4, C1-2, B1	**Saxitoxins**	Neurotoxic, PSP**	White and Maranda (1978), Cembella et al. (1987), Anderson et al. (1990), Bricelj et al. (1990)
Alexandrium lusitanicum	M	GTX1-4	**Saxitoxins**	Neurotoxic, PSP** *Antialgal	Blanco and Campos (1988), Mascarenhas et al. (1995)
Alexandrium minutum	M	GTX1-4, uncharacterized	**Saxitoxins** **Uncharacterized**	Neurotoxic, PSP** Toxic to marine organisms **Artemia* toxicity *Cytotoxic	Hallegraeff (1988), Oshima et al. (1989a), Hallegraeff et al. (1991), Franco et al. (1994), Mascarenhas et al. (1995), Lush and Hallegraeff (1996), Perovic et al. (2000), Chen and Chou (2001)
Alexandrium monilatum	M	Uncharacterized hemolysin	**Hemolysins**	Ichthyotoxic *Neurotoxic *Toxic to polychaetes and molluscs	Gates and Wilson (1960), Ray and Aldrich (1967), Sievers (1969), Clemons et al. (1980b), Bass et al. (1983), Erker et al. (1985)

Alexandrium ostenfeldii	M	GTX2-3, B2, C1-2, spirolides	**Saxitoxins**	Neurotoxic, PSP**	Hansen et al. (1992), Mackenzie et al. (1996b), Cembella et al. (1998, 2000), Hu et al. (2001)
Alexandrium tamarense	M	STX, NEO, GTX1-4, B1, C1, C2, C4, ?tetrodotoxin (TTX), hemolysins, ROS, uncharacterized	**Saxitoxins** **Tetrodotoxin** **Hemolysins** **ROS** **Uncharacterized**	Neurotoxic, PSP** Toxic to marine organisms **Artemia* toxicity *Cytotoxic	Needler (1949), Prakash (1963, 1967), White and Maranda (1978), Oshima and Yasumoto (1979), Betz and Blogoslawski (1981), White (1981b), Anderson et al. (1982), Schantz (1984), Maranda et al. (1985), Ogata and Kodama (1986), Ogata et al. (1987), Cembella et al. (1987, 1988), Lassus et al. (1989), Kodama et al. (1990), Lee et al. (1992), Kim et al. (1993, 1999a), Kodama et al. (1993, 1996), Perovic et al. (2000)
Alexandrium tamiyavanichi	M	STX, GTX1-4, B1, C1-4	**Saxitoxins**	Neurotoxic, PSP**	Oshima et al. (1990), Wisessang et al. (1991)
Amphidinium carterae	M	Hemolysins 1-5	**Hemolysins**	*Antimicrobial *Cytotoxic *Ichthyotoxic	McLaughlin and Provasoli (1957), Iwaka and Sasner (1975), Nakajima et al. (1981), Nagai et al. (1990), Yasumoto (1990), Yasumoto et al. (1990), Quod et al. (1995)
Amphidinium operculatum (= *A. klebsii*)	M	Amphidiniols 1-8 (hemolysins)	**Hemolysins**	*Antimycotic *Ichthyotoxic *Toxic to mice	McLaughlin and Provasoli (1957), Nagai et al. (1990), Nakajima et al. (1981), Satake et al. (1991), Bourdeau et al. (1995), Paul et al. (1995, 1996, 1997)
Ceratium furca	M	?Toxin – uncharacterized	**Water quality**	?Ichthyotoxic/harmful to fish *Neurotoxic	Mijares et al. (1985)
Ceratium hirundinella	F	Nontoxic	**Water quality**	Harmful to fish	Nicholls et al. (1980)
Ceratium spp.	M	Nontoxic	**Water quality**	Harmful to fish and invertebrates	Cho (1979), Mahoney and Steimle (1979), Onoue (1990)
Cochlodinium catenatum	M	Uncharacterized	**Multiple toxins**	Harmful to corals, fish, and shellfish	Miyajima (1934) cited in Grindley and Taylor (1964), Guzmán et al. (1990)

TABLE 1. (continued)

Cochlodinium helix	M	?Nontoxic	**NDIT**	?Harmful to fish	Hallegraeff (1992a)
Cochlodinium polykrikoides (= *C. heterolobatum*, *Cochlodinium type'78*)	M	ROS, hemolysins, uncharacterized sulfated polysaccharides, zinc-bound carbamoyl hydroxy neosaxitoxin	**Multiple toxins**	*Antiviral *Ichthyotoxic *Molluscicidal	Ho and Zubkoff (1979), Onoue and Nozawa (1989b), Yuki and Yoshimatsu (1989), Hasui et al. (1995a), Lee (1996), Kim et al. (1999a)
Coolia monotis	M	Cooliatoxin	**Ciguatoxins**	**Artemia* toxicity *Toxic to mice *Toxic to molluscs	Yasumoto et al. (1987), Tindall et al. (1984), Holmes et al. (1995), Rhodes and Thomas (1997)
Dinophysis acuminata	M	Okadaic acid (OA)	**Okadaic acid**	Gastro-intestinal, DSP** *Tumorigenic	Yasumoto et al. (1985), Lee et al. (1989), Blanco et al. (1995), Vale and Sampayo (2000)
Dinophysis acuta	M	Dinophysistoxins (DTX-1, DTX-2, DTX-2B, DTX-2C), OA, pectenotoxin (PTX-2), PTX-2 seco acids (PTX-2SAs), 7-*epi*-PTX-2SA	**Okadaic acid** **Pectenotoxins**	Gastro-intestinal, DSP** **Artemia* toxicity *Cytotoxic *Tumorigenic	Lee et al. (1989), Jung et al. (1995), James et al. (1997b, 1998, 1999), Daiguji et al. (1998a), Draisci et al. (1998, 2000a), Vale and Sampayo (2000), Suzuki et al. (2001)
Dinophysis caudata	M	Uncharacterized	**NDIT**	?Harmful to fish	Okaichi (1967), Santhanam and Srinivasan (1996)
Dinophysis fortii	M	DTX-1, OA, PTX-2	**Okadaic acid** **Pectenotoxins**	Gastro-intestinal, DSP** **Artemia* toxicity *Cytotoxic *Tumorigenic	Yasumoto et al. (1979b, 1980, 1985), Lee et al. (1989), Jung et al. (1995), Draisci et al. (1996, 2000a), James et al. (1999a), Suzuki and Mitsuya (2001)
Dinophysis miles	M	Unidentified toxins	**NDIT**	?DSP**	Kodama (pers. comm.) in Taylor et al. (1995)
Dinophysis mitra	M	DTX-1	**Okadaic acid**	Gastro-intestinal, DSP** *Tumorigenic	Yasumoto et al. (1985), Lee et al. (1989)
Dinophysis norvegica	M	DTX-1, OA	**Okadaic acid**	Gastro-intestinal, DSP** *Tumorigenic	Lee et al. (1989)
Dinophysis rotundata	M	DTX-1	**Okadaic acid**	Gastro-intestinal, DSP** *Tumorigenic	Lee et al. (1989), Blanco et al. (1995)
Dinophysis tripos	M	DTX-1	**Okadaic acid**	?DSP** *Tumorigenic	Lee et al. (1989)
Gambierdiscus australes	M	Ciguatoxin (CTX)-like, maitotoxin (MTX)-like	**Ciguatoxins**	?Ciguatera**	Chinain et al. (1999)
Gambierdiscus pacificus	M	CTX-like, MTX-like	**Ciguatoxins**	?Ciguatera**	Chinain et al. (1999)
Gambierdiscus polynesiensis	M	CTX-like, MTX-like	**Ciguatoxins**	?Ciguatera**	Chinain et al. (1999)
Gambierdiscus toxicus	M	P-CTX 3C-4A, B (scaritoxin), gambiertoxins, gambieric acids (A-D),	**Ciguatoxins**	Neurotoxic, gastro-intestinal, Ciguatera** *Antimycotic	Yasumoto et al. (1979a, 1987, 1993a, 1993b), Miller et al. (1984), Dickey et al. (1984), Tindall et al. (1984),

		MTX1-3, hemolysins, gambierol		*Artemia toxicity *Cytotoxic *Ichthyotoxic *Lethal to mice	Escalona de Motta et al. (1986), Yokayama et al. (1988), Nagai et al. (1990, 1992, 1993), Terao et al. (1990), Murata et al. (1993), Satake et al. (1993a, 1993b, 1993c, 1997c), Lewis et al. (1994, 2000), Quod et al. (1995), Fairey et al. (1997), Igarashi et al. (1999)
Gambierdiscus yasumotoi	M	Uncharacterized	**NDIT**	?Ciguatera** ** Lethal to mice	Holmes (1998)
Goniodoma pseudogonyaulax	M	Goniodomin	**NDIT**	*Antimycotic *Hepatotoxic *Immunotoxic	Murakami et al. (1988), Terao et al. (1990)
Gonyaulax grindleyi (= *Protoceratium reticulatum*)	M	Yessotoxin (YTX) 45,46,47-trinoryessotoxin	**Yessotoxins**	Harmful/toxic to marine organisms *Antimycotic *Cytotoxic *Lethal to mice	Grindley and Nel (1970), Murata et al. (1987), Takahashi et al. (1996), Satake et al. (1997a), Ogino et al. (1997), Satake et al. (1999), Draisci et al. (2000a), de la Rosa et al. (2001)
Gonyaulax polygramma	M	Not suspected	**Water quality**	Harmful to marine organisms	Lam (1988)
Gonyaulax spinifera	M	Not suspected	**Water quality**	Harmful to marine organisms	Forbes (1990)
Gymnodinium aureolum (= *Gyrodinium aureolum*, *Gyrodinium* cf. *aureolum*)	M	?Hemolysins	**Hemolysins**	?Ichthyotoxic Harmful to marine invertebrates	Mahoney et al. (1990), Heinig and Campbell (1992)
Gymnodinium catenatum	M	STX, NEO, trace GTX2-3, GTX4, B1-2, C1-4	**Saxitoxins**	Neurotoxic, PSP** *Artemia* toxicity	Oshima et al. (1987, 1990, 1993a, 1993b), Anderson et al. (1989), Lush and Hallegraeff (1996)
Gymnodinium pulchellum	M	Uncharacterized, hemolysin, hemagglutinin	**Uncharacterized**	Ichthyotoxic *Neurotoxic ?Respiratory irritation** ?Harmful to shellfish	Onoue and Nozawa (1989a), Steidinger et al. (1998b)
Gymnodinium sp.	M	Polysaccharide	**NDIT**	*Cytotoxic	Hasui et al. (1995b, 1996), Sogawa et al. (1998)
Gyrodinium corsicum	M	Uncharacterized	**Uncharacterized**	Ichthyotoxic	Paulmier et al. (1995)
Gyrodinium sp.	M	Unknown	**Uncharacterized**	Ichthyotoxic	Kim et al. (1995)

TABLE 1. (continued)

Gyrodinium spirale	M	Unknown	**NDIT**	?Poor water quality or harmful to marine fauna	Lassus and Belin (1991)
Heterocapsa circularisquama	M	Uncharacterized, hemolysins	**Uncharacterized Hemolysins**	Toxic to molluscs *Antialgal *Antiprotozoal *Toxic to rotifers	Matsuyama et al. (1995), Uchida et al. (1995), Kamiyama (1997), Kamiyama and Arima (1997), Kim et al. (2000c), Oda et al. (2001)
Karenia brevis (= *Gymnodinium breve*)	M	Brevetoxins (PbTx1-3, PbTx5-10) (hemolysins)	**Brevetoxins**	Neurotoxic, NSP** Respiratory irritation** Ichthyotoxic Toxic to marine organisms **Artemia* toxicity	Woodcock (1948), McFarren et al. (1965), Paster and Abbott (1969), Kim and Padilla (1976, 1977), Baden et al. (1979), Roberts et al. (1979), Medlyn (1980), Lin et al. (1981), Baden and Mende (1982), Chou et al. (1985), Baden (1989), Schulman et al. (1990), Daugbjerg et al. (2000)
Karenia brevisulcata (= *Gymnodinium brevisulcatum*)	M	Uncharacterized	**Uncharacterized**	Antialgal Harmful to invertebrates Harmful to macroalgae Ichthyotoxic Respiratory irritation** **Artemia* toxicity	Chang (1999a, 1999b), Daugbjerg et al. (2000)
Karenia digitata	M	Uncharacterized	**Uncharacterized**	Ichthyotoxic	Baba et al. (1997), Dickman and Tang (1999), Yang and Hodgkiss (1999), Dickman (2000)Yang et al. (2000)
Karenia mikimotoi (= *Gymnodinium mikimotoi*) (= *G. nagasakiense*) and as *Gyrodinium aureolum* and *G.* cf. *nagasakiense*	M	Hemolysins, ?ROS	**Hemolysins**	Ichthyotoxic Toxic to invertebrates *Harmful to zooplankton	Abe and Hirayama (1979), Hirayama (1978) in Iizuka (1979), Gentien and Arzul (1990), Yasumoto et al. (1990), Arzul et al. (1994), Gentien (1998), Parrish et al. (1998), Daugbjerg et al. (2000), Hansen et al. (2000)
Karenia cf. *mikimotoi* (= *Gymnodinium* cf. *mikimotoi*)	M	Hemolysins	**Hemolysins**	Ichthyotoxic *Antialgal	Arzul et al. (1995a), Sola et al. (1999)
Karenia sp.	M	Gymnodimine (Gym), gymnodimine B	**Gymnodimine**	Ichthyotoxic ?Toxic to other marine organisms *Ichthyotoxic *Molluscidal *Neurotoxic	Seki et al. (1995, 1996), Mackenzie et al. (1996a), Stewart et al. (1997), Miles et al. (2000), Heil et al. (2001), Haywood and Steidinger (pers. comms.)
Karenia sp.	M	Brevetoxin-like?	**Uncharacterized**	NSP-like	Haywood et al. (1996), Haywood (pers. comm.)
Karlodinium micrum (= *Gymnodinium galatheanum*)	M	Unknown	**Uncharacterized**	Harmful to fish *Harmful to molluscs?	Nielsen and Strømgren (1991), Nielsen (1993), Daugbjerg et al. (2000)
Karlodinium veneficum (= *Gymnodinium veneficum*)	M	Unidentified	**Uncharacterized**	*Ichthyotoxic *Toxic to zooplankton	Marshall and Orr (1953), Abbott and Ballantine (1957), Ballantine and

					Abbott (1957), Daugbjerg et al. (2000)
Lingulodinium polyedrum (= *Gonyaulax polyedra*)	M	YTX, homoyessotoxin (homoYTX)	**Yessotoxins**	Harmful/toxic to marine organisms *Neurotoxic	Schradie and Bliss (1962), Tindall et al. (1984), Bruno et al. (1990), Satake et al. (1997b), Tubaro et al. (1998), Draisci et al. (1999, 2000a)
Noctiluca scintillans (= *N. miliaris*)	M	Water quality - ammonia	**Water quality** **Disease**	Harmful to fish	Okaichi and Nishio (1976)
Ostreopsis heptagona	M	Uncharacterized	**Ciguatoxins**	?Ciguatera**	Norris et al. (1985)
Ostreopsis lenticularis	M	Ostreotoxin (OTX), hemolysins	**Ciguatoxins**	?Ciguatera** *Neurotoxin	Fukuyo (1981), Carlson and Tindall (1985), Escalona de Motta et al. (1986), Tindall et al. (1987, 1990), Mercado et al. (1995), Rivera Rentas et al. (1995), Carballeira et al. (1998), Wright and Cembella (1998)
Ostreopsis mascarenensis	M	Uncharacterized	**Ciguatoxins**	?Ciguatera**	Quod (1994)
Ostreopsis ovata	M	Uncharacterized hemolysin	**Ciguatoxins**	?Ciguatera**	Fukuyo (1981), Nakajima et al. (1981), Yasumoto et al. (1987)
Ostreopsis siamensis	M	Ostreocins (palytoxin analogs), uncharacterized hemolysin	**Ciguatoxins**	?Ciguatera** *Cytotoxic	Fukuyo (1981), Nakajima et al. (1981), Usami et al. (1995), Wright and Cembella (1998)
Peridinium polonicum	F	Glenodinine, polonicumtoxins	**Uncharacterized**	Ichthyotoxic	Hashimoto (1968), Oshima et al. (1989b)
Pfiesteria piscicida	M, B	Uncharacterized – putative pPfTx	**Uncharacterized**	Ichthyotoxic Human health** Harmful to invertebrates *Cytotoxic	Burkholder et al. (1992, 1995, 1999, 2001), Burkholder and Glasgow (1995, 1997), Glasgow et al. (1995), Fairey et al. (1999), Kimm-Brinson et al. (2001)
Pfiesteria shumwayae	M, B	Uncharacterized	**Uncharacterized**	Ichthyotoxic ?Human health	Glasgow et al. (2001)
Pfiesteria sp.	M	Unknown	**Uncharacterized**	?*Ichthyotoxic	Landsberg et al. (1994)
Prorocentrum arenarium	M	OA	**Okadaic acid**	?Ciguatera** *?Tumorigenic	Ten-Hage et al. (2000a)
Prorocentrum balticum	M	Not suspected	**NDIT**	Harmful to fish	Silva (1953), Paredes (1962) cited in Grindley and Taylor (1964), ICES (1998)

TABLE 1. (continued)

Prorocentrum belizeanum	M	OA	**Okadaic acid** **Ciguatoxins**	?Ciguatera** *?Tumorigenic	Morton et al. (1998)
Prorocentrum borbonicum	M	Borbotoxins	**Ciguatoxins**	?Ciguatera *?Tumorigenic *Neurotoxic	Turquet et al. (1998), Ten-Hage et al. (1998, 2000b, 2002)
Prorocentrum concavum	M	OA	**Okadaic acid** **Ciguatoxins**	?Ciguatera* * *Ichthyotoxic *?Tumorigenic	Tindall et al. (1984), Dickey et al. (1990), Hu et al. (1993), Quod et al. (1995)
Prorocentrum faustiae	M	OA, DTX-1	**Okadaic acid** **Ciguatoxins**	?Ciguatera** *?Tumorigenic	Morton (1998)
Prorocentrum hoffmannianum	M	OA, hoffmanniolide	**Okadaic acid** **Ciguatoxins**	?Ciguatera** *?Tumorigenic	Aikman et al. (1993), Morton and Bomber (1994), Morton et al. (1994), Hu et al. (1999)
Prorocentrum lima	M	OA, OA-diol esters (OA-DE1, OA-DE2), prorocentrolide, DTX1-4, DTX-1B, 7-deoxy-okadaic acid	**Okadaic acid** **Ciguatoxins**	Gastro-intestinal, DSP** ?Ciguatera** **Artemia* toxicity *Cytotoxic *Ichthyotoxic *Tumorigenic	Murakami et al. (1982), Torigoe et al. (1988), Cembella (1989), Marr et al. (1992), Jackson et al. (1993), Hu et al. (1993, 1995b), Norte et al. (1994), Demaret et al. (1995), Quod et al. (1995), Ammar et al. (1996), Quilliam et al. (1996), Sechet et al. (1998), James et al. (2000), Holmes et al. (2001)
Prorocentrum maculosum	M	OA, OA-DE3, OA-DE4, DTX-5a, DTX-5b, prorocentrolide B	**Okadaic acid** **Ciguatoxins**	?Ciguatera** *?Tumorigenic	Hu et al. (1992, 1995a, 1996), Wright and Cembella (1998)
Prorocentrum mexicanum	M	Toxins – uncharacterized	**Okadaic acid**	?Ciguatera** *Toxic to mice	Tindall et al. (1984)
Prorocentrum micans	M	Unidentified, ROS	**Suspected** **Water quality**	Suspect in human shellfish poisoning ?Harmful to marine organisms *Antialgal *Harmful to fish	Pinto and Silva (1956), Uchida (1977), Lembeye and Campodónico (1984), Clement and Lembeye (1993), Kim et al. (1999a)
Prorocentrum minimum	M	?Venerupin, uncharacterized, prorocentrin, β-diketone	**Uncharacterized**	?VSP** Harmful to marine organisms *Neurotoxic	Nakazima (1965a, 1965b, 1965c, 1968), Okaichi and Imatomi 1979, Andersen et al. (1980), Trick et al. (1983), Luckenbach et al. (1993), Wikfors and Smolowitz (1993, 1995), Wikfors et al. (1993), Grzebyk et al. (1997), Denardou-Queneherve et al. (1999)

Prorocentrum sp.	M	Uncharacterized	**Uncharacterized**	Harmful to shellfish	Yomgjia et al. (1995)
Protoperidinium crassipes	M	Azaspiracids (AZ, AZ-2, and AZ-3 in shellfish)	**Azaspiracid**	AZP** *Toxic to mice	Ito et al. (1998, 2000), Satake et al. (1998b, 1998c), Ofuji et al. (1999a, 1999b), Draisci et al. (2000b), James et al. (2000), Gribble (2002)
Pyrodinium bahamense var. *compressum*	M	STX, NEO, B1-B2	**Saxitoxins**	Neurotoxic, PSP** Harmful/toxic? to marine organisms	Maclean (1973, 1979); Harada et al. (1982, 1983), Oshima et al. (1984, 1987, 1990), Rosales-Loessener et al. (1989), Usup et al. (1994, 1995), Orellana-Cepeda et al. (1998)
Scrippsiella trochoidea	M	Not suspected	**NDIT**	?Harmful to marine organisms	Whitelegge (1891)
***Amyloodinium ocellatum*	M	Not suspected	**Disease**	Harmful to fish	Brown (1934); Paperna (1980); Noga et al. (1991); Landsberg et al. (1994, 1996)
***Hematodinium* sp.	M	Not suspected	**Disease**	Harmful to crustacea	Newman (1975); Meyers et al. (1987); Messick (1994)
***Piscinoodinium* sp.	M	Not suspected	**Disease**	Harmful to fish	Shaharom-Harrison et al. (1990), Ferraz and Sommerville (1998)
Diatoms					
Amphora coffeaeiformis	M	Domoic acid (DA)	**Domoic acid**	?Neurotoxic, ?ASP**	Maranda et al. (1990)
Cerataulina pelagica	M	Unidentified	**NDIT**	Harmful to fish	Taylor et al. (1985)
Chaetoceros concavicornis	M	Barbs/setae	**Mechanical** **Disease**	Harmful to fish and invertebrates	Bell (1961), Yang and Albright (1992), 1994), Albright et al. (1993), Rensel (1993)
Chaetoceros convolutus	M	Barbs/setae	**Mechanical** **Disease**	Harmful to fish and invertebrates	Yang and Albright (1992, 1994), Albright et al. (1993), Rensel (1993), Tester and Mahoney (1995)
Chaetoceros curvisetus	M	Unidentified	**NDIT**	*Harmful to copepods	Ban et al. (1997)
Chaetoceros debilis	M	Unidentified	**NDIT**	?Harmful to fish *Harmful to copepods	Bruno et al. (1989), Ban et al. (1997)
Chaetoceros difficilis	M	Unidentified	**NDIT**	*Harmful to copepods	Ban et al. (1997)
Chaetoceros gracilis	M	Unidentified	**NDIT**	*Harmful to copepods	Ban et al. (1997)
Chaetoceros socialis	M	Barbs/setae	**Mechanical**	Harmful to fish	ICES (2000)
Chaetoceros wighami	M	Barbs/setae	**Mechanical**	Harmful to fish	Bruno et al. (1989), Johnson (1988)
Corethron sp.	M	Barbs/spines	**Mechanical**	Harmful to fish	Speare et al. (1989)

TABLE 1. (continued)

Coscinodiscus spp.	M	Oily film	**NDIT**	Harmful to birds	Tåning (1951) and Grontved (1952) cited in Hasle and Fryxell (1995)
Cylindrotheca closterium	M	Unidentified	**NDIT**	*Harmful to copepods	Ban et al. (1997)
Ditylum brightwellii	M	Unidentified	**NDIT**	*Harmful to copepods	Ban et al. (1997)
Leptocylindrus minimus	M	Spines	**Mechanical**	Harmful to fish	Clement and Lembeye (1993)
Navicula cryptocephala	M	Unidentified	**NDIT**	*Harmful to copepods	Ban et al. (1997)
Nitzschia navis-varingica	M	DA	**Domoic acid**	?Neurotoxic, ?ASP**	Kotaki et al. (2000)
Nitzschia palea	M	Unidentified	**NDIT**	*Harmful to copepods	Ban et al. (1997)
Nitzschia sp.	M	Uncharacterized hemolysin and neurotoxin	**Hemolysins**	*?Neurotoxic	Freitas et al. (1995)
Phaeodactylum tricornutum	M	Apo-fucoxanthinoid pigments	**Uncharacterized**	*Harmful to copepods	Shaw et al. (1995a, 1995b), Ban et al. (1997)
Pseudo-nitzschia australis	M	DA	**Domoic acid**	Neurotoxic, ?ASP** Toxic to birds, marine mammals	Work et al. (1992, 1993), Garrison et al. (1992), Villac et al. (1993), Scholin et al. (2000)
Pseudo-nitzschia delicatissima	M	DA	**Domoic acid**	*Neurotoxic, ?ASP**	Smith et al. (1991)
Pseudo-nitzschia fraudulenta	M	DA	**Domoic acid**	*Neurotoxic, ?ASP**	Rhodes et al. (1998)
Pseudo-nitzschia multiseries	M	DA	**Domoic acid**	Neurotoxic, ASP** Harmful to invertebrates	Bates et al. (1989), Wright et al. (1989), Douglas and Bates (1992), Villac et al. (1993), Whyte et al. (1996)
Pseudo-nitzschia multistriata	M	DA	**Domoic acid**	?Neurotoxic, ?ASP**	Sarno and Dahlmann (2000)
Pseudo-nitzschia pseudodelicatissima	M	DA	**Domoic acid**	*Neurotoxic, ?ASP**	Martin et al. (1990)
Pseudo-nitzschia cf. *pseudodelicatissima*	M	DA	**Domoic acid**	*Neurotoxic, ?ASP**	Pan et al. (2001)
Pseudo-nitzschia pungens	M	DA	**Domoic acid**	*Neurotoxic, ?ASP**	Rhodes et al. (1996, 1998), Trainer et al. (1998)
Pseudo-nitzschia seriata	M	DA	**Domoic acid**	*Neurotoxic, ?ASP**	Lundholm et al. (1994)
Pseudo-nitzschia turgidula	M	DA	**Domoic acid**	*Neurotoxic, ?ASP**	Rhodes et al. (1996, 1998)
Rhizosolenia chunii	M	Uncharacterized	**Uncharacterized**	Harmful to molluscs	Parry et al. (1989)
Skeletonema costatum	M	Unidentified compounds	**Mechanical Water quality**	Harmful to fish and copepods *Antibacterial	Ianora et al. (1995), Kent et al. (1995), Ban et al. (1997), Naviner et al. (1999)
Synedra acus	M	Unidentified	**NDIT**	*Harmful to copepods	Ban et al. (1997)

Thalassiosira aestivalis	M	?uncharacterized	**Mechanical**	Harmful to fish	Kent et al. (1995)
Thalassiosira mala	M	Mucilage colonies	**NDIT**	?Mechanical damage Harmful to bivalves	Takano (1956) cited in Hasle and Fryxell (1995), Takano (1965)
Thalassiosira nordenskioeldii	M	Unidentified	**NDIT**	*Harmful to copepods	Ban et al. (1997)
Thalassiosira pseudonana	M	Apo-fucoxanthinoid pigments	**Uncharacterised**	*Harmful to copepods	Shaw et al. (1995a, 1995b)
Thalassiosira rotula	M	?uncharacterized	**Mechanical** **Uncharacterised**	Harmful to fish and invertebrates	Poulet et al. (1994), Kent et al. (1995), Ban et al. (1997), Buttino et al. (1999)
Thalassiosira spp.	M	Mucilage colonies	**NDIT**	?Mechanical damage	Hasle and Fryxell (1995)
Thalassiosira wiessflogii	M	Unidentified	**NDIT**	*Harmful to copepods	Ban et al. (1997)
Raphidophytes					
Chattonella antiqua	M	Brevetoxin-like (CaTx), ROS	**Brevetoxins** **ROS**	Ichthyotoxic *Antimycotic ?Neurotoxic	Shimada et al. (1983, 1991), Nagai et al. (1990), Tanaka et al. (1994), Khan et al. (1996a)
Chattonella marina	B, M	Brevetoxin-like (CmTx), ROS, hemolysins, hemagglutinins	**Brevetoxins** **ROS**	Ichthyotoxic *?Neurotoxic	Onoue and Nozawa (1989a), Onoue et al. (1990), Ahmed et al. (1995), Khan et al. (1995), Oda et al. (1997), Hallegraeff et al. (1998), Kim et al. (2000b)
Chattonella verruculosa	M	Uncharacterized	**ROS** **Brevetoxins**	Ichthyotoxic	Yamamoto and Tanaka (1990) cited in Imai et al. (1998), Baba et al. (1995) cited in Imai et al. (1998)
Chattonella cf. *verruculosa*	M	PbTx-2, PbTx-3, PbTx-9	**ROS** **Brevetoxins**	Ichthyotoxic	Bourdelais et al. (2002)
Fibrocapsa japonica	M	Brevetoxin-like (FjTx-1) PbTx, ROS, fibrocapsin	**Brevetoxins** **ROS** **Uncharacterized**	Ichthyotoxic ?Toxic to marine mammals *Neurotoxic *Toxic to plankton	Uye and Takamatsu (1990), Khan et al. (1996b), Oda et al. (1997), Nannen et al. and Rademaker et al. in ICES (1998)
Heterosigma akashiwo (= *H. carterae*, *Olisthodiscus carterae*)	M	Brevetoxin-like (HaTx), ROS	**Brevetoxins** **ROS**	Ichthyotoxic, ?*Neurotoxic **Artemia* toxicity	Chang et al. (1990), Yang et al. (1995), Khan et al. (1996c), Lush and Hallegraeff 1996), Oda et al. (1997), Twiner and Trick (2000)

TABLE 1. (continued)

Olisthodiscus luteus	M	ROS	**ROS**	?Ichthyotoxic *Antimycotic *Toxic to plankton	Nagai et al. (1990), Uye and Takamatsu (1990), Oda et al. (1997), Kim et al. (1999b)
Prymnesiophytes					
Chrysochromulina birgeri	B	Uncharacterized	**NDIT**	?*Ichthyotoxic	Carver and Eikrem, pers. comm. in Edvardsen and Paasche (1998)
Chrysochromulina brevifilum	M	Uncharacterized	**NDIT**	*Old culture slightly toxic to bryozoa	Parke et al. (1955), Jebram (1980) cited in Moestrup and Thomsen (1998)
Chrysochromulina breviturrita	F	Uncharacterized	**NDIT**	Toxic to tadpoles	Nicholls et al. (1982)
Chrysochromulina kappa	M	Uncharacterized	**NDIT**	*Old culture toxic to bryozoa	Parke et al. (1955), Jebram (1980) cited in Moestrup and Thomsen (1998)
Chryschromulina leadbeateri	M	Uncharacterized	**Hemolysins**	Ichthyotoxic **Artemia* toxicity (weak)	Throndsen and Eikrem (1991) cited in Moestrup and Thomsen (1998), Edvardsen (1993)
Chryschromulina parva	F	Uncharacterized	**NDIT**	Ichthyotoxic	Hansen et al. (1994)
Chrysochromulina polylepis	M	Hemolysins, unidentified compounds	**Hemolysins**	Harmful to invertebrates Ichthyotoxic *Antialgal **Artemia* toxicity *Cytotoxic *?Neurotoxic	Manton and Parke (1962), Underdal et al. (1989), Nielsen et al. (1990), Yasumoto et al. (1990), Edvardsen and Paasche (1992), Edvardsen (1993), Meldahl et al. (1993, 1994), Stabell et al. (1993), Schmidt and Hansen (2001)

Chrysochromulina strobilus	M	Uncharacterized	**NDIT**	*Old culture toxic to bryozoa	Parke et al. (1959), Leadbeater and Manton (1969), Jebram (1980) cited in Edvardsen and Paasche (1998)
Phaeocystis globosa	M	Uncharacterized	**Uncharacterized**	Ichthyotoxic	Lu and Huang (1999)
Phaeocystis pouchetii	M	Uncharacterized	**Uncharacterized**	Ichthyotoxic	Eilertsen and Raa (1995), Aanesen et al. (1998)
Phaeocystis scrobiculata	M	Uncharacterized	**NDIT**	?Ichthyotoxic	Tangen pers.comm. in Møestrup and Thomsen (1998)
Prymnesium calathiferum	M	Uncharacterized	**Hemolysins**	*Ichthyotoxic	Chang (1985)
Prymnesium parvum	M, B	Toxins – prymnesin 1 and 2 (hemolysins)	**Hemolysins**	Ichthyotoxic Toxic to invertebrates Toxic to tadpoles **Artemia* toxicity *Cytotoxic	Shilo (1981), Kozakai et al. (1982), Igarishi et al. (1995, 1996), Meldahl et al. (1994), Moestrup (1994)
Prymnesium patelliferum	M, B	Toxins – hemolysins	**Hemolysins**	Ichthyotoxic **Artemia* toxicity	Arlstad 1991 in Moestrup and Thomsen (1998), Green et al. (1982), Larsen et al. (1993), Meldahl et al. (1993, 1994)
Prymnesium saltans	B	Uncharacterized	**NDIT**	Ichthyotoxic	Wang and Wang (1992), Edvardsen and Paasche (1998)
Silicoflagellates					
Dictyocha speculum (= *Distephanus speculum*)	M	Nontoxic	**Mechanical**	Harmful to fish	Fanuko (1989), Erard-Le Denn and Ryckaert (1990), Henriksen et al. (1993)

TABLE 1. (continued)

Pelagophytes					
Aureococcus anophagefferens	M	Bioactive compound (dopamine-mimetic)	**Mechanical**	Harmful to invertebrates, ecosystem impacts	Bricelj and Kuenstner (1989), Gainey and Shumway (1991)
Aureoumbra lagunensis	M	Nontoxic, can produce dimethyl sulfide	**Mechanical**	Harmful to invertebrates, ecosystem impacts	Stockwell et al. (1993)
Ciliates					
Mesodinium rubrum	M	Nontoxic	**Suspected**	?Harmful to invertebrates and fish	Horstman (1981), Crawford et al. (1993)
Cyanobacteria					Skulberg et al. (1993), Sivonen (1996)
Anabaena circinalis	F	Anatoxin-a, STX, GTX1-4, B1-B2, C1-C2, dcGTX2-3 (decarbomoylGTX), dcSTX (decarbomoylSTX)	**Saxitoxins** **Anatoxins**	Neurotoxic, ?PSP** ?Hepatotoxic ?Ichthyotoxic *_Artemia_ toxicity *Toxic to zooplankton	May and McBarron (1973), Mills and Wyatt (1974), McBarron et al. (1975), Devlin et al. (1977), Sivonen et al. (1989a), Kiviranta et al. (1991), Stevens and Krieger (1991), Humpage et al. (1994), Negri and Jones (1995), Negri et al. (1995, 1997, 1998), Onodera et al. (1996), Vezie et al. (1996), Jones and Negri (1997)
Anabaena flos-aquae	F/B	Anatoxin–a, anatoxin-a(s), microcystins	**Anatoxins** **Microcystins**	Hepatotoxic Ichthyotoxic Neurotoxic ?Tumorigenic *_Artemia_ toxicity *Toxic to zooplankton	Jackim and Gentile (1968), Sawyer et al. (1968), Carmichael and Gorham (1977), Devlin et al. (1977), Alam et al. (1978), Mahmood and Carmichael (1986b, 1987), Sivonen et al. (1989a, 1992), Matsunaga et al. (1989), Harada et al. (1991), Kiviranta et al. (1991), Gilbert (1994), Rodger et al. (1994)
Anabaena lemmermannii	F	Anatoxin-a(s)	**Anatoxins**	Neurotoxic *_Artemia_ toxicity	Fitch et al. (1934), Sivonen et al. (1989a), Kiviranta et al. (1991), Henrickson et al. (1997), Onodera et al. (1997)
Anabaena minutissima var. *attenuata*	F	Uncharacterized	**NDIT**	Harmful to zooplankton	Burns et al. (1989), Forsyth et al. (1992)
Anabaena planctonica	F	Anatoxin-a, microcystin analog	**Anatoxins**	*Hepatotoxic *Neurotoxic	Sivonen et al. (1989a), Bruno et al. (1994)
Anabaena spiroides	F	Unidentified	**NDIT**	Hepatotoxic *Acetylcholinesterase inhibitor	Berg et al. (1986), Chengappa et al. (1989), Monserrat et al. (2001)
Anabaena spiroides var. *contracta*	F	Unidentified	**NDIT**	?Neurotoxic ?Hepatotoxic	Beasley et al. (1983), Yoo et al. (1995)

Anabaena variabilis	F	Unidentified	**NDIT**	?Neurotoxic ?Hepatotoxic	Andrijuk et al. (1975), Yoo et al. (1995)
Anabaena sp.	F	Anatoxin-a	**Anatoxins**	Neurotoxic	Park et al. (1993)
Anabaena sp. strain 186	F	Microcystins	**Microcystins**	Hepatotoxic ?Tumorigenic	Namikoshi et al. (1998)
Anabaenopsis milleri	F	Microcystins	**Microcystins**	Hepatotoxic ?Tumorigenic	Lanaras et al. (1989), Lanaras and Cook (1994)
Aphanizomenon flos-aquae	F	NEO, STX, mueggelone	**Saxitoxins** **Mueggelone**	Neurotoxic, ?PSP** Toxic to freshwater organisms *Ichthyotoxic **Artemia* toxicity	Jackim and Gentile (1968), Sawyer et al. (1968), Gentile and Maloney (1969), Alam et al. (1978), Ikawa et al. (1982, 1985), Mahmood and Carmichael (1986a), Papendorf et al. (1997)
Aphanizomenon ovalisporum	F	Cylindrospermopsin (CY)	**Cylindrospermopsin**	*Hepatotoxic	Banker et al. (1997), Sukenik et al. (1998)
Aphanizomenon sp.	F	Anatoxin-a	**Anatoxins**	Neurotoxic	Sivonen et al. (1989a)
Coelosphaerium kützingianum	F	Uncharacterized	**NDIT**	?	Fitch et al. (1934), Carmichael 1994 cited in Yoo et al. (1995)
Cylindrospermum sp.	F	Anatoxin–a, scytophycins	**Anatoxins**	Neurotoxic, *Cytotoxic?	Sivonen et al. (1989a), Jung et al. (1991)
Cylindrospermopsis raciborskii	F	CY, STX, NEO, GTX, deoxy-CY	**Cylindrospermopsin** **Saxitoxins**	Hepatoenteritis** Hepatotoxic ?Neurotoxic, ?PSP** *Carcinogenic *Neurotoxic	Hawkins et al. (1985), Thomas et al. (1998), Lagos et al. (1999), Humpage et al. (2000), Falconer and Humpage (2001), Li et al. (2001a)
Fischerella ambigua	F	Fischerellins	**NDIT**	*Antialgal	Gross et al. (1991)
Fischerella epiphytica	F	Uncharacterized	**NDIT**	*Toxic to protists	Ransom et al. (1978)
Fischerella muscicola	F	Fischerellins, fischerindole L	**NDIT**	*Antialgal *Antimycotic *Herbicidal *Toxic to rotifers and crustaceans	Gross et al. (1991), Park et al. (1992), Hagmann and Juttner (1996), Papke et al. (1996)
Gloeotrichia echinulata	F	Uncharacterized	**NDIT**	*Inhibits RNA synthesis *Toxic to zooplankton	Porter (1887) in Schwimmer and Schwimmer (1968), Ingram and Prescott (1954), Mills and Wyatt (1974), Codd and Bell (1985)
Gloeotrichia sp.	F	Gloeolactone	**NDIT**	**Artemia* toxicity *Antimicrobial	Stierle et al. (1998)
Gomphosphaeria lacustris	F	Uncharacterized	**NDIT**	*Hepatotoxic	Berg et al. (1986), Gorham and Carmichael (1988)
Gomphosphaeria nägeliana	F	Uncharacterized	**NDIT**	*Hepatotoxic	Berg et al. (1986)

TABLE 1. (continued)

Hormothamnion enteromorphoides	M	Hormothamnione, hormothamnin-A	**Anatoxins**	*Antimicrobial *Cytotoxic *Ichthyotoxic	Gerwick et al. (1986, 1989, 1992)
Lyngbya gracilis	M	Debromoaplysiatoxin	**NDIT**	?Tumorigenic	Carmichael et al. (1990) in Paerl and Millie (1996)
Lyngbya majuscula (with *Tolypothrix* for identification of kalkipyrone)	M	Lyngbyatoxin-A, B, C, antillatoxin, antillatoxin B, aplysiatoxin, anhydrodebromoaplysiatoxin, barbamide, curacins, debromoaplysiatoxin, hermitamides, kalkipyrone, kalkitoxin, lyngbyabellins, majusculamides, malyngamides, methyloscillatoxin, oscillatoxin, tanikolide	**Multiple toxins**	Dermatotoxic** Gastrointestinal inflammation** *Antimycotic *Antineoplastic **Artemia* toxicity *Cytotoxic *Ichthyotoxic *Molluscicidal *Neurotoxic *Tumorigenic	Grauer and Arnold (1961), Moikeha and Chu (1971), Cardellina et al. (1979), Sims and Zandee Van Rillan (1981), Carter et al. (1984), Fujiki et al. (1984a), Entzeroth et al. (1985), Sugimura (1985), Gerwick et al. (1986, 1989, 1994), Moore and Entzeroth (1988), Aimi et al. (1990), Orjala et al. (1995a, 1995b), Orjala and Gerwick (1996), Graber and Gerwick (1998), Berman et al. (1999), Singh et al. (1999), Milligan et al. (2000a, 2000b), Tan et al. (2000), Li et al. (2001b), Nogle et al. (2001)
Lyngbya wollei	B	dcSTX dcGTX2-3, LWTX1-6 (lyngbyawolleitoxin)	**Saxitoxins**	Neurotoxic, ?PSP**	Carmichael et al. (1997), Onodera et al. (1997)
Microcystis aeruginosa	F	Microcystins, microcystilide A, kawaguchipeptin B, fatty acids (lysins), anatoxin-a (few strains)	**Microcystins**	Gastroenteritis** Hepatoenteritis**, Hepatotoxic** Ichthyotoxic Pneumonia** Respiratory irritation** Skin blistering** Toxic to zooplankton *Antibacterial *Antiviral **Artemia* toxicity *Cytotoxic *Tumorigenic	Hughes et al. (1958), Falconer (1989), Turner et al. (1990), Kiviranta et al. (1991), De Mott et al. (1991), Nishiwaki-Matsushima et al. (1992), Park et al. (1993), Tsukamoto et al. (1993), Vezie et al. (1996), Ishida et al. (1997), Mundt et al. (1997), Bury et al. (1998a), Jochimsen et al. (1998), Sbiyyaa et al. (1998), Rohrlack et al. (1999a, 1999b)
Microcystis flos-aquae	F	Microcystins, unidentified toxin	**Microcystins**	*Toxic to *Daphnia*	Jungmann (1992, 1995), Jungmann and Benndorf (1994)

Microcystis viridis	F	Microcystins	**Microcystins**	*Hepatotoxic, *Ichthyotoxic ?Tumorigenic	Watanabe et al. (1986), Sugaya et al. (1990), Namikoshi et al. (1992)
Microcystis wesenbergii	F	Microcystins	**Microcystins**	?Hepatotoxic **Artemia* toxicity	Watanabe et al. (1986), Gorham and Carmichael (1988), Kiviranta et al. (1991), Namikoshi et al. (1992)
Microcystis sp.	F	Uncharacterized	**Microcystins**	Ichthyotoxic *Toxic to zooplankton	Peñaloza et al. (1990)
Nodularia spumigena	B	Nodularin	**Nodularins**	Hepatotoxic **Artemia* toxicity *Toxic to zooplankton	Francis (1878), Carmichael et al. (1988), Eriksson et al. (1988), De Mott et al. (1991), Kiviranta et al. (1991), Rinehart et al. (1994)
Nostoc linckia	F	Uncharacterized	**NDIT**	*Neurotoxic to rodents *Toxic to protists	Phillips et al. (1973), Ransom et al. (1978)
Nostoc paludosum	F	Uncharacterized	**NDIT**	? Neurotoxic	Andrijuk et al. (1975)
Nostoc rivulare	F	Uncharacterized	**NDIT**	?Neurotoxic	Davidson (1959)
Nostoc zetterstedtii	F	Uncharacterized	**NDIT**	*Toxic to ostracods?	Mills and Wyatt (1974)
Nostoc sp. strain 152	F	Microcystins	**Microcystins**	*Hepatotoxic ?Tumorigenic	Namikoshi et al. (1990), Sivonen et al. (1990)
Phormidium corallyticum	M	Uncharacterized	**Disease**	Harmful to corals	Antonius (1973), Rutzler and Santavy (1983), Carlton and Richardson (1995)
Planktothrix acutissima (= *Oscillatoria acutissima*)	F	Acutiphycin, dide-hydroacutiphycin	**NDIT**	*Antineoplastic *Cytotoxic	Barchi et al. (1984)
Planktothrix agardhii (= *Oscillatoria agardhii*)	F	Microcystins, unidentified toxin, oscillamide B, oscillamide C	**Microcystins**	Hepatotoxic ?Tumorigenic **Artemia* toxicity *Toxic to zooplankton	Mills and Wyatt (1974), Østensvik et al. (1981), Skulberg and Skulberg (1985), Berg et al. (1986), Meriluoto et al. (1989), Kiviranta et al. (1991), Luukkainen et al. (1993), Kiviranta and Abdel-Hameed (1994), Reinikainen et al. (1995b), Sano et al. (1998, 2001)
Planktothrix formosa (= *Phormidium formosum*, *Oscillatoria formosa*)	F	Homoanatoxin-a	**Anatoxins**	*Neurotoxic	Skulberg et al. (1992), Lilleheil et al. (1997)

TABLE 1. (continued)

Planktothrix late-virens (= *Oscillatoria late-virens*)	F	Uncharacterized	**NDIT**	*Antialgal	Chauhan et al. (1992), Bagchi et al. (1990, 1993)
Planktothrix mougetii (= *Oscillatoria mougetii*)	F	Microcystin-YR like	**NDIT**	Hepatotoxic ?Tumorigenic	Bruno et al. (1992)
Planktothrix nigro-viridis (= *Oscillatoria nigro-viridis*) (mixed with *Schizothrix calcicola*)	M	Debromoaplysiatoxin?? oscillatoxins, methyloscillatoxin, noroscillatoxin	**NDIT**	?Dermonecrotic ?Hepatotoxic ?Tumorigenic	Mynderse et al. (1977), Entzeroth et al. (1985)
Planktothrix rubescens (= *Oscillatoria rubescens*)	F	Homoanatoxin-a, microcystin-RR, oscillamide B, oscillamide C	**Anatoxins** **Microcystins**	Neurotoxic Hepatotoxic **Artemia* toxicity ?Tumorigenic	Skulberg and Skulberg (1985), Berg et al. (1986), Bruno et al. (1992), Carmichael (1992), Luukkainen et al. (1993), Feuillade et al. (1996), Sano et al. (2001)
Planktothrix sp. (= *Oscillatoria* sp.)	M	Unknown	**Disease**	Coral disease	Richardson (1992)
Planktothrix sp.	F	STX	**Saxitoxins**	*Neurotoxic	Pomati et al. (2000)
Planktothrix sp. (= *Oscillatoria* sp.)	F	Anatoxin-a	**Anatoxins**	Neurotoxic	Sivonen et al. (1989a), Edwards et al. (1992), James et al. (1997a)
Pseudanabaena catenata	M	Uncharacterized	**NDIT**	Neurotoxic	Gorham et al. (1982)
Schizothrix calcicola (mixed with *Oscillatoria nigro-viridis*)	M	Debromoaplysiatoxin, oscillatoxin, methyloscillatoxin, noroscillatoxin	**NDIT**	Gastroenteritis** ?Dermonecrotic** ?*Tumorigenic	Mynderse et al. (1977), Entzeroth et al. (1985), Carmichael and Falconer (1993), Carpenter and Carmichael (1995)
Scytonema hofmanni	F	Cyanobacterin	**NDIT**	*Antialgal *Antimicrobial? *?Toxic to zooplankton	Mason et al. (1982), Gleason et al. (1986), Klapes (1990)
Spirulina subsalsa	M	Uncharacterized	**Disease**	?Toxic to shrimp	Lightner (1978)

Synechococcus sp. (strain Miami BCII 6S)	M	Hemolysin	**Hemolysins**	?Ichthyotoxic	Mitsui et al. (1989)
Synechocystis sp.	F	Uncharacterized	**NDIT**	*Hepatotoxic	Carmichael and Gorham (1978), Lincoln and Carmichael (1981)
Synechocystis sp.	M	Nakienones A-C, nakitriol	**NDIT**	*Cytotoxic	Nagle and Gerwick (1995)
Tolypothrix byssoidea	M	Toxin - tubercidin	**NDIT**	*Cytotoxic	Barchi et al. (1983)
Tolypothrix sp. (together with *Lyngbya majuscula*)	M	Kalkipyrone	**NDIT**	**Artemia* toxicity *Ichthyotoxic	Graber and Gerwick (1998)
Trichodesmium erythraeum	M	Uncharacterized	**Uncharacterized**	Antibacterial Harmful to marine fauna ?*Hepatotoxic ?*Neurotoxic *Ciguatoxin-like	Ramamurthy and Krishnamurthy (1967), Ramamurthy (1970), Hahn and Capra (1992), Endean et al. (1993)
Trichodesmium thiebautii	M	Anatoxin-a-like	**Uncharacterized**	Harmful to marine fauna **Artemia* toxicity *Toxic to zooplankton *Neurotoxic	Chellam and Alagarswami (1981), Hawser et al. (1991, 1992), Hawser and Codd (1992), O'Neil and Roman (1994), Carpenter and Carmichael (1995)
Umezakia natans	F	CY	**Cylindrospermopsin**	*Hepatotoxic	Harada et al. (1994), Terao et al. (1994)

TABLE 2. Dinoflagellate species and documented mortalities (wild or aquaculture) or health impacts on aquatic organisms

Species	Organisms affected in mortality event	Year	Location	Reference
Dinoflagellates				
Akashiwo sanguinea (= *Gymnodinium sanguineum*)	Pacific oyster (*Ostrea lurida*)	1929	Oakland Bay, Washington, USA	Nightingale (1936)
	Pacific oyster (*Ostrea lurida*)	1935	Oakland Bay, Washington, USA	Nightingale (1936)
	Pacific oyster (*Ostrea lurida*)	1936	Olympia, Washington, USA	Nightingale (1936)
with *Ceratium fusus*	Pacific oyster (*Ostrea lurida*) larvae	1977?	Puget Sound, Washington, USA	Cardwell et al. (1979) cited in Rensel et al. (1989)
with *Ceratium fusus*	Pen-reared salmon and pandalid shrimp (*Pandalus platyceros*)	1980?	Puget Sound, Washington, USA	Rensel and Prentice (1980)
	Estimated 13 million blue crabs (*Callinectes sapidus*); fish: Gulf menhaden (*Brevoortia patronus*), thread herring (*Opisthonema oglinum*), anchovy (*Anchoa mitchilli*), hardhead catfish (*Arius felis*), inland silverside (*Menidia beryllina*), bluefish (*Pomatomos saltatrix*), Atlantic bumper (*Chloroscombrus chrysurus*), silver perch (*Bairdiella chrysoura*), sand seatrout (*Cynoscion arenarius*), spot (*Leiostomus xanthurus*), southern kingfish (*Menticirrhus americanus*), Atlantic croaker, (*Micropogonias undulatus*), spadefish (*Chaetodipterus faber*), striped mullet (*Mugil cephalus*), threadfin (*Polydactylus octonemus*), southern stargazer (*Astroscopus y -graecum*)	1984	Galveston, Texas, USA	Harper and Guillen (1989)
Alexandrium catenella	Dead baboons found with mollusc shells in claws, possibly poisoned from eating the white mussel (*Donax serra*)	1888	Simonstown, South Africa	Gilchrist (1914) cited in Grindley and Sapeika (1969)
Presumptive	Tons of sardines and seabirds, sea duikers	1901	St. Helena Bay, South Africa	Gilchrist (1914) cited in Pitcher (1998)
	Unusual mortality of pelagic barnacles (*Lepas fasciculatis*); approximately 2,000 dead birds: herring gull (*Larus argenteus*), western gull (*L. occidentalis*), white-winged scoter (*Melanitta deglandi*), California murre (*Uria aalge californica*), Pacific loon (*Gavia arctica pacifica*), tufted puffin (*Lunda cirrhata*), sooty shearwater (*Puffinus griseus*), black-footed albatross (*Diomedea nigripes*). Mortality of cats, chickens	1942	Copalis and Grayland beaches, Washington coast, USA	McKernan and Scheffer (1942)
	7 cats died, 1 sick	1957	Baynes Sound, British Columbia, Canada	Chiang (1988)
	Black mussel (*Chloromytilus meridionalis*), white mussel (*Donax serra*), crabs; more than18 seabirds oystercatchers (*Haematopus moquini*), Southern black-back gulls (*Larus dominicanus*). Hartlaub's gulls (*Larus hartlaubii*)	1978	Lamberts Bay to False Bay, Marcus and other Islands, Saldanha Bay, Ysterfontein shore, South Africa	Popkiss et al. (1979), Hockey and Cooper (1980)
	Mass mortality of white mussel (*Donax serra*), black mussel (*Chloromytilus meridionalis*); sea birds	1980	Elands Bay, west coast of South Africa	Horstman (1981)
	1 cat died, 1 cat sick	1981	Church House, British Columbia, Canada	Chiang (1988)
	Mortality of 3,000 yellowtail (*Seriola quinqueradiata*), 5,000 red seabream (*Pagrus major*)	1982	Kitaura Bay, Miyazaki Prefecture, Japan	Ogata and Kodama (1986)

Presumptive	At least 60 sea otters (*Enhydra lutris*)	1987	Kodiak archipelago, Alaska, USA	De Gange and Vacca (1989)
	1 cat died, 1 cat sick	1987	Porter Beach, Cheimanus, British Columbia, Canada	Chiang (1988)
	Fish, penguins, other marine bird species	1991-1992	Southern Chile and southern Argentina	Carreto and Benavides (1993)
Not confirmed	Chub mackerel (*Scomber japonicus*), PST in viscera of fish and in razor clams (*Siliqua patula*)	1992	Oregon coast, USA	ICES (1993)
	Sardines	1997	St. Helena Bay, South Africa	Pitcher (1998)
Alexandrium minutum	Fish and shellfish mortalities	Since 1980	Izmir Bay, Turkey	Koray (1992)
Reported as *A. tamarense* (see Lush and Hallegraeff (1996)	Cultured prawn (*Penaeus monodon*)	1989	Taiwan	Su et al. (1993)
	Fish: grouper (*Epinephelus* sp.), (*Murena* sp.); rock crabs (*Eriphia* and *Pachygrapsus*) moved onto beach	1994	Alexandria Harbor, Egypt	Halim and Labib (1996)
(with *Gymnodinium catenatum*) suspected	Monk seal *Monachus monachus*	1997	Coastal western Sahara, Africa	Hernández et al. (1998), Reyero et al. (1999)
Alexandrium monilatum	Fish	1930s-1949	Offats Bayou, Galveston, Texas, USA	Gunter (1942)
	Fish	1949	Offats Bayou, Galveston, Texas, USA	Connell and Cross (1950)
	Fish	1951	Indian River, Florida, USA	Howell (1953)
	Fish	1955	Offats Bayou, Galveston, Texas, USA	Gates and Wilson (1960)
	Jack (*Caranx* spp.), needlefish (*Strongylura marina*), whiting, pinfish (*Lagodon rhomboides*)	1966	Fort Myers to Naples, southwestern Florida, USA	Williams and Ingle (1972)
	Cnidarians: (*Bunodosoma cavernata*); polychaetes: (*Onuphis magna*), ragworm (*Nereis* sp.); molluscs: double moon shell (*Polinices duplicatus*), Florida dogwinkle (*Thais haemastoma*), gray augur (*Terebra cinerea*), (*Anadara ovalis*), Brazil ark (*A. brasiliana*), Florida coquina ((*Donax variabilis*), surfclam (*Spisula solidissima*), lettered olive (*Oliva sayana*), striped false limpet (*Siphonaria pectinata*), eastern oyster (*Crassostrea virginica*); crustaceans: (*Emerita benedicti*), (*Arenaeus cribarius*), hermit crab (*Clibanarius vittatus*), (*Isocheles wurdemanni*), (*Hepatus epheliticus*), spotted porcelain crab (*Porcellana sayana*), blue crab (*Callinectes sapidus*), stone crab (*Menippe mercenaria*), green porcelain crab (*Petrolisthes armatus*); echinoderms: brittle star (*Microphiolis atra*), six-keyhole sand dollar (*Mellita quinquesperforata*), holothurians; fish: crested blenny (*Hypleurochilus geminatus*), whip eel (*Basanichthys scuticaris*), stippled clingfish (*Gobiesox punctulatus*)	1971-1972	Galveston, Texas, USA	Wardle et al. (1975)
	Thousands of dead fish	1977	Port St. John, Florida, USA	Norris (1983)
	Zooplankton and ichthyoplankton	1998	Coastal Mississippi, USA	ICES (1999)

TABLE 2. (continued)

Alexandrium tamarense	Toxic blue mussel (*Mytilus edulis*), great scallop (*Pecten maximus*), moribund and dead molluscs: cockle (*Cardium edule*), scallop (*Chlamys opercularis*), Baltic macoma (*Macoma balthica*), (*Venus striatula*); dead fish: sand eel (*Ammodytes* sp.), 636 bird mortalities: shags (*Phalacrocorax aristotelis*), fulmar (*Fulmarus glacialis*), gannet (*Sula bassana*), cormorant (*Phalacrocorax corbo*), common scoter (*Melanitta nigra*), eider (*Somateria mollissima*), great black-backed gull (*Larus marinus*), lesser black-backed gull (*Larus fuscus*), herring gull (*Larus argenteus*), common gull (*Larus canus*), black- headed gull (*Larus ridibundus*), kittiwake (*Rissa tridacyla*), common tern (*Sterna hirundo*), Arctic tern (*Sterna paradisaea*), roseate tern (*Sterna dougallii*), sandwich tern (*Sterna sandvicensis*), razorbill (*Alca torda*), guillemot (*Uria aalge*), puffin (*Puffinus arcticus*); suspected poisoning in homing pigeons (*Columba* sp.)	1968	Sunderland to Holy Island, northeastern England	Adams et al. (1968), Coulson et al. (1968), Ingham et al (1968)
	Mortality of gulls, shorebirds, 620 waterfowl, and 1600 black ducks	1972	Northern coast of Massachusetts, USA	Sasner et al. (1975), Bicknell and Walsh (1975)
As *A. excavata*	Atlantic herring (*Clupea harengus harengus*)	1976	Bay of Fundy, east coast Canada	White (1977)
	490 birds: shag (*Phalacrocorax aristotelis*), fulmar (*Fulmarus glacialis*), gannet (*Sula bassana*), cormorant (*Phalacrocorax corbo*), eider (*Somateria mollissima*), lesser black backed gull (*Larus fuscus*), herring gull (*Larus argenteus*), common gull (*Larus canus*), kittiwake (*Rissa tridacyla*), common tern (*Sterna hirundo*), Arctic tern (*Sterna paradisaea*), sandwich tern (*Sterna sandvicensis*), guillemot (*Uria aalge*)	1978	northeastern England	Armstrong et al. (1978)
As *A. excavata*	Bluefish (*Pomatomus saltatrix*), spiny dogfish (*Squalus ananthias*), skates (*Raja* spp.), monkfish (*Lophius americanus*), sandlance (*Ammodytes* sp.). More than 70 bird mortalities of common terns (*Sterna hirundo*), other terns and gulls	1978	Monomoy National Wildlife Refuge, Massachusetts, USA	Nisbet (1983)
	Salmon (*Salmo salar*), rainbow trout (*Oncorhynchus mykiss*), flounder (*Platichthys flesus*), whelk (*Buccinium undatum*)	1984	Trongisvagur, Faroe Islands	Mortensen (1985)
	Marine mammals, birds, and fish	1986	Bering Sea, north east Kamchatka	Konovalova (1989, 1993)
	14 humpback whales (*Megaptera novaeangliae*)	1987	Cape Cod Bay, Massachusetts, USA	Geraci et al. (1989)
	Farmed rainbow trout (*Oncorhynchus mykiss*)	1987	Trongisvagur, Faroe Islands	Moestrup and Hansen (1988)
	Farmed Atlantic salmon (*Salmo salar*), rainbow trout (*Oncorhynchus mykiss*), wild herring (*Clupea harengus*), flatfish, catfish (*Anarhichas minor*), a few dead eider ducks	1992	Trondheimsfjord, Norway	Tangen et al. (1992)
	Chub mackerel (*Scomber japonicus*)	1993	El Rincon, Argentina	Montoya et al. (1996)
Mixed bloom with *A. minutum*	Cultured fish seabass (*Dicentrarchus labrax*) and sea bream (*Sparus aurata*); wild fish	1994 and on	Ghar el Melh, Tunisia	Romdhane et al. (1998)
	Sand lance (*Ammodytes hexapterus*), herring gulls (*Larus argentatus*), domestic cats (*Cattus felis*)	1996	Gaspé Peninsula, Canada	ICES (1998)

	2000 cultured salmon	2000	Shelburne Harbor, Nova Scotia, Canada	ICES (2001)
Ceratium furca	200 tons of sardine (*Cetengraulis edentulus*)	1982	Carenero, Venezuela	Mijares et al. (1985)
	Low number of salmonids	1987	West coast of Norway	Tangen (1988)
	Rock lobster (*Jasus lalandi*)	1997	Elands Bay, west coast South Africa	Pitcher (1998), Pitcher and Cockcroft (1998)
Ceratium fusus with *Akashiwo sanguinea* (as *Gymnodinium sanguineum*)	Oyster larvae	1977?	Puget Sound, Washington, USA	Cardwell et al. (1979) cited in Rensel et al. (1989)
	Farmed oysters – low dissolved oxygen	1978	Jinhae Bay, Korea	Cho (1979)
With *Akashiwo sanguinea* (as *Gymnodinium sanguineum*)	Pen-reared salmon and pandalid shrimp (*Pandalus platyceros*)	1980?	Puget Sound, Washington, USA	Rensel and Prentice (1980)
	39,000 yellowtail (*Seriola quinqueradiata*)	1990	Kagoshima Bay, Japan	Onoue (1990)
Ceratium hirundinella	600 rainbow trout (*Onchorhynchus mykiss*), white suckers (*Catostomus commersoni*), black bass (*Micropterus salmoides*), bullheads (*Ictalurus nebulosus*)	1976	Heart Lake, Ontario, Canada	Nicholls et al. (1980)
Ceratium spp. (*C. furca, C. fusus, C. lineatum, C. tripos*)	Benthic organisms	1980	West coast of Sweden	Edler (1984)
Ceratium tripos	Surfclam (*Spisula solidissima*), ocean quahog ((*Arctica islandica*), sea scallop (*Placopecten magellanicus*), American lobster (*Homarus americanus*), benthic fish – anoxic conditions associated with bloom	1976	New York Bight, USA	Mahoney and Steimle (1979)
Cochlodinium catenatum	Implicated in fish mortalities	1910-1911	Yokohama Harbor, Japan	Okamura (1916) cited in Nightingale (1936), Miyajima (1934) cited in Grindley and Taylor (1964)
	Shellfish	1934	Japan	Miyajima (1934) cited in Schwimmer and Schwimmer (1968)
With low concentration of *Alexandrium monilatum*	Mass mortality of fish: scarids, balistids, acanthurids, pomacentrids, tetraodontids; hermit crabs, brachyuran crabs; gastropods; corals: (*Pocillopora elegans*), (*P. damicornis*), (*Tubastrea coccinea*)	1985	Cano Island, Costa Rica and Uva Island, Panama	Guzmán et al. (1990)
Cochlodinium helix	Implicated in fish mortalities	Not listed	Moreton Bay, Australia	Hallegraeff (1992a)
C. polykrikoides = (*C. heterolobatum*)	Larval eastern oysters (*Crassostrea virginica*)	1977	York River, Virginia, USA	Ho and Zubkoff (1979)
	Yellowtail (*Seriola quinqueradiata*), red sea bream (*Pagrus major*)	1977?	Yatsushiro Bay, Kyushu Island, Japan	Kumanda et al. (1977) cited in Onoue et al. (1985)
	Fish in cage culture	1982	Naktong estuary, Dangdong Bay, Korea	Kim (1998) and reports therein

TABLE 2. (continued)

	Fish in cage culture	f984	Naktong estuary, Dangdong Bay, Korea	Kim (1998) and reports therein
	Fish in cage culture	1988 and on	Naktong estuary, Dangdong Bay, Korea	Kim (1998) and reports therein
Cochlodinium sp.	Mortality of devil fish (*Mobula japonica*), moray eel (*Muraenesox cinereus*), oriental spotted bass (*Lateolabrax japonicus*), cultured grouper (*Epinephelus akaara*), black sea bream (*Sparus macrocephalus*); Japanese littleneck clam (*Venerupis philippinarum*), jellyfish	June 1990	Weitou Bay to Quanzhou Bay, Fujian, China	Qi et al. (1993a)
	Atlantic salmon (*Salmo salar*), chinook salmon (*Onchorhynchus kisutch*)	1999	Vancouver Island, British Columbia	Whyte et al. (2001)
Dinophysis caudata	Fish ?	1967?	Gulf of Thailand, Seto Inland Sea, Japan	Okaichi (1967)
	Absence of zooplankton and decline in fish and diatoms – indirect evidence for mortalities?	1993-1994	Tuticorin Bay, India	Santhanam and Srinivasan (1996)
Gonyaulax grindleyi (= *Protoceratium reticulatum*)	Molluscs: white mussel (*Donax serra*), black mussel (*Chloromytilus meridionalis*), mussel (*Mytilus crenatus*), winkles (*Oxystele tigrina*), (*O. variegata*), South African turban (*Turbo sarmaticus*), whelks (*Bullia digitalis*), (*B. laevissima*), (*Burnupena cincta*), limpets (*Patella compressa*), (*P. granatina*), (*P. granularis*), squid (*Eledone* sp.); echinoderms: sea cucumbers (*Cucumaria frauenfeldii*), (*Thyone aurea*); cnidarians: sea anemone (*Bunodosoma capensis*); crustaceans: (*Plagusia chabrus*), rock lobster (*Jasus lalandii*); fish: sucker fish (*Chorisochismus dentex*)	1966-1967	Elands Bay to Lamberts Bay, west coast South Africa	Grindley and Nel (1968)
	White mussel (*Donax serra*), black mussel (*Chloromytilus meridionalis*)	1974	Elands Bay, west coast South Africa	Horstman (1981)
Gonyaulax polygramma	Fish, molluscs, shrimp	1899	Bay of Toba, Japan	Nishikawa (1903) cited in Schwimmer and Schwimmer (1968)
	Fish, molluscs, shrimp	1900	Bay of Agu, Shima Province, Japan	Nishikawa (1903) cited in Schwimmer and Schwimmer (1968), Anon (1933) cited in Grindley and Taylor (1964)
	100 tons of invertebrates and fish; crustaceans: (*Callianassa kraussi*), *C. rotundicaudata*), (*Cirolana hirtipes*), (*Codonophilus imbricata*), (*Cryptodromiopsis spongiosa*), (*Cyclograpsus punctatus*), (*Dehaanius dentatus*), (*Diogenes brevirostris*), (*Hymenosoma orbiculare*), rock lobster (*Jasus lalandi*), (*Ovalipes punctatus*), shrimp (*Palaemon pacificus*), (*Plagusia chabrus*), (*Portunus biguttatus*), (*Thaumastoplax spiralis*); echinoderms: (*Asterina exigua*), (*Cucumaria sykion*), (*C. stephensoni*), (*Marthasterias glacialis*), (*Ophiarachnella capensis*), (*Parechinus angulosus*), (*Spatangus capensis*); molluscs: limpets (*Amblychilepas scutella*), whelks (*Bullia laevisima*), (*Burnupena cincta*), Chinese hat (*Calyptraea chinensis*), helmet shell (*Cassis achatina*), chitons (*Chaetopleura papilio*), (*Chiton tulipa*), whelk (*Clavatula simuata*), slipper limpet (*Crepidula procellana*), chiton (*Dinoplax gigas*), abalone (*Haliotis midae*), (*H. sanguinea*), chitons (*Helcion pectunculus*), (*H. pruinosa*), lima (*Lima torundata*), mussels (*Mytilus meridionalius*), (*M. perna*), moon shell (*Natica genuana*), octopus (*Octopus* sp.), (*Oxystele sinensis*), (*O. variegata*), limpets (*Patella argenvillei*), (*P. barbara*), (*P. cochlear*), (*P. compressa*), (*P. granularis*), (*P. longicosta*), (*P. miniata*), (*P. oculus*), (*P. tabularis*), squid (*Sepia* sp.), false limpet (*Siphonaria deflexa*), razor shell (*Solen capensis*), (*Tapes corrugatus*, tellin (*Tellina gilchristi*), thais (*Thais squamosa*), (*Thecalia*	1962	False Bay, Cape Town, South Africa	Grindley and Taylor (1962, 1964)

	concamerata), tivela (*Tivela compressa*), turban (*Turbo cidaris*), South African turban (*T. sumarticus*), warty venus (*Venus verrucosa*); asciidians (*Pyura stolonifera*); sponges: (*Hymeniacedon perlevis*); cnidarians: (*Bunodosoma capensis*); planktonic copepods: (*Paracalanus parva*); diatoms; forams; fish: tope shark (*Galeorhinus galeus*), great white shark (*Carcharodon carcharias*), Cape numbfish (*Narke capensis*), beaked salmon (*Gonorhynchus gonorhynchus*), South African pilchard (*Sardinops ocellatus*), barbel (*Tachysurus fossor*), stockfish (*Merluccius capensis*), sand tonguefish (*Trulla capensis*), grouper (*Acanthistius* sp.)?, grouper (*Epinephelus* sp.)?, scad (*Trachurus trachurus*), bluefish (*Pomatomus saltator*), southern meagre (*Johnius hololepidotus*), doublesash butterflyfish (*Chaetodon marleyi*), galjoen (*Dichistius capensis*), white stumpnose (*Rhabdosargus globiceps*), blacktail (*Diplodus sargus*), zebra seabream (*Diplodus cervinus*) (as *D. trifasciatus*), blue musselcracker (*Cymatoceps nasutus*), red stumpnose seabream (*Chrysoblephus gibbiceps*), Roman seabream (*Chrysoblephus laticeps*), white steenbras (*Lithognathus lithognathus*), fransmadam (*Boopsoidea inornata*), salema (*Sarpa salpa*), steentje seabream (*Spondyliosoma emarginatum*), red steenbras (*Petrus rupestris*), chub mackerel (*Scomber japonicus*), mullet (*Liza ramada*), silverside (*Atherina breviceps*, (*Cirrhibarbus capensis*), (*Clinus superciliosus*), lace klipfish (*Bleniocilmus brachycephalus*), mousey klipfish (*Fucomimus mus*), (*Halidesmus scapularis*), suckerfish (*Chorisochismus dentex*), serpent eel (*Ophisurus serpens*), frogfish (*Gymnobatrachus apiatus*) – associated with low dissolved oxygen			
	Fish and invertebrates – associated with low dissolved oxygen	1976	Gulf of Cariaco, Venezuela	Ferraz-Reyes et al. (1979)
	Fish and shellfish, excess mucus around fish gills, possible low d.o.	1988	Tolo Harbour, Hong Kong	Lam (1988), Lam and Yip (1990)
	Marine organisms	1988	Gulf of Cariaco, Venezuela	La Barbera-Sanchez et al. (1993)
	Molluscs: 287, 000 pearl oysters (*Pinctada martensii*), 67,600 scallops (*Chlamys nobilis*); fish: 78,700 red sea bream (*Pagrus major*), 1,500 Japanese croaker (*Nibea japonica*), 16,600 Japanese flounder (*Paralichthys olivaceus*), 12,000 chicken grunt (*Parapristipoma trilineatum*), 900 yellowtail (*Seriola quinqueradiata*), 6,000 crimson seabream (*Evynnis japonica*), 16,800 Chinese sea bass (*Lateolabrax* sp.)	1994	Uwajima Bay, Japan	Koizumi et al. (1996)
Gonyaulax spinifera	Shellfish mortality – associated with hypoxia	1990	Vancouver Island, British Columbia, Canada	Forbes (1990)
Gymnodinium aureolum (many European reports likely to be *K. mikimotoi*)	Fish: sea trout (*Salmo trutta*), rainbow trout (*Oncorhynchus mykiss*), cod (*Gadus morhua*), eel (*Anguilla anguilla*), coalfish (*Pollachius virens*)	1966	Oslo to Bergen, Norway	Braarud and Heimdal (1970), Tangen (1977)
	Oceanic fish:, several species, mainly cod (*Gadus morhua*); lugworms (*Arenicola marina*); other invertebrates	1968	west coast of Denmark	Hansen and Sarma (1969), Hansen et al. (1969) cited in Tangen (1977)
	Lugworms (*Arenicola marina*); heart urchins (*Echinocardium cordatum*)	1971	East Irish Sea, north Wales	Ballantine and Smith (1973), Helm et al. (1974)
	Lugworms (*Arenicola marina*); molluscs: gapers (*Mya* sp.), razor shells (*Ensis* sp.), edible cockle (*Cardium edule*), palourdes (*Tapes decussata*); fish: sole (*Solea* sp.), plaice (*Pleuronectes platessa*), flounder (*Platichthys flesus*), sand eels (*Ammodytes* sp.)	1976	southeastern Ireland	Ottway et al. (1979)

TABLE 2. (continued)

	Fish: Atlantic salmon (*Salmo salar*), rainbow trout (*Oncorhynchus mykiss*), coalfish (*Pollachius virens*), sprat (*Sprattus sprattus*), cod (*Gadus morhua*), eel (*Anguilla anguilla*), black goby (*Gobius niger*); lugworms (*Arenicola* sp.), mussels (*Mytilus* sp.), starfish	1976	southwestern Norway	Tangen (1977), Dahl and Tangen (1993)
G. cf. *aureolum*	Mussels, light mortality and growth inhibition in scallops (*Pecten maximus*)	1978	Brest Bay, Brittany, France	Erard-le-Denn et al. (1990)
	Benthic invertebrates: sponges; bryozoans (*Alcyonium* sp.); mollusss: (*Acrocnida brachiata*), (*Cardium echinatum*, (*Callista chione*), (*Lapidoplax digitata*), razorshell (*Ensis siliqua*), (*Mactra stultorum*), (*Solecurtus scopula*); lugworms (*Arenicola marina*); echinoderms (*Echinus esculentis*), (*Marthasterias glacialis*), (*Caryophyllia smithi*), heart urchins (*Echinocardium cordatum*); crustaceans: (*Cancer pagrurus*), fish: sand eels (*Ammodytes tobianus*), lesser weever (*Trachinus vipera*), dragonet (*Callionymus lyra*), great pipefish (*Syngnathus acus*), ballan wrasse (*Labrus bergylta*); moribund (*Luraria lutraria*)	1978	southwestern England	Boalch (1979, Forster (1979), Griffiths et al. (1979)
	Mass mortality of marine organisms, including bivalves (*Mesoderma mactroides*)	1978	southern Brazil	Machado (1979), Rosa and Buselato (1981)
	Benthic invertebrates: limpets (*Patella* spp.), mussels (*Mytilus* spp.), Atlantic dogwinkle (*Nucella lapillus*), common top shell (*Calliostoma zizyphinus*), (*Phalliusia mamillata*), moribund (*Gibbula umbilicaris*), (*Tealis felina*), common periwinkle (*Littorina littorea*), whelks (*Buccinium undatum*); hermit crab (*Pagurus bernhardus*); sea anemones (*Actinia equina*), (*Hydractinia echinata*); (*Paracentrotus lividus*) losing spines; wild fish: father lasher (*Myxocephalus bubalis*), straight-nosed pipefish (*Nerophis ophiodon*), eel (*Anguilla anguilla*), sand smelt (*Atherina presbyter*), blenny (*Blennius montagui*), wrasse (*Crenilabrus melops*), black goby (*Gobius niger*), rock goby (*G. paganellus*), two-spotted goby (*Gobiusculus flavescens*), sand goby (*Pomatoschistus minutus*), painted goby (*P. pictus*), sand eel (*Hyperoplus lanceolatus*), shanny (*Lipophrys pholis*), ling (*Molva molva*), pipefish (*Syganthus acus*), sea scorpion (*Taurulus bubalis*), horse mackerel (*Trachurus trachurus*), farmed salmonids	1979	southwestern Ireland	Cross and Southgate (1980), Jenkinson and Connors (1980)
	Farmed fish (*Salmo salar*)	1980	Firth of Clyde, west Scotland	Jones et al. (1982)
	Bivalves (*Mesoderma mactroides*), cnidarians, echinoderms, menhaden (*Brevoortia* sp.)	1981	Rio Grande do Sol, Brazil	Rosa and Buselato (1981)
	Fish	1981	southern Norway	Dahl and Tangen (1993)
	Fish	1982	southern Norway	Dahl and Tangen (1993)
	Fish	1982	Douarnenez Bay, France	Lassus et al. (1985)
G. cf. *aureolum*	Post-larval scallops (*Pecten maximus*)	1983	Brest Bay, Brittany, France	Erard-le-Denn et al. (1990)
G. cf. *aureolum*	Blue mussels (*Mytilus edulis*), lady crab (*Ovalipes ocellatus*)	1984 1985	Long Beach Island to Ocean City, New Jersey, USA	Mahoney et al. (1990)
	Fish	1985	southern Norway	Dahl and Tangen (1993)
	Fish: salmon	?1987	New Zealand	Chang (1989)
	Post-larvae ceased feeding and mortality in young scallops (*Pecten maximus*)	1988	France	Lassus and Berthome (1988) cited in

					Shumway (1990)
	Fish: rainbow trout (*Oncorhynchus mykiss*), cod (*Gadus morhua*)	1988	southern Norway		Dahl and Tangen (1989, 1990, 1993)
	Molluscs: softshell clam (*Mya arenaria*), blue mussels (*Mytilus edulis*); unidentified marine worms	1988	Maquoit Bay, Maine, USA		Heinig and Campbell (1992)
	Atlantic salmon (*Salmo salar*), rainbow trout (*Oncorhynchus nerka*)	1990	Skagerrak-Kattegat, south Norway		Tangen (1990a), Dahl and Tangen (1993)
	Invertebrates: lugworms (*Arenicola marina*); moribund cockle (*Cardium edule*), macoma (*Macoma* spp.), venus (*Venus striatula*), tellina (*Tellina tenuis*), (*Scrobicularia* spp.), heart urchins (*Echinocardium cordatum*); urochordates	1990	southern Wales		Olive and Cadnam (1990)
	Cultured seabass (*Dicentrarchus labrax*), bogue (*Boops boops*); wild fish	1991 and on	Bougrara, Tunisia		Romdhane et al. (1998)
	Atlantic salmon (*Salmo salar*) in one fish farm	1991	Flekkefjord, southwestern Norway		ICES (1993)
	Clam larvae	1992	Southern Brittany, France		ICES (1993)
	Farmed Atlantic salmon (*Salmo salar*)	1992	Flekkefjord, southwestern Norway		ICES (1993)
	Bivalves: wedge shell (*Mesodesma mactroides*), donax clam (*Donax hanleyanus*); crustaceans: (*Emerita brasiliensis*); fish: mullet (*Mugil* sp.)	1993	Cassino Beach, south Brazil		Odebrecht et al. (1995)
	Fish, molluscs, echinoderms	1994	Broadhaven, Dyfed, Wales		ICES (1995)
as *G. cf. nagasakiense*	Wild and farmed fish: (*Pleuronectes* sp.), (*Solea* sp.), eels, congers; shellfish: banded wedge shell (*Donax vittatus*), (*Cardium* sp.), (*Venerupis* sp.), (*Tellina* sp.), (*Glycimeris* sp.), oysters (*Ostrea* sp.), (*Crassostrea* sp.), (*Solen* sp.), mussels (*Mytilus* sp.), limpets (*Patella* sp.), abalone (*Haliotis* sp.), (*Littorina* sp.); sea urchins (*Echinocardium cordatum*); lugworms (*Arenicola* sp.)	1995	Brittany, France		Arzul et al. (1995c), ICES (1996)
	Fish and benthic invertebrates	1997	Western and southern Kattegat, Denmark		ICES (1998)
	Abalone	1998	Streamstown Bay, west coast Ireland		ICES (1999)
Gymnodinium pulchellum (as (*Gymnodinium* sp.)	Benthic fish, molluscs, and crustacea	1950	Port Phillip Bay, Melbourne, Australia		Wood (1964), Maclean (1979)
as. *Gymnodinium* sp.	Fish	1959	Port Phillip Bay, Melbourne, Australia		Maclean (1979)
as *Gymnodinium* sp. type 84K	Fish - natural and in aquaculture	1984	Kagoshima Bay, Japan		Onoue et al. (1985)
	Fish	1994	Port Phillip Bay, Melbourne, Australia		Hallegraeff (1991)
	Fish: common snook (*Centropomus undecimalis*), striped mullet (*Mugil cephalus*), hardhead catfish (*Arius felis*), red drum (*Sciaenops ocellatus*), sheepshead (*Archosargus probatocephalus*), black drum (*Pogonias cromis*); blue crab (*Callinectes sapidus*), shrimp (*Penaeus* spp.)	1996	Indian River, Florida, USA		Steidinger et al. (1998b)
Gymnodinium sp.	Hundreds of inshore fish	1976	False Bay, west coast of South Africa		Brown et al. (1979)
Gymnodinium sp.	Shellfish	1978	South Brazil		Machado (1979)
Gymnodinium sp.	Wild and cultured fish	1983	Tolo Harbor, Hong Kong		Phillips pers. comm. in Maclean (1984)

TABLE 2. (continued)

Gymnodinium sp.	Farmed penaeid shrimp and fish – associated poor water quality	1989	Huanghua, China	Xu et al. (1993)
Gymnodinium sp.	Death of thousands of vlei sardine (*Hepsetia breviceps*), blacktail (*Diplodus sargus*), chitons (*Chiton tulipa*), (*Dinoplax gigas*), limpets (*Patella compressa*), (*P. longicosta*), (*P. barbara*), (*P. argenvillei*), abalone (*Haliotis midae*), (*H. spadicea*), periwinkle (*Oxystele sinensis*), (*O. variegata*), turbans alikreukel (*Turbo sarmaticus*), (*T. cidaris*), whelks (*Charonia lampas pustulata*), (*Burnupena papyraceen*), (*B. cincta*), Mediterranean mussel (*Mytilus galloprovincialis*), brown mussel (*Perna perna*), octopus (*Octopus vulgaris*)	1988-1989	False Bay, South Africa	Horstman et al. (1991)
Gymnodinium sp.	Farmed salmon	1990	Faroe Islands	ICES (1991)
Gymnodinium sp.	Larval abalone	1995-1996	Walker Bay, west coast South Africa	Pitcher and Matthews (1996)
Gymnodinium sp.	Marine organisms	1993	Bream Bay, New Zealand	MacKenzie et al. (1995)
Gymnodinium sp.	Salmon, abalone and other molluscs, sipunculids, worms	1999	Chiloe, Chile	Clement et al. (1999)
Gyrodinium corsicum? (as *G.* cf. *nagasakiense* and as *Gymnodinium* sp.)	500 kg of sea bass (*Dicentrarchus labrax*), bogue (*Boops boops*	1993	Bay of Diana, Corsica	Arzul et al. (1994), ICES (1994)
Gyrodinium corsicum	Cultured fish: sea bass (*Dicentrarchus labrax*), gilthead sea bream (*Sparus auratus*	1994	Bay of Diana, Corsica	Paulmier et al. (1995)
	Cultured fish: gilthead sea bream (*Sparus auratus*); Mediterranean mussel (*Mytilus galloprovincialis*); wild fauna	1994	Alfacs Bay, Ebro Delta, Spain	Garcés et al. (1999)
	Wild fish and mussels	1997	Alfacs Bay, Ebro Delta, Spain	ICES (1998)
	Mediterranean mussel (*Mytilus galloprovincialis*)	1998	Alfacs Bay, Ebro Delta, Spain	ICES (1999)
Gyrodinium sp.	Caged fish: yellowtail (*Seriola quinqueradiata*), Japanese flounder (*Paralichthys olivaceus*), other demersal fish	1992	South sea of Korea	Kim et al. (1995)
Gyrodinium spirale	Oysters	1985	Thau Basin, southern France	Tournier and Guillou (1985) cited in Lassus and Belin (1991)
Heterocapsa circularisquama	Japanese littleneck clam (*Venerupis philippinarum*), Mediterranean mussel (*Mytilus galloprovincialis*), loss of 1560 tonnes	1988	Uranouchi Bay, Kochi Prefecture, Japan	Matsuyama et al. (1995) , Matsuyama (1999)
	Mass mortality of Japanese littleneck clam (*Venerupis philippinarum*), Mediterranean mussel (*Mytilus galloprovincialis*), Pacific oyster (*Crassostrea gigas*), razor shell (*Solen strictus*), surfclam (*Mactra chinensis*)	1989	Fukuoka Bay, Fukuoka Prefecture, Japan	Yamamoto and Tanaka (1990)
	30-90% mortality loss of >18 million pearl oyster (*Pinctada fucata*); mass mortality of Pacific oyster (*Crassostrea gigas*), Mediterranean mussel (*Mytilus galloprovincialis*), scallop (*Chlamys nobilis*)	1992	Ago Bay, Japan	Matsuyama et al. (1995, 1996), Matsuyama (1999)
	50-90% decrease of harvest of Japanese littleneck clam (*Venerupis philippinarum*), mass mortality of Pacific oyster (*Crassostrea gigas*)	1993	Lake Hamana, Japan	Matsuyama (1999)
	40-90% mortality of pearl oyster (*Pinctada fucata*) in areas with extensive assemblages	1994	Ago Bay, Japan	Matsuyama et al. (1996), Matsuyama (1999)

	Mean 65.4% mortality of pearl oyster (*Pinctada fucata*) in 2 year-old individuals; mean 69.5% mortality of Japanese littleneck clam (*Venerupis philippinarum*); mass mortality of Pacific oyster (*Crassostrea gigas*), razor shell (*Solen strictus*), (*Mactra veneriformis*), (*Musculista senhousia*), (*Anomalocardia squamosa*), (*Dosinorbis japonica*), (*Glossaulax didyma*)	1994	Kusu-ura Bay, Japan	Yoshida and Miyamoto (1995) cited in Matsuyama (1999)
	5-36% mortality of pearl oyster (*Pinctada fucata*)	1995	Ago Bay, Japan	Matsuyama (1999)
	36-68% mortality loss of 610 tonnes of Pacific oyster (*Crassostrea gigas*), 5-36% mortality of pearl oyster (*Pinctada fucata*), >70% mortality loss of 210 tonnes of Japanese littleneck clam (*Venerupis philippinarum*), 10-55% mortality of Mediterranean mussel (*Mytilus galloprovincialis*)	1995	Hiroshima Bay, Seto Inland Sea, Japan	Matsuyama et al. (1997a)
	Mass mortality of pearl oyster (*Pinctada fucata*), loss of 1.5 million individuals	1996	Ago Bay, Japan	Matsuyama (1999)
	Mass mortality of pearl oyster (*Pinctada fucata*), Pacific oyster (*Crassostrea gigas*), Mediterranean mussel (*Mytilus galloprovincialis*)	1997	Obama Bay, Japan	Matsuyama (1999)
	Mass mortality in spat and adult Pacific oyster (*Crassostrea gigas*), 75% mortality of Mediterranean mussel (*Mytilus galloprovincialis*) in assemblage areas, mortality of natural populations of abalone (*Sulculus diversicolor*)	1997	Hiroshima Bay, Japan	Matsuyama (1999)
	Loss of 210 tonnes of Japanese littleneck clam (*Venerupis philippinarum*)	1997	Buzen Sea, Japan	Etou et al. (1998)
	50% decrease of spat yield in Japanese littleneck clam (*Venerupis philippinarum*), considerable mortality of Pacific oyster (*Crassostrea gigas*), (*Mactra veneriformis*)	1997	Suo-nada, Japan	Matsuyama (1999)
	30-98% mortality loss of 5,000 tonnes of Pacific oyster (*Crassostrea gigas*), 50-90% mortality of Japanese littleneck clam (*Venerupis philippinarum*)	1998	Hiroshima Bay, Japan	Matsuyama (1999)
	Considerable mortality of (*Atrina pectinata*)	1998	Suo-nada, Japan	Matsuyama (1999)
Karenia brevis (= *Gymnodinium breve*)	Fish	1844	Florida, USA	Ingersoll (1882)
	Fish	1854	Florida, USA	Ingersoll (1882)
	Fish	1865	Key West, Florida, USA	Glazier (1882)
	Fish, conch, and sponges	1878	southwestern Florida, USA	Jefferson (1879), Jefferson et al. (1879), Glazier (1882), Moore (1882)
	Fish: mullet (*Mugil cephalus*), gar (*Lepisosteus* sp.), hardhead catfish (*Arius felis*), snapper (*Lutjanus griseus*), Warsaw grouper (*Epinephelus nigritis*), perch (*Diplectrum formosum*), kingfish (*Menticirrhus americanus*), spotted trout (*Cynoscion nebulosus*)), sharks, rays, eels; oysters; birds: terns, gulls, frigate birds, ducks, vultures, sick cormorants	1880	Tampa Bay to Key West, Florida, USA	Glazier (1882), Ingersoll (1882), Moore (1882), Walker (1884)
	Fish	1882	Florida, USA	Anonymous (1956) cited in Rounsefell and Nelson (1966)
	Fish	1883	Florida, USA	Anonymous (1956) cited in Rounsefell

TABLE 2. (continued)

				and Nelson (1966)
	Fish	1885	Egmont Ket to Charlotte Harbor, Florida, USA	Glenman (1887)
	Fish	1908	Florida, USA	Anonymous (1956) citedin Rounsefell and Nelson (1966)
	63 species of fish; sea urchins (*Arbacia*), horseshoe crabs (*Limulus polyphemus*), sponges (*Ircinia* sp.)	1916	Southwestern Florida, USA	Taylor (1917a, 1917b)
	Fish	1932	Florida, USA	Anonymous (1956) cited in Rounsefell and Nelson (1966)
	Fish	1935	Port Aransas, Texas, USA	Burr (1945), Lund (1935) cited in Rounsefell and Nelson (1966), Gunter (1952)
	Estimated 50 million fish: hardhead catfish (*Arius felis*), gafftopsail catfish (*Bagrus marinus*), porgies (*Calamus* sp.), sand sea trout (*Cynoscion arenarius*), spotted seatrout (*Cynoscion nebulosus*), pinfish (*Lagodon rhomboides*), halfbeak (*Hyporhamphus unifasciatus*), silver jenny (*Eucinostomus gula*), Atlantic bumper (*Chloroscombrus chrysurus*), oyster toadfish (*Opsanus tau*), Gulf menhaden (*Brevoortia patronus*), ?purplemouth moray (*Gymnothorax vicinus*), ?spotted moray (*G. moringa*), cowfish (*Lactophrys quadricornis*), white grunt (*Haemulon plumieri*), bluestriped grunt (*H. sciurus*), sailors choice (*H. parra*), gray angelfish (*Pomacanthus arcuatus*), southern kingfish (*Menticirrhus americanus*), Gulf kingfish (*M. littoralis*), leopard searobin (*Prionotus scitulus*), longnose batfish (*Ogcocephalus vespertilio*), shortnose batfish (*O. radiatus*), spiny box fish, butterfish (*Peprilus paru*), Atlantic moonfish (*Selene setapinnis*), Atlantic spadefish (*Chaetodipterus faber*), snook (*Centropomus undecimalis*), barracuda (*Sphyraena barracuda*), spot (*Leiostomus xanthurus*), striped mullet (*Mugil cephalus*), eel (*Ophichthus* sp.), speckled worm eel (*Myrophis punctatus*), jack crevalle (*Caranx hippos*), bluerunner (*C. chrysos*), round scad (*Decapterus punctatus*), ladyfish (*Elops saurus*), leatherjacket (*Oligoplites saurus*), Atlantic needlefish (*Strongylura marina*), queen triggerfish (*Balistes vetula*), planehead filefish (*Monacanthus hispidus*), northern puffer (*Sphoeroides maculatus*)), checkered puffer (*S. testudineus*), striped burrfish (*Chilomycterus schoepfi*), blackcheek tonguefish (*Symphurus plagiusa*), sole (*Achirus* sp.), yellowtail amberjack (*Seriola lalandi*), Spanish mackerel (*Scomberomorus maculatus*), scaled sardine (*Harengula pensacolae*), sheepshead (*Archosargus probatocephalus*), cobia (*Rachycentron canadus*), tarpon (*Tarpon atlanticus*), tripletail (*Lobotes surinamensis*), redfish (*Sciaenops ocellatus*), black drum (*Pogonias cromis*), black grouper (*Mycteroperca bonaci*), warsaw grouper (*Epinephelus nigritus*); molluscs: eastern oysters (*Ostrea virginicus*), quahogs (*Mercenaria* sp.), Florida coquina (*Donax variabilis*); crustaceans: blue crabs (*Callinectes sapidus*), horseshoe crabs (*Limulus polyphemus*), lady crabs (*Hepatus epheliticus*), shrimp (*Penaeus* sp.), barnacles (*Balanus* sp.); bottlenose dolphins (*Tursiops truncatus*); turtles; pelicans, seagulls	1946-1947	Dry Tortugas to Boca Grande, Florida, USA	Gunter et al. (1947, 1948), Davis (1948), Galstoff (1948)
	Fish	1951	Florida, USA	Anonymous (1956) cited in Rounsefell and Nelson (1966)

	Fish	1952	Florida, USA	Anonymous (1956) cited in Rounsefell and Nelson (1966)
	Several thousand fish: yellowtail amberjack (*Seriola lalandi*), whiting, jack crevalle (*Caranx hippos*), redfish (*Sciaenops ocellatus*), pompano (*Trachinotus carolinus*), eel, ladyfish (*Elops saurus*), catfish (*Arius felis*), toadfish (*Opsanus tau*), mullet (*Mugil cephalus*), speckled trout (*Cynoscion nebulosus*), puffer (*Sphoeroides* sp.), angelfish, porcupine fish (*Diodon hystrix*), red snapper (*Lutjanus campechanus*), shiner, flounder (*Paralichthys albigutus*), grouper, sheepshead (*Archosargus probatocephalus*); horseshoe crab (*Limulus polyphemus*)	1953-1954	Southwestern Florida, USA	Lackey and Hynes (1955)
	Fish	1955	Rio Grande to Port Isabel, Texas, USA	Wilson and Ray (1956)
	Fish	1959-1960	Venice to Clearwater, Florida, USA	Finucane (1960, 1961) cited in Rounsefell and Nelson (1966)
	Lancelet (*Branchiostoma* sp.), fish: hardhead catfish (*Arius felis*), gafftopsail catfish (*Bagrus marinus*), porgy (*Calamus* sp.), spotted seatrout (*Cynoscion nebulosus*), sand seatrout (*C. arenarius*), sand perch (*Diplectrum formosum*), pinfish (*Lagodon rhomboides*), halfbeak (*Hyporhamphus* sp.), goldspotted killifish (*Floridichthys carpio*), longnose killifish (*Fundulus similis*), oyster toadfish (*Opsanus tau*), Gulf menhaden (*Brevoortia patronus*), cowfish (*Lactophrys quadricornis*), trunkfish (*L. trigonus*), white grunt (*Haemulon plumieri*), tomtate (*H. aurolineatum*), southern stargazer (*Astroscopus y-graecum*), silver perch (*Bairdiella chrysura*), southern kingfish (*Menticirrhus americanus*), sharksucker (*Echeneis naucrates*), balloonfish (*Diodon holocanthus*), leopard searobin (*Prionotus scitulus*), longnose batfish (*Ogcocephalus vespertilio*), shortnose batfish (*O. radiatus*), spiny box fish, butterfish (*Peprilus triacanthus*), harvestfish (*P. alepidotus*), Atlantic moonfish (*Selene setapinnis*), Atlantic spadefish (*Chaetodipterus faber*), Atlantic midshipman (*Porichthys porasissimus*), short bigeye (*Pristigenys alta*), spot (*Leiostomus xanthurus*), striped mullet (*Mugil cephalus*), eel (*Ophichthus* sp.), palespotted eel (*O. ocellatus*), speckled worm eel (*Myrophis punctatus*), sooty eel (*Basanichthys teres*), bank cusk-eel (*Ophiodon holbrooki*), crevalle jack (*Caranx hippos*), blue runner (*C. chrysos*), ladyfish (*Elops saurus*), leatherjacket (*Oligoplites saurus*), redfin needlefish (*Strongylura notata*), queen triggerfish (*Balistes vetula*), gray triggerfish (*B. capriscus*), orange filefish (*Aluerus schoepfi*), bay anchovy (*Anchoa mitchelli*), northern puffer (*Sphoeroides maculatus*), striped burrfish (*Chilomycterus schoepfi*), blackcheek tonguefish (*Symphurus plagiusa*), tidewater silverside (*Menidia beryllina*), lined sole (*Achirus lineatus*), thread herring (*Opisthonema oglinum*), inshore lizardfish (*Synodus foetens*), yellowtail amberjack (*Seriola lalandi*), Spanish mackerel (*Scomberomorus maculatus*), scaled sardine (*Harengula pensacolae*), pompano (*Trachinotus carolinus*), sheepshead (*Archosargus probatocephalus*), cobia (*Rachycentron canadus*), sailfish (*Istiophorus platypterus*), black drum (*Pogonias cromis*), black grouper (*Mycteroperca bonaci*), red grouper (*Epinephelus morio*); crustaceans: blue crabs (*Callinectes sapidus*). horseshoe crabs (*Limulus polyphemus*); marine mammals: 7 manatees (*Trichechus manatus latirostris*)	1963	Tampa Bay and Pine Island area, Florida, USA	Finucane et al. (1964) and Moe (1964) cited in Rounsefell and Nelson (1966). Layne (1965)
	Fish	1967-1968	St. Petersburg Beach, Florida, USA	Morton and Burklew (1969)

TABLE 2. (continued)

	Fish: red grouper (*Epinephelus morio*), graysby (*E. cruentatus*), jewfish (*E. itajara*), gag (*Mycteroperca microlepis*), scamp (*M. phenax*), belted sandfish (*Serranus subligarius*), gray snapper (*Lutjanus griseus*), southern sea bass (*Centropristis melana*), gray triggerfish (*Balistes capriscus*), porgy (*Calamus* sp.); lancelets: (*Branchiostoma caribbaeum*); invertebrates: (*Acanthohaustorius* sp.), (*Omphis eremita oculata*), (*Trevisia* sp.), crustaceans: amphipods, (*Diopatra cuprea*), (*Mulinia lateralis*), crabs (*Pinnixa* sp.), (*Glotidia pyramidatum*), (*Scolopios rubra*), (*S. fragilis*), (*Scololepis squamata*), decapods; polychaetes: ragworm (*Nereis succinea*), (*Glycera americana*), (*G. capitata*), (*Clymenella mucosa*), (*Laeonereis culveri*, (*Branchioasychus americanus*), (*Phoronis architecta*); corals; ascideans; molluscs: minor jackknife (*Ensis minor*), bruised nassa (*Nassarius vibex*)	1971	Tampa Bay, Florida, USA	Simon and Dauer (1972), Smith (1976)
	Massive fish kills: tomtate (*Haemulon aurolineatum*), striped mullet (*Mugil cephalus*), ladyfish (*Elops saurus*), bay anchovies (*Anchoa mitchelli*), spinner shark (*Carcharinus macullpinnis*), black tip shark (*C. limbatus*); birds: several thousand lesser scaup (*Aythya affinis*), double-crested cormorant (*Phalacrocorax auritus*), red-breasted merganser (*Mergus merganser*)	1973-1974	West coast Florida, USA	Quick and Henderson (1974, 1975), Forrester et al. (1977)
	Fish	1976-1977	Southwestern and southeastern Florida, USA	Roberts (1979)
	Fish striped mullet (*Mugil cephalus*), hardhead catfish (*Arius felis*); birds double-creasted cormorant (*Phalacrocorax auritus*); 39 manatees (*Trichechus manatus latirostris*)	1982	West coast Florida, USA	O'Shea et al. (1991)
	Red drum (*Sciaenops ocellatus*)	1986	Port Aransas, Texas, USA	Riley et al. (1989)
	740 dolphins (*Tursiops truncatus*), bay scallop (*Argopecten irradians*) mortalities and failed recruitment	1987-1988	Atlantic coast between New Jersey and Florida, USA	Fowler and Tester (1989), Geraci (1989), Summerson and Peterson (1990), Morris et al. (1991)
	Mass fish mortalities, reports of dead birds and a dolphin	1990	Southwestern Florida, USA	ICES (1991)
	Fish	1990-1991	Laguna Madre, Texas, USA	ICES (1991)
	Fish: grunts, pinfish (*Lagodon rhomboides*), grouper, hardhead catfish (*Arius felis*), flounder, hogfish, eels, spadefish (*Chaetodipterus faber*), filefish, damselfish, angelfish, silver trout (*Cynoscion nothus*)	1992-1993	Southwestern Florida, USA	ICES (1993)
	Fish	1994-1996	Southwestern Florida, USA	ICES (1995, 1996), Steidinger et al. (1995)
	Gulf menhaden (*Brevoortia patronus*)	1995	Laguna Madre, Texas, USA	ICES (1996)
	149 manatees (*Trichechus manatus latirostris*), fish, turtles	1996	Southwestern Florida, USA	Bossart et al. (1998), Landsberg and Steidinger (1998)
	Fish	1997	Florida	ICES (1998)
	14 million fish	1997	Texas	ICES (1998)
	Fish	1998-	Southwestern Florida, USA	ICES (1999)

		1999		
Karenia brevisulcata	Fish: eel, flounder, yellow-eye mullet (*Aldrichetta forsteri*), barracouta (*Thyrsites atun*), mackerel, leather jacket, stargazer, kahawai (*Arripis trutta*), tuna, striped marlin (*Tetrapturus audax*), broadbill swordfish (*Xiphias gladius*); invertebrates: sea urchins, sea slug, starfish, abalone; brown seaweed (*Macrocystis pyrifera*)	1997-1998	Central east coast, New Zealand	Chang (1999a, 1999b)
Karenia digitata (as *Gymnodinium* sp.)	Red sea bream (*Pagrus major*), Japanese flounder (*Paralichthys olivaceus*), sea bass (*Lateolabrax japonicus*)	1995	Shimonoseki Port, western Japan	Baba et al. (1997)
	80,000 cultured fish red sea bream (*Pagrus major*), file fish (*Acanthurus xanthopterus*), yellowtail (*Seriola quinqueradiata*), horse mackerel (*Trachurus japonicus*)	1997	Bingo-nada, Inland Sea of Japan, west Japan and Hong Kong	Yang et al. (2000)
(as *Gymnodinium mikimotoi* and *Gyrodinium* sp.)	1500 metric tons of farmed fish: coral trout (*Plectropomus* sp.), brown coral cod (*Cephalopholis boenak*), giant grouper (*Epinephalus lanceolatus*), yellow grouper (*E. awoara*), mud grouper (*E. bruneus*), tiger grouper (*E. fuscoguttatus*), brown spotted grouper (*E. chlorostigma*), mangrove snapper (*Lutjanus argentimaculatus*), red snapper, Russell's snapper (*Lutjanus russelli*), Japanese sea perch, black seabream, head grunt (*Pomadasys argenteus*), eel, red pargo (*Pagrus major*), yellow croaker (*Larimichthys polyactis*), purplish amberjack (*Seriola dumerili*), pompano (*Trachinotus blochii*); cultured red macroalgae *Porphyra tenuera*	1998	Southern China and Hong Kong	Dickman and Tang (1999), Yang and Hodgkiss (1999), Dickman (2000)
Karenia mikimotoi (= (*G. nagasakiense*) as *Gymnodinium* sp. presumptive	Pearl oyster (*Pinctada fucata*)	1893	Gokasho Bay, Toba, Japan	Miyake (1893) cited in Miyajima (1934) cited in Nightingale (1936) and cited in Schwimmer and Schwimmer (1968)
as *Gymnodinium* sp. presumptive	Pearl oyster (*Pinctada fucata*)	1910	Gokasho Bay, Toba, Japan	Miyajima (1934) cited in Nightingale (1936)
	Pearl oyster (*Pinctada fucata*)	1926	Gokasho Bay, Toba, Japan	Miyajima (1934) cited in Nightingale (1936)
	Pearl oyster (*Pinctada fucata*) and fish	1933-1934	Gokasho Bay, Toba, Japan	Miyajima (1934) cited in Grindley and Taylor (1964), Oda (1935) cited in Matsuoka et al. (1989); Sommer et al. (1937)
	Shellfish: pearl oyster (*Pinctada fucata*), ark shell (*Anadrona broughtoii*), octopus; sea cucumber	1965	Omura Bay, Kyushu Island, Japan	Shiokawa and Irie (1966) in Matsuiama et al. (1998), Okaichi (1989)
	700,000 yellowtail (*Seriola quinqueradiata*)	1979	Bungo Channel, Seto Inland Sea, Japan	Okaichi (1989)
	530,000 yellowtail (*Seriola quinqueradiata*)	1980	Bungo Channel, Seto Inland Sea, Japan	Okaichi (1989)
	Molluscs	1981	Chinhae Bay, Korea	Park (1982) cited in Kim et al. (1995); Cho (1981) cited in Kim (1998)
	290,000 red sea bream (*Pagrus major*)	1982	Hiuchi, Seto Inland Sea, Japan	Okaichi (1989)
	5.6 million yellowtail (*Seriola quinqueradiata*) and other fish species	1985	Suoh and Iyo, Seto Inland Sea, Japan	Okaichi (1989)

TABLE 2. (continued)

	Fish: Moses perch (*Lutjanus johni*), red snapper (*L. argentimaculatus*), croaker (*Otolithus argenticus*), Indian flathead (*Thysanophrus indicus*), marine catfish (*Tachysurus* sp.), sole (*Scylla serrata*); crab (*Portunus pelagicus*)	1989	Someshwar to Uchila, west India	Karunasagar and Karunasagar (1992)
	Farmed fish (*Tilapia* sp.), (*Eroplus* sp.), milkfish (*Chanos* sp.)	1989	Kodi, Karnataka State, India	Karunasagar (1993)
	Fish?	1991?	southeastern Tasmania	Hallegraeff (1991)
	Molluscs: pearl oyster (*Pinctada fucata*), Pacific oyster (*Crassostrea gigas*), clam (*Meretrix lusoria*), ark shell (*Anadara broughtoii*), abalone (*Haliotis discus*), horned turban (*Turbo cornutus*)	1994?	Japan	Yamaguchi et al. (1994) cited in Matsuyama et al. (1998a)
Gymnodinium sp. (= *K. mikimotoi*?)	Wild fish	1994	Gulf of Gabes, Tunisia	Arzul et al. (1995)
Karenia sp. (as *Gymnodinium* sp.)	30 tons of wild mullet (*Liza macrolepis*), 150 tons of caged sobiaty (*Acanthopagrus cuvieri*)	1999	Kuwait Bay, Kuwait	Al-Yamani et al. (2000), Husain and Faraj (2000), Heil et al. (2000), (A. Haywood and K. Steidinger, pers.comms.)
Karlodinium micrum (=*Gymnodinium galatheanum*)	Fish	1940s	Walvis Bay, South Africa	Brongersma-Sanders (1948)
	Fish	1950	Walvis Bay, South Africa	Braarud (1957)
	Fish and other marine life	1965	Walvis Bay, South Africa	Pieterse and Van der Post (1967)
	Fish	1997	Swakopmund, Namibia	Pitcher (1998)
	Fish	1999	Murray River estuary, Australia	Cosgrove et al. (2000)
K. cf. *micrum* (as *G.* cf. *galatheanum*)	Fish: eels, bream, flathead mullet	?	Lake Illawara, New South Wales, Australia	Hallegraeff (1992a)
Lingulodinium polyedrum (= *Gonyaulax polyedra*) (as *Gonyaulax* sp.)	Approx. 400 animals, holothurians (*Trachostoma arenata*), stingray (*Mylobatis californicus*), Haller's round ray (*Urolophus halleri*), guitarfish (*Rhinobatus productus*), thornback guitarfish (*Platyrhinoidis triseriata*) (as *T. triseriatus*), horn shark (*Heterodontus* francisci) (as *Gyropleurodus francisci*), dogfish (*Galeus californicus*), blindfish (*Typhlogobius californicus*), red perch, smelt; octopus; (*Tevila crassatelloidis*), flat porcelain crab (*Petrolisthes cinctipes*), brown rock crab (*Cancer antennarius*), morbid sand crab (*Emerita analoga*) (as *Hippa analoga*)	1901	Santa Barbara to San Diego, California, USA	Torrey (1902)
	Dead bottom fauna including fish and shellfish	1907	San Pedro to San Diego, California, USA	Kofoid (1911)

	Fish and shore fauna	1917	Santa Barbara, California, USA	Allen (1917) cited in Schwimmer and Schwimmer (1968)
	Marine organisms?	1949?	Portugal	Pinto (1949)
	Molluscs: limpets (*Lottia* as *Acmaea conus*), (*Tectura* as *A. depicta*), ?(*A. undose*), barrel-bubble ?(*Acteocina californica*), California venus (*Chione californiensis*), frilled venus (*Chione undatella*), California cone (*Conus californicus*), onyx slippersnail (*Crepidula onyx*), California semele (*Cumingia californica*), Californian beanclam (*Donax californicus*), Gould beanclam (*D. gouldii*), blister glassy-bubble (*Haminoea vesicula*), Pacific eggcockle (*Laevicardium substriatum*), straight horsemussel (*Modiolus rectus*), western mud nassa (*Nassarius tiarula*) (as *N. tegulus*), beatic dwarf olive (*Olivella baetica*), purple dwarf olive (*O. biplicata*), kelp scallop (*Leptopecten* [as *Pecten*] *l. latiauratus*), moonsnail (*Neverita reclusiana*) (as *Polinices reclusianus imperforatus*), Mexican pyramidella (*Pyramidella mexicana*), California tagelus (*Tagelus californianus*), banded pheasant (*Eulithidium compta*) (as *Tricolia compta*), ?(*Vesica gouldiana*); sipunculids (*Sipunculus nudus*); fish: Californian anchovy (*Engraulis mordax*)	1958	Ensenada, Baja California, Mexico	Stohler (1959)
	Demersal fish and shellfish	1980	Kaštela Bay, Adriatic Sea, Croatia	Marasović (1989, 1990)
	Demersal fish and shellfish	1985	Kaštela Bay, Adriatic Sea, Croatia	Marasović (1989, 1990)
	Demersal fish and shellfish	1987	Kaštela Bay, Adriatic Sea, Croatia	Marasović (1989, 1990)
	Demersal fish and shellfish	1989	Kaštela Bay, Adriatic Sea, Croatia	Marasović (1990)
	Demersal fish and shellfish	1990	Kaštela Bay, Adriatic Sea, Croatia	Marasović (1990)
Noctiluca scintillans	Geelbek fish	1869	Stumpnose Bay, South Africa	Gilchrist (1914) cited in Schwimmer and Schwimmer (1968)
	Fish, mussels, klip fish	1907	Saldanha Bay, South Africa	Gilchrist (1914) cited in Schwimmer and Schwimmer (1968)
	Fish and other marine animals including shellfish	1907	False Bay, Simonstown, South Africa	Gilchrist (1914) cited in Schwimmer and Schwimmer (1968)
	Mullet, massbanker	1928	Walvis Bay, South Africa	Marchand (1928) cited in Schwimmer and Schwimmer (1968)
	Marine fauna: anemones: (*Cavernularis*) sipunculids: fish: tetrodons, diodons, fish fry, probably due to anoxia associated with heavy bloom	1935	Madras coast of India	Aiyar (1936) cited in Schwimmer and Schwimmer (1968)
	Fish	1948	Walvis Bay, South Africa	Brongersma-Sanders (1948)
	Giant sea catfish (*Arius thallasinus*), Bengal tongue sole (*Cynoglossus semifasciatus*), orangefin ponyfish (*Leiognathus bindus*), Japanese threadfin bream (*Synagris japonicus*), shrimp scad (*Alepes djedaba*) (as *Caranx kalla*), shark (*Carcharias* sp.), sole	1948	Malabar and Kanara coasts, India	Bhimachar and George (1950)

TABLE 2. (continued)

	Localized mortality of inshore fish: – mackerel, hottentot (*Pachymetopon blochii*), mooinooientjie, steentjie (*Spondyliosoma emarginatum*), various sharks	1967	False Bay, Simonstown, South Africa	Horstman (1981)
	Fish	1969	St. Lucia estuary, Natal, South Africa	Grindley and Heydorn (1970)
	Fish	1973	Central west coast of India	Devassy (1989)
	Demersal fish and benthic invertebrates	1986	Jakarta Bay, Indonesia	Adnan (1989)
	Brown mussel (*Perna perna*)	1988	Punta Patilla Bay, Venezuela	La Barbera Sanchez (1991)
	Bottom fauna	1989	Northern Adriatic Sea, Italy	Boni et al. (1989)
	Shrimp (*Penaeus orientalis*) mortality, impact on the brown macroalga (*Laminaria*) industry, shrimp disease	1989-1990	Hebei Province, China	Fengqi (1990), Chen and Gu (1993), Qi et al. (1993b)
	Fish	1992	Hong Kong	Ho and Hodgkiss (1992)
	Farmed Atlantic salmon (*Salmo salar*)	1997	Southwestern Ireland	ICES (1998)
Peridinium polonicum	Fish: freshwater minnow (*Zacco platypus*), crucian carp (*Carassius carassius*), common carp (*Cyprinus carpio*), pond smelt (*Hypomesus olidus*)	1962	Lake Sagami, Tokyo, Japan	Hashimoto et al. (1968)
Pfiesteria piscicida	Numerous fish species	1985	New and Neuse rivers, North Carolina, USA	Burkholder et al. (1995), Burkholder and Glasgow (1997)
	Blue crab (*Callinectes sapidus*)	1986	Pamlico River, North Carolina, USA	Burkholder et al. (1995) Burkholder and Glasgow (1997)
	Numerous fish species	1987	Pamlico River, North Carolina, USA	Burkholder et al. (1995)
	Striped mullet (*Mugil cephalus*), spotted sea trout (*Cynoscion nebulosus*), Atlantic menhaden (*Brevoortia tyrannus*)	1988	Pamlico River, North Carolina, USA	Burkholder et al. (1995)
	Northern quahogs (*Mercenaria mercenaria*); fish: southern flounder (*Paralichthys lethostigmata*), spot (*Leiostomus xanthurus*), hogchoker (*Trinectes maculatus*), Atlantic menhaden (*Brevoortia tyrannus*), Atlantic croaker (*Micropogonias undulatus*)	1989	Pamlico and Neuse rivers, North Carolina, USA	Burkholder et al. (1995)
	Southern flounder (*Paralichthys lethostigmata*), spot (*Leiostomus xanthurus*), hogchoker (*Trinectes maculatus*), Atlantic menhaden (*Brevoortia tyrannus*); blue crab (*Callinectes sapidus*)	1990	Pamlico River, North Carolina, USA	Burkholder et al. (1995)
	Several million Atlantic menhaden (*Brevoortia tyrannus*), southern flounder (*Paralichthys lethostigmata*), spot (*Leiostomus xanthurus*), hogchoker (*Trinectes maculatus*), white perch (*Morone americana*), channel catfish (*Ictalurus punctatus*), striped mullet (*Mugil cephalus*), American eel (*Anguilla rostrata*), sheepshead (*Archosargus probatocephalus*)	1991	Pamlico and Neuse rivers, North Carolina, USA	Burkholder et al. (1995)
	Several thousand Atlantic menhaden (*Brevoortia tyrannus*), Atlantic croaker (*Micropogonias undulatus*), southern flounder (*Paralichthys lethostigmata*)	1992	Pamlico and Neuse rivers, Taylors Creek, North Carolina, USA	Burkholder et al. (1995)
	Cultured 25,000 hybrid striped bass (*Morone saxatilis*) x (*Morone chrysops*)	1992	Near Pamlico River, North Carolina, USA	Burkholder et al. (1995)

	Several hundred thousand Atlantic menhaden (*Brevoortia tyrannus*), spot (*Leiostomus xanthurus*), blue crab (*Callinectes sapidus*)	1993	Pamlico and Neuse rivers, North Carolina, USA	Burkholder et al. (1995)
	Cultured 8,000 northern quahogs (*Mercenaria mercenaria*) larvae	1994	Camp Lejeune, White Oak River, North Carolina, USA	Burkholder et al. (1995)
	Millions of fish: Atlantic menhaden (*Brevoortia tyrannus*), southern flounder (*Paralichthys lethostigmata*), spot (*Leiostomus xanthurus*), striped mullet (*Mugil cephalus*), American eel (*Anguilla rostrata*), spotted sea trout (*Cynoscion nebulosus*)	1995	New, Pamlico, Neuse, and Roanoke rivers and estuaries	Burkholder and Glasgow (1997)
	Millions of fish: Atlantic menhaden (*Brevoortia tyrannus*)	1996	Cape Fear, Neuse, and New estuaries, North Carolina, USA	Burkholder and Glasgow (1997)
	Thousands of Atlantic menhaden (*Brevoortia tyrannus*)	1997	Pocomoke and Chicamicomico rivers, Chesapeake Bay, Maryland, USA	Burkholder (1998), Burkholder et al. (1999)
P. shumwayae (as *Pfiesteria*-like sp.)	>1000 fish affected	1995	New River, North Carolina, USA	Burkholder and Glasgow (1997)
	>100,000	1995	Pamlico estuary, North Carolina, USA	Burkholder and Glasgow (1997)
	Thousands of fish affected	1996	Neuse estuary, North Carolina, USA	Burkholder and Glasgow (1997)
Prorocentrum balticum (as *Exuviella baltica*)	Fish	1951	Bay of Luanda, Angola, Africa	Silva (1953) cited in Schwimmer and Schwimmer (1968), Nümann (1957) cited in Rounsefell and Nelson (1966)
	Farmed Atlantic salmon (*Salmo salar*)	1997	Ireland	ICES (1998)
Prorocentrum micans	Few dead cormorants and fish	1956	Between Arica and Iquique, Chile	Manning (1957) cited in Avaria (1979)
	Fish	1968	New Jersey, USA	Ogren and Chess (1969) cited in Mahoney (1989)
	White mussel (*Donax serra*)	1973	Dwarskersbos, South Africa	Horstman (1981)
	Fish	1975-1976	Callao, Peru	Rojas de Mendiola (1979)
	Wild fish and caged salmon	1984	South Chile	Lembeye and Campodónico (1984) cited in Clement and Lembeye (1993)
	40-50% mortality of blue mussels (*Myrilus edulis*) due to low dissolved oxygen	1988	North Brittany, France	Lassus and Berthome (1988) in Shumway (1990)
Prorocentrum minimum	Fish – associated water quality?	1977	Bohai Bay, China	Yu (1987) cited in Tseng et al. (1993)
	Fish: pike conger (*Congresox* sp.), saddle grunt (*Pomadasys maculatum*), small scaled terapon (*Terapon puta*), flathead (*Platycephalus* sp.), milk shark (*Scoliodon* sp.), spotted croaker (*Protonibea diacanthus*), sea catfish (*Arius* sp.), blotched croaker (*Nibea maculata*), long-toothed salmon (*Otolithes ruber*)	1987	Gwadar Bay, southwestern Pakistan	Rabbani et al. (1990)
	Old oysters	1988	France	Lassus and Berthome (1988) cited in Shumway (1990)

TABLE 2. (continued)

Prorocentrum sp.	Flat oyster (*Ostrea rivularis*)	1994	Zhaijiang, south China	Yongjia et al. (1995)
Prorocentrum sp.	Fish	2000	Zhoushan archipelago, Zhejiang, China	ICES (2001)
Pyrodinium bahamense var. *compressum*	Dead turtles, fish, and porpoises washed ashore in Milne Bay area (including Trobriands) and Talasea; vectors molluscs (*Anadara maculosa*)	1956	Trobriand Islands, Talasea, West New Britain, Papua New Guinea	Maclean (1973)
	Dead fish and turtles; vectors brachiopods (*Lingula*), oyster (*Saccostrea cucullata*)	1961	Talasea, New Britain, Papua New Guinea	Maclean (1973)
	Dead fish and turtles	1963	Talasea, Papua New Guinea	Maclean (1973)
	Skipjack tuna (*Katsuwomus pelamis*)	1970	Bootless Bay, Port Morseby, Papua New Guinea	Maclean (1973)
	Turtles and fish	1971	Lae, Morobe Harbour, Port Moresby, Papua New Guinea	Maclean (1973)
	Red tide visible, dead mullet and (*Gerres* sp.) and dead oysters	1972	Lae Morobe Harbour, Port Moresby, Papua New Guinea	Maclean (1973)
	Dead bivalves; mortalities of reef and pelagic fish, invertebrates: corals, hydroids, sponges, molluscs, crustaceans, echinoderms – low dissolved oxygen	1976	Sabah, Malaysia	Maclean (1979, 1984), Sang and Ming (1984)
	Mortality of 10 dogs and 1 hen; vectors - fish: goldstriped sardinella (*Sardinella gibbosa*), Indian oil sardine (*S. longiceps*), yellostripe scad (*Selaroides leptolepis*)	1983	Lewotobi and Lewouran, east Flores, east Indonesia	Adnan (1993)
	Dead clams reported at Sipitang and Xota Kinabaluh	1988	Setabu area in Nunukan, South Sebatik Island; also Kota Kinabalu, Sabah	Adnan (1993)
	Fish, 145 turtles, several hundred lobsters	1996	SW coast of Mexico	Orellana-Cepeda et al. (1998)
Scrippsiella trochoidea (as *Glenodinium rubrum*)	Implicated in mortality of oysters, mussels, limpets, starfish, worms, ascidians; absence of crustaceans and small fish	1891	Sydney Harbor, Australia	Whitelegge (1891) Hallegraeff (1992a)
	Implicated in fish kill	?1914	Rio de Janeiro, Brazil	Faria (1914) cited in Odebrecht et al. (1995)
With *Anabaena spiroides*	Large numbers of fish dying rapidly	1956-1957	Lagoa Rodrigo de Freitas and Bay of Guanabara, Brazil	Oliveira et al. (1957) cited in Schwimmer and Schwimmer (1968)
With *Heterosigma akashiwo*	Fish	1988	Island of Eysturoy, Faroe Islands	Shannon (1988)

TABLE 3. Diatom species and documented mortalities (wild or aquaculture) or health impacts on aquatic organisms

Species	Event and organism affected	Date	Location	Reference
Diatoms				
Cerataulina pelagica	Bloom, anoxia, clogging of fish gills	1983	Northeast New Zealand	Taylor et al. (1985)
Chaetoceros criophilum	Fish	1961	Southeast Tasmania	?
C. concavicornis with *C. convolutus*	Atlantic salmon (*Salmo salar*), chinook salmon (*Oncorhynchus tschawytscha*), coho salmon (*O. kisutch*), rainbow trout (*O. mykiss*)	1987, 1988	British Columbia, Canada	Taylor (1988, 1993), Albright et al. (1993)
C. concavicornis with *C. convolutus*	Atlantic salmon (*Salmo salar*)	1987, 1988	Puget Sound, Washington, USA	Rensel et al. (1989)
C. convolutus	Lingcod (*Ophiodon elongatus*)	1960?	British Columbia, Canada	Bell (1961)
	Salmonids	1989	British Columbia, Canada	Stockner (1989)
	Low mortalities: mucus and diatoms in gills of Atlantic salmon (*Salmo salar*)	1991	Chiloe, Chile	Clement and Lembeye (1993)
	Crustacea: red king crab (*Paralithodes camtschatica*)	1992	Captains Bay, Unalaska Island, Alaska	Tester and Mahoney (1995)
C. debilis (as *C. debile*) and *C. wighami* with *Dictyocha speculum*	Farmed salmon	1988	Shetland Isles, Scotland	Bruno et al. (1989)
C. socialis	Farmed salmon	1999	Bay of Fundy, Canada	ICES (2000)
C. wighami	Atlantic salmon (*Salmo salar*)	1988	Upper Loch Torridon, west coast Scotland	Bruno et al. (1989), Johnson (1988)
Corethron sp.	Coho salmon (*Oncorhynchus kisutch*)	1987	British Columbia	Speare et al. (1989)
Coscinodiscus centralis	Discolored water, oily film, adherence to bird's feathers, mortality	1947	North Sea	Tåning (1951) and Grøntved (1952) cited in Hasle and Fryxell (1995)
Coscinodiscus concinnus	Discolored water, oily film, adherence to bird's feathers, mortality	1947	North Sea	Tåning (1951) and Grøntved (1952) cited in Hasle and Fryxell (1995)
Leptocylindrus minimus	Salmon and trout detected with high concentrations >26,000 cells/ml, implicated in kills but mechanism unknown	1989	south Chiloe, Chile	Clement and Lembeye (1993)
	Salmon and trout	1993	south Chiloe, Chile	Clement (1994)
Pseudo-nitzschia australis	43 brown pelicans (*Pelecanus occidentalis*), 95 cormorants (*Phalacrocorax penicillatus*)	1991	Santa Cruz, California, USA	Work et al. (1992, 1993)
	More than 400 California sealions (*Zalophus californianus*)	1998	Monterey Bay, California, USA	Gulland et al (1998), Lefebvre et al (1999), Scholin et al. (2000)
Pseudo-nitzschia sp.	More than 150 dead brown pelicans (*Pelecanus occidentalis*), other seabirds	1996	Baja California, Mexico	Sierra Beltran et al. (1996), Ochoa et al. (1996)
Rhizosolenia chunii	Unmarketable seafood due to bitter taste; extensive inflammation and degeneration of digestive glands; shellfish mortality 3-8 months after bloom – mussels (*Mytilus planulatus*), scallops (*Pecten alba*), oysters (*Ostrea angasi*)	1987	Port Phillip Bay, Australia	Parry et al. (1989)

TABLE 3. (continued)

Rhizosolenia sp.	Salmonids	1987	Jervis Inlet, British Columbia, Canada	Taylor (1988)
Skeletenoma costatum	Fish farms	1990	Skaggerak-Kattegat, southern Norway	Tangen (1991a)
	Atlantic herring (*Clupea harengus*) eggs, due to bloom smothering and anoxia	1990	Arran, Firth of Clyde, Scotland	Morrison et al. (1991)
S. costatum with *Thalassiosira aestivalis* and *T. rotula*	Farmed Atlantic salmon (*Salmo salar*)	1994	Quadra Island, British Columbia, Canada	Kent et al. (1995)
Thalassiosira mala	Mucilaginous colonies, discolored water, clogged gills, mortality of bivalves	1951	Tokyo Bay, Japan	Takano (1956, 1965) cited in Hasle and Fryxell (1995)

TABLE 4. Prymnesiophyte species and documented mortalities (wild or aquaculture) or health impacts on aquatic organisms

Species	Event and organism affected	Date	Location	Reference
Prymnesiophytes				
Chrysochromulina birgeri	Fish	1996	Nova Scotia, Canada	Carver and Eikrem, pers. comm. in Edvardsen and Paasche (1998)
C. breviturrita	Tadpoles	1979	Dickie Lake, Ontario, Canada	Nicholls et al. (1982)
C. leadbeateri	Atlantic (*Salmo salar*) and sea urchins	1991	Vestfjorden, north Norway	Johanessen et al. (1991) cited in Hansen et al. (1995), Rey and Aure (1991), Tangen (1991b), Aune et al. (1992), Eikrem and Throndsen (1993), Heidal and Mohus (1995)
C. parva	Roach (*Rutilus rutilus*), perch (*Perca fluviatilis*), pike (*Esox lucius*)	1991	Freshwater lake, Zealand, Denmark	Hansen et al. (1994)
With *Prymnesium parvum*	Fish	1991, 1992	Bay of Holminge, near Stockholm, Sweden	Holmquist and Willén (1993)
C. polylepis	Mortalities or animals that were affected by the bloom: invertebrates: pelican's foot (*Aporrhais pespelicani*), (*Ascidiella* sp.), ragworm (*Nereis* sp.), starfish (*Asteria rubens*), waved whelk (*Buccinium undatum*), sea squirt (*Ciona intestinalis*), (*Corella parallelogramma*), sea urchins (*Echinus esculentus*), gray topshell (*Gibbula cinneria*), common periwinkle (*Littorina littorea*), whelk (*Nassarius reticulatus*), dog whelk (*Nucella lapillus*), limpets (*Patella* cf. *vulgata*), blue mussels (*Mytilus edulis*), (*Sabella penicilus*), (*Styela rustica*), (*Alcyonium digitatum*), (*Cyprina islandica*), bryozoa (*Electra pilosa*), (*Hiatella arctica*), (*Ophiura albida*), (*Psammechinus miliaris*), barnacles (*Balanus improvisus*), crabs (*Cancer pagurus*), (*Carcinus maenus*), frilled anemone (*Metridium senile*), hermit crab (*Pagurus* cf. *bernhardus*), (*Uricina felina*); fish rock cook (*Centrolabrus rupestris*), goby (*Gobius* spp.), ballan wrasse (*Labrus bergylta*), cuckoo wrasse (*Labrus bimaculatus*), dragonet (*Callionymus lyra*), fivebeard rockling (*Ciliata mustela*), herring (*Clupea harengus*), rock gunnel (*Pholis gunnellus*), pollock (*Pollachius pollachius*), tadpole fish (*Raniceps raninus*), sea trout (*Salmo trutta*), pipefish (*Syngnathus* spp.), poor cod (*Trisopterus minutus*), garfish (*Belone belone*), lumpsucker (*Cyclopterus lumpus*), snake pipefish (*Entelurus aequoreus*), Atlantic salmon (*Salmo salar*), cod (*Gadus morhua*), sunfish (*Molva molva*), whiting (*Merlangius merlangus*), Norwegian topknot (*Phrynorhombus norvegicus*), plaice (*Platichthys flesus*); Frayed, discolored thalli in macroalgae: sea beech (*Delesseria sanguinea*), red macroalgae (*Dilsea carnosa*), (*Eudhora cristata*), (*Lomentaria clavellosa*), red fern (*Ptilota plumosa*), (*Phycodrys rubens*), green macroalgae (*Chaetomorpha melangonium*), brown macroalgae (*Desmarestia aculeata*), sea oak (*Halidrys siliquosa*), sea brush (*Odonthalia dentata*), leaf weed (*Coccotylus* = *Phyllophora truncata*), tubed weed (*Polysiphonia urceolata*)	1988	Skagerrak and Kattegat, Norway, Sweden and Denmark	Underdal et al. (1989), Robertson (1991)

TABLE 4. (continued)

Chrysochromulina sp.	Salmon	1993	Byfjorden Bergen, west coast Norway	ICES (1994)
Chrysochromulina spp.	Caged rainbow trout (*Oncorhynchus mykiss*)	1992	Lillebælt, Denmark	Knipschildt (1992), Moestrup (1992), Hansen et al. (1995)
Phaeocystis globosa	60,000 tons of caged fish	1997	Fujian and Guangdong Provinces, China	Lu and Huang (1999)
Phaeocystis pouchetii	Littoral invertebrates: lugworm (*Arenicola marina*), Baltic macoma (*Macoma baltica*)	1988	Conwy estuary, Wales	Rogers and Lockwood (1990)
	Fish (various species) and crabs	1992	Conwy to Abergele, Wales	ICES (1993)
	Fish	1997	North Guangdong Province and south Fujian Province, China	Songhui and Hodgkiss (1999)
Phaeocystis scrobiculata	Fish: salmon	1992	Norway	Tangen (pers. comm.) in Moestrup and Thomsen (1995)
Prymnesium calathiferum	Fish and shellfish	1983	Bream Bay, New Zealand	Chang (1985)
Prymnesium parvum	Fish	1890	Baltic coast of Germany	Strodtmann (1898), and Lenz (1933) cited in Moestrup (1994)
	Fish	1909	Wateneverstorfer Lakes, Germany	Lenz (1933) cited in Edvardsen and Paasche (1998)
	Fish	1914	Wateneverstorfer Lakes, Germany	Lenz (1933) cited in Edvardsen and Paasche (1998)
	Fish	1920	Wateneverstorfer Lakes, Germany	Lenz (1933) cited in Edvardsen and Paasche (1998)
	Fish: roach (*Rutilus rutilus*), reed roach, whitebait, bream (*Abramis brama*), pike (*Esox lucius*), tench (*Tinca tinca*), eel (*Anguilla anguilla*)	1920	Workumer Niewland Polder, Holland	Liebert and Deerns (1920)
	Fish	1932	Wateneverstorfer Lakes, Germany	Lenz (1933) cited in Edvardsen and Paasche (1998)
	Fish	1938	Ketting Nor, Denmark	Otterstrøm and Steemann Nielsen (1939)
	Fish	1939	Selsø Lake, Denmark	Otterstrøm and Steemann Nielsen (1939)
	Fish in aquaculture (e.g., common carp *Cyprinus carpio*)	1945 and on	Israel	Reich and Aschner (1947), Sarig (1971)
	Fish	1953	Black Sea, Bulgaria	Petrova (1966), Moncheva et al. (1995)
	Fish	1959	Black Sea, Bulgaria	Petrova (1966), Moncheva et al. (1995)
	Fish	1962-1964	Fenland Drainage system, Norfolk, England	Farrow (1969)
	Fish	1963	Black Sea, Bulgaria	Petrova (1966), Moncheva et al. (1995)
	Common carp (*Cyprinus carpio*), other fish	1969	Yuzhnyy fish farm, Ukraine	Krasnoshchek and Abramovich (1971)

	200,000 fish: pike (*Esox lucius*), perch (*Perca fluviatilis*), roach (*Rutilus rutilus*), bream (*Abramis brama*), eel (*Anguilla anguilla*)	1969	Norfolk Broads, England	Holdway et al. (1978)
	Fish	1970	Norfolk Broads, England	Holdway et al. (1978)
	Fish	1971	Kazankov fish farm, Ukraine	Krasnoshchek et al. (1972)
	Fish	1972	Obidos Lagoon, Portugal	Silva (1980) cited in Sampayo (1989)
	Fish	1973	Norfolk Broads, England	Holdway et al. (1978)
	Common carp (*Cyprinus carpio*)	1975	Fehmarn, Germany	Hickel (1976)
	Fish	1975	Norfolk Broads, England	Holdway et al. (1978)
	Fish	1977	Ebro Delta, Mediterranean Sea, Spain	Comin and Ferrer (1978)
	Fish?	1978?	England	Holdway et al. (1978)
	Eels (*Anguilla anguilla*) in pond	1978	Schleswig-Holstein, Germany	Dietrich and Hesse (1990)
	Recurrent fish mortalities	?	Vasse-Wonnerup estuary, West Australia	W. Hosja (pers. comm.) in Hallegraeff (1992a)
	Several million fish: gar (*Lepisosteus osseus*), common carp (*Cyprinus carpio*), largemouth bass (*Micropterus salmoides*), flathead catfish (*Pylodictus olivaris*), Rio Grande darter (*Etheostoma grahami*), mosquitofish (*Gambusia affinis*); bivalves: (*Corbicula fluminea*)	1985-1986, 1988	Pecos River, Texas, USA	James and de la Cruz (1989)
	Fish	1988-1990	Shandong, China	Yang et al. (1993)
Misidentified as *P. saltans* (see Moestrup, 1994)	Eel (*Anguilla anguilla*), bream (*Abramis brama*), silver bream (*Blicca bjoerkna*), roach (*Rutilus rutilus*), rudd (*Scardinius erythrophthalmus*), pike-perch (*Stizostedion lucioperca*), pike (*Esox lucius*), bighead (*Aristichthys nobilis*), perch (*Perca fluviatilis*)	1990	Bodden water, near Isle of Rugen, Germany?	Tangen (1990b), Kell and Noack (1991), Moestrup (1994)
Misidentified? should be *P. patelliferum*?	Bleak (*Alburnus alburnus*), crucian carp (*Carassius carassius*), three-spined stickleback (*Gasterosteus aculeatus*), pike (*Esox lucius*), roach (*Rutilus rutilus*), rudd (*Scardinius erythrophthalmus*), perch (*Perca fluviatilis*)	1990	Dragsfjärd, Finland	Lindholm and Virtanen (1992)
Misidentified?	Atlantic salmon (*Salmo salar*), rainbow trout (*Oncorhynchus mykiss*)	1990	Hylsfjord and Sandsfjord, Stavanger, Norway	Tangen (1990a, 1991b)
	Fish	1990	Botshol, Utrecht, Holland	Rip et al. (1992)
Misidentified with *Chrysochromulina parvum*	Fish	1991, 1992	Bay of Holminge, near Stockholm, Sweden	Holmquist and Willen (1993)

TABLE 4. (continued)

Prymnesium cf. *parvum* (possibly (*P. patelliferum*?)	Farmed salmon	1993	Ryfylke, southwest Norway	ICES (1994)
Presumptive *P. parvum*	Lake fish: bleak (*Alburnus alburnus*), silver bream (*Blicca bjoerkna*), crucian carp (*Carassius carassius*), three-spined stickleback (*Gasterosteus aculeatus*), pike (*Esox lucius*), roach (*Rutilus rutilus*), rudd (*Scardinius erythrophthalmus*), perch (*Perca fluviatilis*), ruff (*Acerina cernua*, burbot (*Lota lota*); crayfish (*Astacus astacus*); swan mussels (*Anodonta cygnea*)	1997	Lake Vargsundet, Åland, southwest Finland	Lindholm (1997), Lindholm et al. (1999)
Prymnesium patelliferum (note Green et al. 1982 attributed this report to *P. patelliferum* not *P. parvum* as described by Valkanov 1964)	Fish, polychaetes, crustaceans, molluscs (*Unio*), (*Anodonta*), and protozoans	1959	Varna lake, Bulgaria	Valkanov (1964) and Petrova (1966) cited in Moestrup (1994) and Edvardsen and Paasche (1998)
	Fish?	1963	Varna lake, Bulgaria	Valkanov (1964) cited in Moestrup (1994) and Edvardsen and Paasche (1998)
	Fish?	1964	Burgas lake, Bulgaria	Valkanov (1964) cited in Moestrup (1994) and Edvardsen and Paasche (1998)
Reported as *P. parvum* (see Larsen et al. 1993)	Salmon (*Salmo salar*), rainbow trout (*Oncorhynchus mykiss*), brisling (*Sprattus sprattus*), whiting (*Merlangius merlangus*), cod (*Gadus morhua*); zooplankton	1989	Ryfylke, southwest Norway	Johnsen (1989), Johnsen and Lein (1989), Kaartvedt et al. (1991), Graneli et al. (1993), Larsen et al (1993)
Reported as *P. parvum*	Atlantic salmon (*Salmo salar*)	1991	Ryfylke, southwest Norway	ICES (1993)
	Fish in pond	1991	Jutland, Denmark	Bach and Jacobsen (1991) cited in Moestrup (1994), and in Edvardsen and Paasch (1998)
	Fish	1992?	Tianjin, China	Wang and Wang (1992)
	Fish	1999	Lake Massaciuccoli, Italy	Mattioli and Simoni (1999)
Prymnesium parvum and *P. patelliferum*	Farmed Atlantic salmon (*Salmo salar*)	1995	Ryfylke, southwest Norway	ICES (1996)
Prymnesium saltans	Fish	1983-1986	Ponds in Tianjin, China	Wang and Wang (1992), Edvardsen and Paasch (1998)

TABLE 5. Raphidophyte species and documented mortalities (wild or aquaculture) or health impacts on aquatic organisms

Species	Event and organism affected	Date	Location	Reference
Raphidophytes				
Chattonella antiqua with *Fibrocapsa japonica*	Mass mortality of fish	1970	Bingo-Nada, Seto Inland Sea, Japan	Iwasaki (1971)
	14 million yellowtail (*Seriola quinqueradiata*)	1972	Harima-Nada, Seto Inland sea, Japan	Okaichi (1989)
	3.3 million yellowtail (*Seriola quinqueradiata*)	1977	Harima-Nada, Seto Inland sea, Japan	Okaichi (1989)
	2.8 million yellowtail (*Seriola quinqueradiata*)	1978	Harima-Nada, Seto Inland sea, Japan	Okaichi (1989)
	1.04 million yellowtail (*Seriola quinqueradiata*)	1979	Harima-Nada, Seto Inland sea, Japan	Okaichi (1989)
	380,000 yellowtail (*Seriola quinqueradiata*)	1982	Harima-Nada, Seto Inland sea, Japan	Okaichi (1989)
	300,000 yellowtail (*Seriola quinqueradiata*)	1983	Kii Channel, Seto Inland sea, Japan	Okaichi (1989)
	Yellowtail (*Seriola quinqueradiata*)	1986	Harima-Nada, Seto Inland sea, Japan	Okaichi (1989)
	1.43 million yellowtail (*Seriola quinqueradiata*)	1987	Harima-Nada and Kii Channel, Seto Inland sea, Japan	Okaichi (1989)
C. marina	Fish	1954	Malabar coast, India	Subrahmanyan (1954)
	Fish	1980s	Kagoshima Bay, Japan	Onoue and Nozawa (1989a), Onoue et al. (1990)
	30-50% prawn mortality in ponds where blooms occurred	1985	Johor Straits, Malaysia	Khoo (1985), Maclean (1989)
	Bluefin tuna (*Thunnus maccoyii*)	1996	Boston Bay, Australia	Hallegraeff et al. (1998)
C. verruculosa	Fish in culture	1990?	Tokuyama Bay, China	Yamamoto and Tanaka (1990) in Imai et al. (1998)
	Marine fauna?	1995?	Fukuoka Bay, China	Baba et al. (1995)
C. aff. *verruculosa*	Cultured Atlantic salmon (*Salmo salar*), wild fish, garfish (*Belone belone*), Atlantic herring (*Clupea harengus*), Atlantic mackerel (*Scomber scombrus*)	1998	Farsund-Flekkefjord area, southwestern Norway; west coast of Denmark	ICES (1999), Backe-Hansen et al. (2000)
C. cf. *verruculosa*	1-2.5 million Atlantic menhaden (*Brevoortia tyrannus*)	2000	Bald Eagle Creek, Delaware, USA	Bourdelais et al. (2002)
Chattonella sp.	Fish	1987	Amurskii Bay, Russia	Simakova et al. (1990) cited in Orlova et al. (1998)
Fibrocapsa japonica with *C. antiqua*	Fish	1970	Bingo-Nada, Seto Inland Sea, Japan	Iwasaki (1971)
	Yellowtail (*Seriola quinqueradiata*)	1972	Ehime Prefecture, Japan	Okaichi (1972) cited in Khan et al. (1996b)
Heterosigma akashiwo	Fish	1976	Lummi Island, Washington, USA	Gaines and Taylor (1986) cited in Black et al. (1991)
	Coho salmon (*Oncorhynchus kisutch*), chinook salmon (*O. tschawytscha*)	1986-1989	British Columbia, Canada	Taylor (1988, 1993)

TABLE 5. (continued)

	Cultured sea bass (*Dicentrarchus labrax*)	1987	Ria de Arousa, Spain	Fraga (1988)
	Farmed Atlantic salmon (*Salmo salar*)	1987	Hvalfjörour, Iceland	ICES (1991)
	Cultured Atlantic salmon (*Salmo salar*), wild fish	1988	Chile	Parra et al. (1991) cited in Clement and Lembeye (1993)
with *Scrippsiella trochoidea*	Fish	1988	Island of Eysturoy, Faroe Islands	Shannon (1988)
	Chinook salmon (*Oncorhynchus tschawytscha*)	1989	Big Glory Bay, New Zealand	Chang et al. (1990)
	Atlantic salmon (*Salmo salar*), chinook salmon (*Oncorhynchus tschawytscha*)	1990	Central Puget Sound, Washington, USA	ICES (1991)
	Penned salmon	1992	West coast Vancouver Island, British Columbia, Canada	ICES (1993)
	Farmed Atlantic salmon (*Salmo salar*), rainbow trout (*Oncorhynchus mykiss*)	1994	Camaret Bay, western Brittany, France	Arzul et al. (1995c), ICES (1995)
	Coho salmon (*Oncorhynchus kisutch*), chum salmon (*O. keta*), chinook salmon (*O. tschawytscha*), flat fish, and sculpin	1994	South Puget Sound, Washington, USA	ICES (1995), Hershberger et al. (1997)
	Yellowtail (*Seriola quinqueradiata*)	1995	Kagoshima Bay, Japan	Khan et al. (1996c)
	100,000 cultured salmon	1997	Puget Sound, Washington, USA	ICES (1998)
	Cultured salmon	2000	West coast Vancouver Island, British Columbia, Canada	ICES (2001)

TABLE 6. Silicoflagellates, pelagophytes, and ciliates and documented mortalities (wild or aquaculture) or health impacts on aquatic organisms

Species	Event and organism affected	Date	Location	Reference
Silicoflagellates				
Dictyocha speculum (= *Distephanus speculum*)	Farmed Atlantic salmon (*Salmo salar*)	1979	Loch Striven, west coast Scotland	Droop et al. (1980) cited in Gowen (1987)
	Farmed Atlantic salmon (*Salmo salar*), rainbow trout (*Oncorhynchus mykiss*)	1982	Upper Loch Fyne, west coast Scotland	Gowen et al. (1982) cited in Gowen (1987)
	Benthic invertebrates and cultured Atlantic salmon (*Salmo salar*)	1983	Kattegat, Denmark	Aertebjerg and Borum (1984)
	Rainbow trout (*Oncorhynchus mykiss*)	1987	Douarnenez, France	Erard-le-Denn et al. (1990)
	Farmed Atlantic salmon (*Salmo salar*)	1988	Northwest coast Scotland	Johnson (1988)
	Atlantic salmon (*Salmo salar*)	1996	Merexo Inlet, Galicia, Spain	Prego et al. (1998)

Species	Event and organism affected	Date	Location	Reference
Pelagophytes				
Aureococcus anophagefferens	Molluscs: bay scallop (*Argopecten irradians*), blue mussel (*Mytilus edulis*)	1985?	Long Island, New York; Naragansett Bay, Rhode Island; Barnegat Bay, New Jersey, USA	Cosper et al. (1987), Tracey (1985, 1988) Tracey et al. (1988), Smayda and Fofonof (1989)

Species	Event and organism affected	Date	Location	Reference
Ciliates				
Mesodinium rubrum	Rock lobster (*Jasus lalandii*), angelfish, butterfish, barbel, hottentot (*Pachymetopon blochii*), kingklip (*Genypterus capensis*), sucker fish, hagfish, (*Eptatretus*) sp., silverfish, trumpeter (*Pelates quadrilineatus*), guitar shark, striped shark, spotted lazy shark; thousands of sea urchins – associated with hypoxia	1978	St. Helena Bay, South Africa	Horstman (1981)
	Salmonids – associated either with low dissolved oxygen or supersaturation	1998	Passamaquoddy Bay, Bay of Fundy, Canada	Martin et al. (2000)

TABLE 7. Cyanobacteria species and documented mortalities (wild or aquaculture) or health impacts on aquatic organisms

Species	Event and organisms affected	Date	Location	Reference
Cyanobacteria				
Anabaena circinalis	Fish	1880	Lake near Zirke, Posen, west-central Poland, near the Wartha River	Cohn (1883) in Lampert (1899) in Schwimmer and Schwimmer (1968)
	Fish	1914	Lakes in Hungary	Naday (1914) in Schwimmer and Schwimmer (1968)
(with *M. aeruginosa*)	300 sheep, 5 cattle, and a horse	1959	Lake Bonney, South Australia	Mulhearn (1959) in Ressom et al. (1994), Yoo et al. (1995)
	Honeybees	1971	Burrinjuck Dam Reservoir, New South Wales, Australia	May and McBarron (1973)
	20 lambs	1975	Young, New South Wales, Australia	McBarron et al. (1975)
	Cows	1985	Lake Sääskjärvi, Finland	Ekman-Ekebom et al. (1992)
	Estimated mortality of 1,000 bats, (*Myotis* spp.), and hoary bat (*Lasiurus cinereus*); 24 mallards (*Anas platyrhynchos*) and American wigeon (*A. americana*)	1985	Steele Lake, Alberta, Canada	Pybus and Hobson (1986)
	1600 sheep, fish kills associated with anoxic conditions	1991	Darling River, Australia	Bowling (1992) in Yoo et al. (1995), Hallegraeff (1992b), Humpage et al. (1994)
	14 sheep	1994	Forbes, New South Wales, Australia	Negri et al. (1995)
Anabaena flos-aquae (with *Coelosphaerium kuetzingianum*)	1 sheep, 17 hogs, and approx. 50 chickens	1918	Oaks Lake, Windom, Minnesota, USA	Fitch et al. (1934)
(with *Microcystis flos-aquae* and *Aphanizomenon flos-aquae*)	45 turkeys, 4 ducks, 2 geese, cows, pigs, horses	1933	Lac Qui Parle, Milan, Minnesota, USA	Fitch et al. (1934)
(with *Microcystis flos-aquae*)	3 cattle	1933	Hall Lake, Fairmont, Minnesota, USA	Fitch et al. (1934)
	Pekin ducks, snakes, salamanders, carp, wild birds, horses, calf, herons,	1939	Fort Collins, Colorado, USA	Deem and Thorp (1939), and Durrell and Deem (1939) in Schwimmer and Schwimmer (1968)
	37 hogs, 4 sheep, 2 cattle, 3 horses, several dogs, cats, squirrels, chickens, turkeys, and songbirds	1944-1945	East Okoboji, Lower Garn, and Central lakes, Iowa, USA	Rose (1953)
	Dog; fish buffalo fish (*Megastomatobus cyprinella*), common carp (*Cyprinus carpio*), black bullhead (*Ictalurus melas* as *Amieurus melas*) also died possibly due to associated low dissolved oxygen	1948	Storm Lake, Iowa, USA	Rose (1953)
	7,000 Franklin's gulls, 560 ducks, 400 coots, 200 pheasants, 50 fox squirrels, 18 muskrats, 15 dogs, 4 cats, 2 hogs, 2 hawks, 1 skunk, 1 mink, and numerous songbirds	1952	Storm Lake, Iowa, USA	Rose (1953), Firkins (1953) in Schwimmer and Schwimmer (1968) and Moore (1977)
	20 dogs, 3 cattle, perch, wild ducks	1961	3 lakes, Saskatchewan, Canada	Gorham et al. (1964), Hammer (1968)

(with *Aphanizomenon* and *Microcystis aeruginosa*)	17 cattle	1965	Saskatchewan, Canada	Hammer (1968)
	3 calves, 12-15 cattle	1972	Alberta, Canada	Carmichael et al. (1977), Carmichael and Gorham (1978)
	4 dogs; 7 dogs, 1 horse, and 1 cow were sick; reported deaths of 2 ducks and a beaver were not verified	1976	Long Lake, Washington, USA	Soltero and Nichols (1981)
	30 cows and 8 dogs	1977	Hegben Reservoir, Montana, USA	Juday et al. (1981)
(with *Aphanizomenon flos-aquae* and *Microcystis aeruginosa*)	11 cattle	1984	Montana, USA	Spoerke and Rumock (1986)
	9 dogs and pups and 2 calves	1985	Richmond Lake, South Dakota, USA	Mahmood et al. (1988)
	5 ducks, 13 pigs	1986	Illinois, USA	Cook et al. (1989)
	6 calves	1988	Oklahoma, USA	Short and Edwards (1990)
	2 dogs	1991	Indiana, USA	Carmichael (1991)
	Approximately 1,000 brown trout (*Salmo trutta*)	1992	Fife, Scotland	Rodger et al. (1994)
Anabaena lemmermannii	About 40 cattle	1928	Lake Vesijarvi, Finland	Hindersson (1933) in Schwimmer and Schwimmer (1968)
	79 hogs, 2 horses, many ducks, chicken, cats, wild animals	1948	Fox Lake, Minnesota, USA	Olson (1951, 1952) in Schwimmer and Schwimmer (1968)
	Birds	1993-1994	Lake Knud so, Denmark	Henrickson et al. (1997), Onodera et al. (1997)
Anabaena sp.	Cattle	1914	Winnepeg Lake, Albion, Minnesota, USA	Cotton (1914)
	Cattle and other animals	1924	Fraser Lake, Ontario, Canada	Howard and Berry (1933) in Schwimmer and Schwimmer (1968)
	Fish, mergansers, divers, cats	1940-1942	Lake Ymsen, Mariestad, Skaraborg, Sweden	Berlin (1948) in Schwimmer and Schwimmer (1968)
	25 pigs	1967	Saskatchewan, Canada	Hammer (1968)
	600,000 rainbow trout (*Oncorhynchus mykiss*)	1989	northwestern Spain	Toranzo et al. (1990)
Anabaena spiroides	10 pigs	1981	southwestern Illinois, USA	Beasley et al. (1983)
	20 pigs	1987	Kentucky, USA	Chengappa et al. (1989)
	18 pigs	1989	Oklahoma, USA	Short and Edwards (1990)
Aphanizomenon flos-aquae	Cattle	1900	Lake near Fergus Falls, Minnesota, USA	Nelson (1903) in Fitch et al. (1934)

TABLE 7. (continued)

	Fish	1931-1933	Lake Okoboji and Storm Lakes, Iowa, USA	Prescott (1933, 1938) in Schwimmer and Schwimmer (1968)
	Fish, frogs, newts	1942	Zuiderzee, Holland	Kristensen (1941) in Schwimmer and Schwimmer (1968)
	Carp, northern pike, yellow pike, perch, black crappies, bluegills, suckers, black bullheads, buffalo, hog suckers, eels	1946	Yahara River, below Lake Kegonsa, Wisconsin, USA	Mackenthum et al. (1948)
(with *Microcystis aeruginosa*)	Heavy mortality of wild ducks	1949-1951	Manitoba, Canada	Bossenmaier et al. (1954) in Ressom et al. (1994)
	1 horse, 9 spaniel dogs	1951	Lake Dauphin, Manitoba, Canada	McLeod and Bondar (1952) in Schwimmer and Schwimmer (1968)
	Newfoundland dog	1959	Balgonie, Saskatchewan, Canada	Dillenberg (1959, 1961), and Dillenberg and Dehnel (1960) in Schwimmer and Schwimmer (1968)
	Moderate fish mortalities	1964	Lake Winnisquam, Laconia, New Hampshire, USA	Sawyer et al. (1968)
	Tons of fish died after copper sulphate added	1966	Kezar Lake, New Hampshire, USA	Sawyer et al. (1968)
	2 calves and 1 dog	1966	Saskatchewan, Canada	Hammer (1968)
	Toxic to tadpoles	1980	Farm pond near Durham, New Hampshire, USA	Ikawa et al. (1982)
Cylindrospermopsis raciborskii	13 cows and calves	1998	McKinley Shire, Queensland, Australia	Thomas et al. (1998)
Gloeotrichia echinulata	Horses, hogs, cattle	1882	Lakes Sakatah and Tetonka, Minnesota, USA	Porter (1886) in Fitch et al. (1934)
	Horses, cows	1883	Lakes Gorman, Cordova, Sakatah, and Tetonka, Minnesota, USA	Porter (1886) in Fitch et al. (1934)
Microcystis aeruginosa	Thousands of sheep, cattle, horses, mules, donkeys, dogs, hares, turkeys, ducks, fish	1913-1943	NE Orange Free State and SE Transvaal, South Africa	Steyn (1945), Stephens (1948)
	Livestock, rabbits and water birds	1927	Amersfoort District, South Africa	Steyn (1945)
(with *M. flos-aquae*)	9 cattle	1930	Lake Ann, Howard Lake, Minnesota, USA	Fitch et al. (1934)
	5 horses, 2 dogs, pheasants, heron and snipe	1948	Round Lake, Minnesota, USA	Olson (1951) and Scott (1952) in Schwimmer and Schwimmer (1968)
(with *Anabaena* spp.)	Cattle	1948-1949	Sturgeon Lake, Ontario, Canada	Barnum et al. (1950) and Stewart et al. (1950) in Schwimmer and Schwimmer (1968)

	Horses, livestock, ducks, geese, cats, dogs, waterfowl	1953	Lake Semekhovichi, Zhabchitskii District, Pinsk Province, Russia	Vinberg (1954) in Schwimmer and Schwimmer (1968)
	Common carp (*Cyprinus carpio*), catfish, sheatfish (*Silurus wels*), roach (*Rutilus rutilus*), bream (*Abramis brama*)	1956-1959	Volga River and delta, Russia	Kun et al. (1961) and Mikhailov and Tepli (1961) in Schwimmer and Schwimmer (1968)
(with *M. flos-aquae, Anabaena flos-aquae, Aphaniziomenon*)	Approximately 30 dogs, 1 goose, horses, and cattle	1959	Saskatchewan, Canada	Senior (1960), Dillenberg and Dehnel (1960)
As *Anacystis cyanaea*	20 lambs and 16 sheep, 50 sick sheep	1965 1966	Pleasant Hills and Armatree, New South Wales, Australia	McBarron and May (1966), Yoo et al. (1995)
	Lambs	1966?	Waipukurau, New Zealand	Flint (1966)
	Cattle	1973-1974	Hartbeespoort Dam, near Pretoria, South Africa	Toerien et al. (1976)
(with *Anabaena flos-aquae*)	34 cattle	1975	Saskatchewan, Canada	Carmichael et al. (1977), Carmichael and Gorham (1978)
As *Anacystis cyanaea*	Turkeys	1977	New South Wales, Australia	McBarron (1977) in Ressom et al. (1994)
	4 heifers	1978	Rogaland, Norway	Skulberg (1979) in Ostensvik et al. (1981), Underdal et al. (1999) and in Yoo et al. (1995)
	3 white rhinoceros (*Ceratotherium simum*)	1979	Klipvor Dam, Bophuthatswana, South Africa	Soll and Williams (1985)
	Cattle	1980	Vool Dam, South Africa	Scott et al. 1981
	25 sheep died	1981	New England, Australia	Jackson et al. (1983)
	Fish: pike (*Esox lucius*), pikeperch (*Sander lucioperca*)	1982-1987	Lakes Burtnieku, Dunu, and Riebizers, Latvia	Druvietis (1998)
	72 cows	1984	Goyena, Argentina	Odriozola et al. (1984)
As *Microcystis* sp.	Fish: silverside (*Odontesthes bonariensis*), common carp (*Cyprinus carpio*)	1984?	Aculeo Lake, central Chile	Vila et al. (1984, 1986) in Peñaloza et al. (1990)
	11 cows	1985	Green County, Wisconsin, USA	Galey et al. (1987)
	5 sick cows	1987	Mississippi, USA	Kerr et al. (1987)
	4 cows	1988	Oklahoma, USA	Short and Edwards (1990)
	Farmed fish	1988	Forez, France	Sevrin-Reyssac and Pletikosic (1990)
	7 mallard ducks	1989	Oklahoma, USA	Short and Edwards (1990)
	20 sheep and 15 dogs	1989	Rutland Water, Leicestershire, England	Edney (1990), Done and Bain (1993)
	Dog	1991	California, USA	De Vries et al. (1993)
	Sheep	1992	Lake Mokoan, Victoria, Australia	Carbis et al. (1995)
	3 Holstein heifers	1992	Central Michigan, USA	Fitzgerald and Poppenga (1993)

TABLE 7. (continued)

	11 sheep and photosensitivity in 20	1994	Malmesbury District, South Africa	Van Halderen et al. (1995)
	20 spot-billed ducks	1995	Nishinomiya, Hyogo Prefecture, Japan	Matsunaga et al. (1999)
	Approx. 30 herons and ducks	1995	Jehay, Belgium	Wirsing et al. (1998)
	Fish: long whiskered catfish (*Paraplotosus nigribarbis*)	1996	Patos lagoon, southern Brazil	Yunes et al. (1998)
	3 lambs	1997	Malmesbury District, South Africa	Harding (1997)
	Cattle	1997	South Georgia, USA	Frazier et al. (1998)
	Cattle	1998	Colorado, USA	Puschner et al. (1998)
Microcystis flos-aquae	13 sheep, 8 lambs, and numerous chickens	1933	Hall Lake, Fairmont, Minnesota, USA	Fitch et al. (1934)
Nodularia spumigena	Sheep, horses, pigs, dogs, and cattle	1878	Lake Alexandrina, nr Murray River, Australia	Francis (1878), Schwimmer and Schwimmer (1968)
	400 ducks	1963	Jasmunder Bodden, Germany	Kalbe and Tiess (1964)
(with *Anabaenopsis elenkinii*)	Fish	1964	Black Sea lagoon, Paliastomi, Georgia	Devidze (1998)
	34 sheep and 52 lambs	1974-1975	Broomhill District, SW Australia	Main et al. (1977)
	30 dogs sick, 20 died	1975	Aarhus, Baltic Sea, Denmark	Lindstrøm (1976) in Nehring (1993)
(with *Rhizosolenia fragilissima*)	Fish	1977	Black Sea lagoon Paliastomi, Georgia	Devidze (1998)
	9 dogs die either from drinking or ingesting cyanobacteria (hepatic necrosis)	1982	Gotland, Sweden	Edler et al. (1985)
	16 young cattle	1983	Stelasund, Germany	Gußmann et al. (1985)
	1 dog and 3 puppies	1984	Porvoo, Baltic coast, Finland	Persson et al. (1984)
	2 dogs	1990	Banter See, Germany	Nehring (1991, 1993)
	Fish	1992	Black Sea lagoon, Paliastomi, Georgia	Devidze (1998)
	Cattle and sheep	1993 - 1994	Malmesbury, South Africa	Van Halderen et al. (1995)
	Bull terrier	1994	Zeekocvlei, Cape Town South Africa	Harding et al. (1995)
(with *Rhizosolenia calcar- avis*)	Fish	1997	Black Sea lagoon, Paliastomi, Georgia	Devidze (1998)

	24 cattle	1997	Burlington, Colorado, USA	Puschner et al. (1998)
	2 dogs	1997	Gulf of Finland, Finland	ICES (1998)
Nostoc rivulare	Fish, frogs, chickens, ducks, turkey, and cattle	1956-1958	Waco, Texas, USA	Davidson 1959
Planktothrix agardhii	3 cows	1978	Cheshire, England	Reynolds (1980)
	Roach (*Rutilus rutilus*)	1982	Lake Vesijarvi, Lahti, Finland	Persson et al. (1984)
	Waterfowl, fish, muskrat	1984	Aland, Finland	Eriksson et al. (1986) in Eriksson et al. (1989)
	6 young cattle	1994	Soulseat Loch, Scotland	Codd (1996)
	2 cattle	1995	Soulseat Loch, Scotland	Codd (1996)
Planktothrix (= *Oscillatoria* sp.) benthic sp.	4 dogs	1990-1991	Loch Insh, Scotland	Edwards et al. (1992), Gunn et al. (1992)
	Dogs	1992	Scotland	Gunn et al. (1992)
Benthic sp.	Dogs	1992-1994	Caragh Lake, County Kerry, Ireland	James et al. (1997a)
	290 dairy cows, plus 70 with acute photosensitivity	1996	Kareedouw district, South Africa	Harding (1997)
	18 goats	1996	Alldays, northeast South Africa	Harding (1997)
Planktothrix sp.	Fish and bivalves	1997	Lake Varese, Italy	Giovannardi et al. (1999)
Trichodesmium erythraeum	Fish	1873	East Indian Archipelago	Veenhuyzen (1879) in Schwimmer and Schwimmer (1968)
Presumptive	Fish other marine animals	1940	Balikpapan, east coast of Borneo	Mohler (1940) in Schwimmer and Schwimmer (1968)
	Marine fauna: (*Alcyonium pachycladon*), (*Peachia* sp.), (*Gyrostoma* sp.), (*Eurythoe complanata*), (*Clibanarius longitarsis*), (*Alpheus rapax*), (*Palinurus* sp.), (*Calappa philargia*), (*Neptunus pelagicus*), (*Goniosoma* sp.), xanthid crabs (*Aergatis* sp.), (*Ocypoda* spp.), (*Gonodactylus* spp.), (*Squilla raphidea*), sea cucumbers (*Holothuria atra*), (*H. paradalis*), (*H. scabra*), (*Salmacis bicolor*), (*Pinna aegilatera*), (*Haliotis varia*), (*Cypraea arbica*), (*C. moneta*),(*Xancus pyrum*), sea hare (*Aplysia benedicti*); fish: eel (*Muraena* sp.), milkfish (*Chanos* sp.) fry, leopard hind (*Cephalopholis leopardus*) (as *Serranus leopardus*), Jarbua terapon (*Terapon jarbua*), redtail butterflyfish (*Chaetodon collare*), bannerfish (*Hemiochus macrolepidotus*), Emperor angelfish (*Pomacanthus imperator*) (as *Holocanthus imperator*), spotted scat (*Scatophagus argus*), plaintail turkeyfish (*Pterois russelli*), little spinefoot (*Siganus spinus*) (as *Teuthis marmorata*), redcoat (*Sargocentron rubrum*) (as *Holocentrum rubrum*), Indian threadfin (*Polynemus indicus*), shaggy angler (*Antennarius hispidus*), largescale mullet (*Liza macrolepis*) (as *Mugil troscheli*), (*M. waigensis*), (*Platyglossus* sp.), (*Tetraodon* sp.) – associated poor water quality, low dissolved oxygen	1942	Krusadai Island, Sri Lanka	Chacko (1942)

TABLE 7. (continued)

	Fish in ponds - associated with anoxia due to *Trichodesmium* decomposition from a bloom that washed ashore	1983	Chonburi to Chantaburi, east coast of Thailand	Suvapepun (1989, 1992)
	Shrimp	1991	East coast of Thailand	Suvapepun (1992)
T. thiebautii	Pearl oyster (*Pinctada martensii*)	1973	Gulf of Mannar, India	Chellam and Alagarswami (1981)

that a susceptible organism will come into contact with the HAB. Whether HAB species are benthic or planktonic, predatory or photosynthetic, or in a resting cyst phase will influence which communities of marine organisms might be affected by exposure to that HAB species. The degree of harm incurred may, in turn, depend on whether the organisms can detect blooms or toxins and then avoid them. For example, terrestrial animals such as cattle, sheep, goats, birds, wasps, and other wildlife do not necessarily avoid surface cyanobacterial scums — they preferentially drink water from these areas and become intoxicated (Lopez Rodas and Costas, 1999).

In other cases, there may be no obvious mechanism by which some organisms could detect toxins, and so they may inadvertently consume toxic HAB species or prey. In these cases, chronic or sublethal effects may occur. Exposure to harmful microalgae and characterized (see Section V) toxins is either direct or indirect; major routes and groups of organisms affected are listed in Table 8 and are outlined below.

A. DIRECT EXPOSURE

1. Intact Cells

a. Intracellular Toxins

Organisms are directly exposed to microalgal cells and their toxins either by drinking them or ingesting them via various feeding modes (e.g., filter feeding, predation). Zooplankton, sponges, and shellfish that filter feed can take up toxic cells directly from the water column; many of these organisms retain toxins in the viscera. Planktivorous fish that actively prey on toxic microalgae can also absorb toxins. Because filter feeders and predators are not necessarily discriminatory, they can be exposed to most of the known major microalgal toxins (Tables 1, 7, 9, 10, 11).

Most of the known toxic cyanobacteria are waterborne and may form massive subsurface blooms (e.g., *Planktothrix*) or may accumulate at the surface if aerotopes (e.g., *Microcystis*) are present (Christoffersen, 1996). Many organisms associated with water may therefore come into contact with cyanobacteria. These organisms include plankton, macrophytes, pelagic and benthic fish and invertebrates, littoral invertebrates, and waterfowl (Christoffersen, 1996), as well as amphibians, reptiles, and mammals. Toxic cyanobacterial blooms can also have a devastating impact on terrestrial organisms that drink water (Table 7). Poisoning usually does not occur unless there is a heavy bloom that forms a dense scum along the surface of the water (Carmichael, 1996). In calm weather, cyanobacteria can form a thin surface scum that may be dispersed over the entire surface of a lake. Wind and wave action frequently can concentrate cells along the shoreline (Carmichael, 1988). Wildlife or domestic animals therefore may have limited subsurface water from which to drink (Codd *et al.*, 1989). Depending on bloom density and toxin content, animals ingesting between a few milliliters and several liters can experience acute or lethal toxicity (Carmichael, 1996).

Numerous toxic microalgae have sedimentary cyst or resting stages as part of their life cycle. In some cases these stages may be more toxic than their free-swimming planktonic forms. In other cases, toxic cells or adsorbed toxins may sink

TABLE 8. Principle routes by which representative groups of organisms are exposed to harmful (as currently characterized) microalgal toxins

Toxin	Aerosol	Water	Ingestion	Mechanical contact	Zooplankton	Molluscs	Crustacea	Fish	Birds	Turtles	Marine mammals	Terrestrial mammals (+ man)
PST			+		+	+	+	+	+	+	+	+
TTX			+			+	+	+				+
PbTx	+								+?	+	+	+
		+			+	?	?	+				
			+		+	+	+	+	+	+	+	+
Gymnodimine			+			+						
OA/DST			+		+	+				+		+
CTX/MTX			+					+				+
Palytoxin			+				+	+				+
YTX			+		+	+						+
PTX			+			+						+
AZ			+			+						+
Hemolysins		+			+	+	+	+				
DA			+		+	+	+	+	+	?	+	+
Anatoxin-a			+		+							+
Anatoxin-a (s)			+						+			
CY			+				+	+				+
Microcystins			+		+	+		+	+			+
Nodularin			+		+							+
ROS		+			+			+				
Lyngbyatoxins			+	+						+		+
		+								+		+
Diatoms				+	+	+	+	+				

AZ = azaspiracids, CTX/MTX = ciguatoxins/maitotoxins, CY = cylindrospermopsin, DA = domoic acid, OA/DST = okadaic acid/dinophysistoxins, PbTx = brevetoxins, PST = paralytic shellfish toxins, PTX = pectenotoxins, ROS = reactive oxygen species, TTX = tetrodotoxin, YTX = yessotoxin

to the bottom, are consumed by benthic organisms, and are then recycled into the food chain. For example, cysts of *Alexandrium* spp. that have been dormant in the sediments for several months are up to 10 times more toxic than the vegetative cells. When newly formed, the cysts can even be up to 1000 times more toxic than the vegetative cells (Dale and Yentsch, 1978). Shellfish therefore could be exposed to high levels of toxins at all times if sediments are filtered during feeding.

b. Extracellular Toxins (Exotoxins) or Exudates

During active growth, many microalgae release exudates such as extracellular toxins (exotoxins) into the surrounding water, and organisms can be affected by such products even in the apparent absence of cells. For example, exotoxins or extracellular bioactive compounds are produced by the dinoflagellates *Karenia mikimotoi* Hansen in Hansen *et al*. (2000) (as *Gyrodinium aureolum* Gentien and Arzul, 1990) and *Prorocentrum lima* (Rausch de Traubenberg and Morlaix, 1995) and by the prymnesiophyte *Prymnesium parvum* (Shilo and Aschner, 1953). Release of exotoxins by microalgae and the long-term persistence of toxins in water are determined by basic physicochemical properties that influence their stability. Release of toxins into a watery milieu may not always pose a threat to organisms if large volumes of water dilute the toxins.

Zooplankton are able to detect toxins via chemoreception. Soluble saxitoxins can be detected by copepods, and it has been suggested that these toxins may act as feeding deterrents (Shaw *et al*., 1997). Compounds that inhibited feeding in the copepod *Calanus pacificus* were derived from the extracellular products of the dinoflagellate *Gonyaulax grindleyi* (Huntley *et al*., 1986). The inhibitory effect of the prymnesiophyte *Chrysochromulina polylepis* on the growth of both diatoms and the tintinnid *Favella ehrenbergii* seem to be mainly due to an extracellular product (Carlsson *et al*., 1990; Myklestad *et al*., 1995). Exudates from the toxic cyanobacterium *Anabaena* sp. can inhibit feeding by cladocerans and copepods (Ostrofsky *et al*., 1983; Burns *et al*., 1989). Redclaw crayfish accumulated cylindrospermopsin by absorbing the toxin from the water containing the cyanobacterium *Cylindrospermopsis raciborskii* and by ingesting it (Saker and Eaglesham, 1999).

c. Cell Surface Contact

Many organisms can be affected by direct cell-to-cell contact with microalgae, either through exposure to microalgal toxins present on the cell surface or through the mechanical damage caused when microalgal anatomical structures penetrate the gills or skin of the exposed organism.

Uchida *et al*. (1995) proposed that the toxic properties of *Heterocapsa circularisquama* are on the cell surface. Cells of the dinoflagellate *Gyrodinium instriatum* were immobilized immediately after contact with *Heterocapsa circularisquama* cells and eventually died. The toxic effects of *H. circularisquama* on the tintinnid *Favella taraikaensis* were also due to cell-to-cell contact. *Heterocapsa circularisquama* adhered to the adoral zone of membranelles of *Favella* and as concentrations of *H. circularisquama* cells increased, so did the likelihood of contact with *Favella* cells. When concentrations of *Heterocapsa* were more than 6.4×10^3 cells/ml, *Favella* cells swelled, become immobilized, and eventually lysed (Kamiyama and Arima, 1997). In another example, after direct contact with the brown tide

pelagophyte *Aureococcus anophagefferens*, adult blue mussels, *Mytilus edulis* (Tracey, 1988; Ward and Targett, 1989), and larval bay scallops, *Argopecten irradians* (Gallager *et al.*, 1989), were inhibited from feeding (Bricelj and Kuenstner, 1989).

Blooms of the marine cyanobacterium *Lyngbya majuscula* cause a type of contact dermatitis (swimmer's itch) in humans swimming or bathing in affected waters. Symptoms include itching, rash, burning, blisters, and deep skin erosions that can be very painful (Fujiki *et al.*, 1985).

Some diatom species, for example, *Chaetoceros concavicornis*, *C. convolutus*, *Skeletonema costatum*, and *Rhizosolenia chunii,* have setae, barbs, processes, or spines that can become trapped in the gills of fish or shellfish, cause mechanical damage that impairs respiration, and eventually cause death (Parry *et al.*, 1989; Speare *et al.*, 1989; Albright *et al.*, 1993; Kent *et al.*, 1995; Tester and Mahoney, 1995). Filaments or colonies of cyanobacteria can reduce the feeding rates of zooplanktonic cladocerans by interfering with movement of the filtering appendages (Gliwicz and Siedlar, 1980; Haney *et al.*, 1995) and by causing them to reject food. When cyanobacteria filaments enter the branchial chamber they are usually rejected by the postabdomen. This rejection not only interrupts the cladoceran's feeding, but it also causes nutritionally required phytoplankton that has collected in the branchial chamber to be expelled (Gilbert, 1990).

2. Lysed Cells

Many species that normally produce intracellular toxins release little into the environment under normal conditions. Under stressful environmental conditions (e.g., salinity change, wind action or currents, or during senescence and collapse of a bloom), HABs release toxins as the cells lyse. For example, during senescence, cyanobacterial blooms release toxins into the water that may cause fish to die (Schwimmer and Schwimmer, 1968; Rodger *et al.*, 1994). For this reason, treating blooms with chemicals or by manipulating the environment can cause toxins to be released into the environment and ultimately may cause damage to aquatic organisms.

Several planktonic species can release toxins that become aerosolized after lysis or that become caught up in bubble-mediated transport. Bubble-mediated transport has been shown to concentrate brevetoxins from *Karenia brevis* at the sea surface, where concentrated toxins are subsequently released as an aerosol (Pierce *et al.*, 1990). Terrestrial organisms and air-breathing mammals and reptiles can be adversely affected by these aerosolized toxins. Airborne toxins of *K. brevis* were implicated in the death of goldfish in ponds along the Florida coast during a 1974 red tide (Quick and Henderson, 1974).

B. INDIRECT EXPOSURE

1. Trophic Toxin Transfer, Bioaccumulation, Biomagnification

Biotoxins are transferred trophically when organisms consume other organisms that have been exposed directly to toxic microalgae and have bioaccumulated, bioconverted, or biomagnified the toxins. In many cases, the organism that was consumed has modified the toxins from the form that was originally produced by

the microalgae. Filter-feeding zooplankton consume and retain toxic microalgae that are then passed one step up the food chain to zooplanktivores. Filter-feeding shellfish also consume toxic microalgae and accumulate the toxins, which in turn become available to both animal and human consumers. This transfer of toxins up the food chain is one of the most common ways in which higher trophic levels, including humans, are affected by microalgal toxins. Several microalgae produce specific toxins that are associated with human shellfish poisonings: Amnesic Shellfish Poisoning (ASP, diatoms *Pseudo-nitzschia* and domoic acid [DA]), Diarrheic Shellfish Poisoning (DSP, dinoflagellates *Dinophysis* and *Prorocentrum*, okadaic acid [OA] and dinophysistoxins [DTX]), Paralytic Shellfish Poisoning (PSP, dinoflagellates *Alexandrium*, *Gymnodinium*, and *Pyrodinium*, paralytic shellfish toxins [PST] — saxitoxins [STX] and derivatives), Neurotoxic Shellfish Poisoning (NSP, dinoflagellates *Karenia*, brevetoxins [PbTx] and analogs), and, more recently, Azaspiracid Shellfish Poisoning (AZP, dinoflagellate *Protoperidinium*, azaspiracid [AZ]) (Table 1). These same toxins can also affect higher-level predators by a similar transfer of toxins up the food chain (e.g., DA for birds [Work *et al.*, 1992], or PST for fish, birds, and mammals [Armstrong *et al.*, 1978; White, 1980; Geraci *et al.*, 1989; Montoya *et al.*, 1996]).

People who consume toxic tropical fish and become sick with tropical fish poisoning or ciguatera are also victims of indirect exposure to microalgal toxins. Some ciguatera toxins are biomagnified and some are biotransformed during their transfer up the food chain from toxic epiphytic dinoflagellates ingested by herbivores, to piscivores that feed on the ciguateric herbivores, and finally to humans consuming ciguateric piscivorous fish (Swift and Swift, 1993). The toxins found in benthic dinoflagellates are transformed into a form available to and harmful to humans by the time that they are concentrated in piscivorous fish. Microcystins from the cyanobacterium *Microcystis aeruginosa* can also be transferred up the food chain and introduced into many trophic levels (Kotak *et al.*, 1996b).

IV. IMPACTS

A. ACUTE

Toxic HABs are usually planktonic and have acute effects. When organisms are rapidly exposed to high concentrations of these toxic blooms, shellfish-poisoning events, significant public-health problems, and mass mortalities of aquatic organisms can result. Exposure to a high concentration of toxin usually invokes an immediate biochemical or cellular response that leads to a physiological, pathological, or behavioral change. Animals directly exposed to metabolic byproducts of HABs may respond in different ways to avoid or minimize toxic effects. A concentration of toxin above a certain threshold may be lethal, whereas concentrations below that threshold may cause only a mild physiological, pathological, or behavioral response. In some cases, over a longer time period, organisms may accumulate toxins until they eventually exceed tolerable concentrations and then the organism may suffer chronic effects. The extent to which organisms will accumulate toxins depends on the solubility (either water soluble [hydrophilic] or lipid soluble [lipophilic]), stability,

and toxicokinetics of the toxins. Physiological tolerances of individual species to the various toxins will also determine the level of toxin accumulation.

B. CHRONIC

For obvious reasons, algal species known to affect human health have received the most attention. Of those algal species whose toxins severely affect lower vertebrate and invertebrate species (many of them commercially important), most is known about the acute, lethal effects. Little information exists about the chronic, sublethal or lethal effects of bioaccumulated or biomagnified algal toxins on human and animal species or whether such effects render organisms more susceptible to disease and what is the fate of these toxins in the ecosystem.

Only recently has attention been drawn to the fact that microalgal toxins and their chronic effects need to be studied at all biological levels and to be recognized as major threats to animal health, sustained fisheries, endangered species, and ecosystems (Shumway and Cucci, 1987; Landsberg, 1995, 1996; Burkholder, 1998). As is true for other contaminants or toxicants, it is likely that the potential long-term effects of biotoxins on the health of aquatic animals or on public health will include increased susceptibility to disease, immunosuppression, abnormal development, or the induction of neoplasia. Animals at all trophic levels who are exposed in the long term to biotoxins through the diet may die or display impaired feeding, avoidance behavior, physiological dysfunction, impaired immune function, reduced growth and reproduction, or pathological effects (Shumway, 1990; Luckenbach *et al.*, 1993; Wikfors and Smolowitz, 1993; Burkholder, 1998).

Rarely are aquatic biotoxins considered to be etiological agents of tumor induction. This is surprising given their widespread geographical distribution and the resultant probability that many aquatic animals are chronically exposed to tumor-promoting biotoxins. Several groups of toxins produced by dinoflagellates and cyanobacteria have been shown to have a variety of short-term effects, and these same toxins can also be tumor promoters in the long term. Microcystins, nodularins, okadaic acid, dinophysistoxin-1, aplysiatoxins, debromoaplysiatoxin, and lyngbyatoxin-a have all been demonstrated to be tumorigenic (Table 1). These tumorigenic properties have only been demonstrated experimentally in small mammals or cell assays (Fujiki and Suganuma, 1993; Falconer and Humpage, 1996; Sueoka and Fujiki, 1998). The prevalence of tumors in aquatic animals has been steadily increasing worldwide for the last 30 years (Geraci *et al.*, 1987; Harshbarger *et al.*, 1993; Landsberg, 1996). In some cases, researchers have found clearly defined correlations between the incidence of certain types of tumor and certain chemical contaminants or oncogenic viruses (Malins *et al.*, 1988; Harshbarger *et al.*, 1993; Anders and Yoshimizu, 1994), yet biotoxins are rarely considered to be potential tumorigenic agents.

C. ORGANISMS AND HABITATS AFFECTED

The majority of documented HAB events are associated with invertebrate, fish, and bird mortalities, but there have also been several accounts of other marine animal mortalities, such as of whales, dolphins, and sea turtles, for which biotoxins have

been implicated (Rounsefell and Nelson, 1966; Geraci, 1989; Geraci *et al.*, 1989; Hokama *et al.*, 1990; Anderson and White, 1992; Hernández *et al.*, 1998). For the purposes of this discussion, the organisms that HABs have been reported to affect will include zooplankton, macroinvertebrates, vertebrates, and, briefly, microalgae. A general chronology of mortality events, organisms affected, and the HAB species associated with the event is provided in Tables 2 to 7. When possible, organisms are listed both by their common and scientific names. These tables do not include general descriptions of red tides that are available in the literature, nor do they include minor fish kills or incidents during which multiple HAB species were identified. In many cases the reports simply document the coincidental occurrence of a bloom and a mortality event; dead animals were not necessarily tested for toxins or were bioassays conducted. Pertinent case histories of many of the larger-scale events are provided below.

The sublethal effects of HAB species on molluscs (Table 9), crustacean zooplankton (Table 10), and noncrustacean plankton (Table 11) are outlined. Allelopathic interactions or antimicrobial effects of HAB species or their toxins on other microbes or microalgae (e.g., Subba Rao *et al.*, 1995; Windust *et al.*, 1997; Naviner *et al.*, 1999) will not be discussed, except for the brief reference to pertinent species in Tables 1 and 11. The effects of harmful microalgae upon zooplankton are not always lethal (Tables 10 and 11). Documented deleterious effects on zooplankton include avoidance; lethargic swimming or paralysis; grazing reduction or inhibition; starvation-induced mortality; and reduced rates of development, growth, and survival. The short-term effects of HABs on shellfish, particularly on bivalves, have been covered in extensive reviews by Shumway (1990, 1995). A summary of sublethal effects by various HAB species on molluscs is outlined in Table 9. Effects of specific toxins and harmful species are given below.

HABs are responsible for numerous fish kills and disease events around the world. At least 60 species are ichthyotoxic, and more than 30 species are harmful to fish (Tables 1 to 7). For many years, fish kills may have been attributed to the low dissolved-oxygen levels generated by high-biomass blooms and were not necessarily considered to be caused by toxicity. For example, from 1980 to 1989, at least 50% of fish kills in the Gulf of Mexico and 69% in the South Atlantic, USA, were attributed to low dissolved oxygen (Lowe *et al.*, 1991). It is possible that many of these kills were associated with harmful algal blooms caused by small, ephemeral dinoflagellates that were not, until recently, recognized as being toxic. Such fish kills would have been attributed to the low dissolved oxygen associated with the bloom rather than direct ichthyotoxicity. Many kills are now known to be caused by blooms of small dinoflagellates such as *Karenia*, *Karlodinium*, *Gymnodinium*, *Gyrodinium*, or *Pfiesteria* (Table 2). The wide variety of life strategies adopted by many HAB species in aquatic systems suggests that fish in numerous trophic niches can be affected.

Traditionally, only planktonic HABs have been recognized as having acute effects, but benthic and predatory HAB species may also kill animals, usually by toxin exposure through the diet. Other biotoxins can be transferred through the food web and cause fish mortalities (e.g., White *et al.*, 1989). Unexplained fish kills and bird and marine mammal mortalities (e.g., Williams and Bunkley-Williams, 1990; Williams *et al.*, 1992; Vidal and Gallo-Reynoso, 1996) may have been caused by biotoxin transfer through the diet (Landsberg, 1995).

TABLE 9. Sublethal or chronic lethal effects of harmful microalgae on molluscs

Microalgal species	Mollusc species	Common name	Impact	Reference
Dinoflagellates				
Akashiwo sanguinea (=*Gymnodinium sanguineum*)	*Ostrea lurida*	Oyster	Closed shell valves, stopped feeding	Nightingale (1936)
Alexandrium catenella	*Crassostrea gigas*	Pacific oyster	Reduced pumping, increased pseudofaeces production	Dupuy and Sparks (1967)
Alexandrium fundyense	*Crassostrea gigas*	Pacific oyster	Reduced clearance rate	Lassus et al. (1996)
Alexandrium minutum	*Crassostrea gigas*	Pacific oyster	Inhibition of shell valve activity	Lassus et al. (1999)
			Reduced clearance rate	Lassus et al. (1999), Laabir and Gentien (1999)
			Reduced biodeposition rate	Lassus et al. (1999)
Alexandrium monilatum	*Ischadium recurvum* (as *Brachidontes recurvus*)	Hooked mussel	Inhibition of byssus production	Sievers (1969)
	Crassostrea virginica	Eastern oyster	Closed shell valves, no filtration	Ray and Aldrich (1976)
Alexandrium tamarense	*Argopecten irradians*	Bay scallop	Reduced clearance rate	Lesser and Shumway (1993)
	Chlamys farreri	Farrer's scallop	Inhibition of egg hatching Reduced larval survival	Yan et al. (2001)
	Crassostrea gigas	Pacific oyster	Reduced clearance rate	Lassus et al. (1996), Laabir and Gentien (1999)
	Geukensia demissa	Ribbed mussel	Shell valve closure	Shumway and Cucci (1987)
			Reduced clearance rate	Shumway and Cucci (1987), Lesser and Shumway (1993)
			Production of mucus	Shumway and Cucci (1987)
			Inhibition of byssus production	Shumway et al. (1987)
	Mercenaria mercenaria	Northern quahog	Shell valve closure	Shumway and Cucci (1987)
			Reduced clearance rate	Lesser and Shumway (1993)
	Mya arenaria	Softshell clam	Shell valve closure	Shumway and Cucci (1987)
			Reduced clearance rate	Shumway and Cucci (1987), Lesser and Shumway (1993), Bricelj et al. (1996)
			Impaired burrowing response	Bricelj et al. (1996)
			Decrease in heart rate	Gainey and Shumway (1988b)
	Mytilus edulis	Blue mussel	Shell valve closure	Shumway and Cucci (1987)
			Production of mucus	Shumway and Cucci (1987)
			Reduced clearance rate	Lesser and Shumway (1993)
			Inhibition of byssus production	Shumway et al. (1987)
			Change in heart rate	Gainey and Shumway (1988b)

	Ostrea edulis	Oyster	Increased rate of particle clearance	Shumway and Cucci (1987)
			Reduced clearance rate	Lesser and Shumway (1993)
			Decrease in heart rate	Gainey and Shumway (1988b)
	Placopecten magellanicus	Sea scallop	Production of mucus	Shumway and Cucci (1987)
			Closure of shell valves	Shumway and Cucci (1987)
			Violent swimming activity	Shumway and Cucci (1987)
			Decrease in oxygen consumption	Shumway et al. (1985)
	Spisula solidissima	Atlantic surfclam	Reduced clearance rate	Lesser and Shumway (1993)
			Decrease in oxygen consumption	Shumway et al. (1985)
Cochlodinium polykrikoides (as *C. heterolobatum*)	*Crassostrea virginica*	Eastern oyster	Larval deformity	Ho and Zubkoff (1979)
Gymnodinium aureolum	*Argopecten irradians*	Bay scallop	Pathological effects	Smolowitz and Shumway (1997)
	Crassostrea virginica	Eastern oyster	Mantle and gill lesions	Nielsen and Strømgren (1991)
	Mytilus edulis	Blue mussel	Reduced clearance rates and marked cellular damage in the gut	Widdows et al. (1979)
Heterocapsa circularisquama	*Mytilus galloprovincialis*	Mediterranean mussel	Retract mantle edge	Matsuyama et al. (1998b)
			Unable to close shell valve	Matsuyama et al. (1998b)
			Inhibition of byssus production	Matsuyama et al. (1998b)
	Pinctada fucata	Pearl oyster	Closed valves, contracted mantle	Matsuyama et al.(1996), Matsuyama (1999)
Karenia brevis (= *Gymnodinium breve*)	*Argopecten irradians*	Bay scallop	Recruitment failure	Summerson and Peterson (1990)
	Fasciolaria lilium hunteria	Banded tulip	Loss of muscle control	Roberts et al. (1979)
	Melongena corona	Crown conch	Loss of muscle control	Roberts et al. (1979)
	Oliva sayana	Lettered olive	Loss of muscle control	Roberts et al. (1979)
Karenia mikimotoi	*Crassostrea gigas*	Pacific oyster	Reduced clearance rate	Laabir and Gentien (1999)
	Haliotis discus	Abalone	Tentacle contraction and escape locomotion	Matsuyama et al. (1995)
	Mytilus galloprovincialis	Mediterranean mussel	Reduced clearance rate	Matsuyama et al. (1998b)
(as *Gyrodinium* cf. *aureolum*)	*Pecten maximus*	Scallop	Growth inhibition	Erard-Le-Denn et al. (1990)
	Sulculus diversicolor	Abalone	Paralysis	Matsuyama et al. (1995)
Karlodinium micrum (=*Gymnodinium galatheanum*)	*Mytilus edulis*	Blue mussel	Reduced growth	Nielsen and Strømgren (1991)
Lingulodinium polyedrum	*Mytilus* sp.	Mussel	Clogged gills	Oguri et al. (1975)
Pfiesteria piscicida	*Argopecten irradians*	Bay scallop	Depressed ability to close shell valves	Burkholder et al. (1995)
	Crassostrea virginica	Eastern oyster	Depressed swimming activity	Krantz et al. (1994)

TABLE 9. (continued)

			Decreased filtering activity	Burkholder and Glasgow (1997)
Prorocentrum lima	*Mytilus edulis*	Blue mussel	Reduced filtration	Pillet and Houvenaghel (1995)
Prorocentrum minimum	*Argopecten irradians*	Bay scallop	Intestinal pathology, poor growth	Wikfors and Smolowitz (1993)
	Crassostrea virginica	Eastern oyster	Impaired nutrition	Wikfors and Smolowitz (1995)
Diatoms				
Pseudo-nitzschia multiseries	*Crassostrea gigas*	Pacific oyster	Reduction in number of hemocytes	Jones et al. (1995a)
Pseudo-nitzschia pungens	*Crassostrea gigas*	Pacific oyster	Shell valve closure	Jones et al. (1995b)
Rhizosolenia chunii	*Pecten alba*	Scallop	Digestive gland lesions, mortalities	Parry et al.(1989)
Prymnesiophytes				
Chrysochromulina polylepis	*Mytilus edulis*	Blue mussel	Inhibition of fertilization and successful development of embryos	Granmo et al. (1988)
			Growth reduction	Nielsen and Strømgren (1991)
	Nucella lapillus	Atlantic dogwinkle	Recruitment failure	Robertson (1991)
Phaeocystis pouchetii	*Mytilus edulis*	Blue mussel	Reproductive failure probably caused by feeding inhibition	Pieters et al. (1980)
Pelagophytes				
Aureococcus anophagefferens	*Argopecten irradians*	Bay scallop	Decreased feeding efficiency	Tracey (1988), Bricelj and Kuenstner (1995)
			Reduced larval shell growth, Increased mortality of larvae	Gallager et al. (1989)
			Reduced adductor weight	Bricelj et al. (1987)
			Recruitment failure	Bricelj et al. (1987)
	Crassostrea virginica	Eastern oyster	Inhibition of gill ciliary activity	Gainey and Shumway (1991)
	Mercenaria mercenaria	Northern quahog	Decreased feeding efficiency	Tracey (1988), Bricelj and Kuenstner (1995)
			Inhibition of gill ciliary activity	Draper et al (1989), Gainey and Shumway (1991)
	Modiolus modiolus	Northern horsemussel	Inhibition of gill ciliary activity	Gainey and Shumway (1991)
	Mytilus edulis	Blue mussel	Decreased feeding efficiency	Tracey (1988), Bricelj and Kuenstner (1995)
			Reproductive failure	Bricelj and Kuenstner (1989)
			Inhibition of gill ciliary activity	Draper et al (1990), Gainey and Shumway (1991)
	Ostrea edulis	Oyster	Inhibition of gill ciliary activity	Gainey and Shumway (1991)
Cyanobacteria				
Anabaena circinalis	*Alathyria condola*	Mussel	Reduced feeding	Negri and Jones (1995)

TABLE 10. Sublethal or chronic lethal effects of harmful microalgae on crustacean zooplankton

Microalgal species	Crustacean species	Impact	Reference
Dinoflagellates			
Akashiwo sanguinea (as *Gymnodinium sanguineum*)	*Acartia tonsa*	Reduced feeding and egg hatching	Fiedler (1982), Turner et al. (1998)
	Calamus pacificus	Reduced feeding	Fiedler (1982)
	Paracalamus parvus	Reduced feeding	Fiedler (1982)
Alexandrium lusitanicum	*Acartia clausi*	Reduced fecundity Reduced hatching success and naupliar production, delayed development	Dutz (1998) Frangópulos et al. (2000)
Alexandrium minutum	*Euterpina acutifrons*	Inactivation and mortality of adults and nauplii	Bagøien et al. (1996)
Alexandrium tamarense (*as A. excavatum*)	*Acartia hudsonica*	Reduced feeding, paralysis	Ives (1985, 1987)
	Calamus finmarchicus	Feeding avoidance	Turriff et al. (1995)
	Calamus helgolandicus	Reduced fecundity	Gill and Harris (1987)
	Calamus pacificus	Reduced feeding	Huntley et al. (1986)
	Centropages hamatus	Reduced feeding, fecundity	Turner et al. (1998)
	Pseudocalamus sp.	Reduced feeding, paralysis	Ives (1985, 1987)
	Temora longicornis	Reduced fecundity	Gill and Harris (1987)
Amphidinium carterae	*Calamus pacificus*	Reduced development and survival	Huntley et al. (1986)
Gonyaulax grindleyi	*Calamus pacificus*	Reduced development and survival	Huntley et al. (1986, 1987)
		Regurgitation	Sykes and Huntley (1987)
	Paracalanus parvus	Reduced feeding	Huntley et al. (1986), Sykes and Huntley (1987)
	Pseudodiapotomus marinus	Reduced feeding	Uye and Takamatsu (1990)
Gymnodinium catenatum	*Euterpina acutifrons*	Inactivation of adults and nauplii	Bagøien et al. (1996)
Gymnodinium flavum	*Calamus pacificus*	Ingestion avoidance	Huntley (1982) in Uye (1986)
Gyrodinium resplendens	*Calamus pacificus*	Reduced development and survival	Huntley et al. (1986)
Karenia brevis (= *Gymnodinium breve*)	*Acartia tonsa*	Lethargy, paralysis	Turner et al. (1996)
	Calamus pacificus	Reduced development and survival lethargy	Huntley et al. (1986,1987)
		Regurgitation	Sykes and Huntley (1987)
		Rapid heart rate, paralysis, lethargy	Sykes and Huntley (1987)

TABLE 10. (continued)

Karenia mikimotoi (as *G. nagasakiense*)	*Acartia omorii*	Rejected feed, reduced fecundity and survival	Uye and Takamatsu (1990)
(as *Gyrodinium aureolum*)	*Calanus helgolandicus*	Reduced movement and fecundity	Gill and Harris (1987)
(as *G. nagasakiense*)	*Pseudodiapotomus marinus*	Reduced feeding	Uye and Takamatsu (1990)
(as *Gyrodinium aureolum*)	*Temora longicorinis*	Reduced movement and fecundity	Gill and Harris (1987)
Prorocentrum lima	*Paracalanus parvus*	Reduced feeding	Huntley et al. (1986)
Scrippsiella trochoidea	*Calanus pacificus*	Reduced feeding	Huntley et al. (1986)
	Calanus helgolandicus	Reduced fecundity	Gill and Harris (1987)
	Temora longicornis	Reduced fecundity	Gill and Harris (1987)
Diatoms			
Chaetoceros curvisetus (as *C. curvisetum*)	*Temora stylifera*	Reduced fecundity and hatching	Ban et al. (1997)
Chaetoceros debilis	*Acartia tonsa*	Reduced fecundity and hatching	Ban et al. (1997)
	Calanus finmarchicus	Reduced fecundity	Ban et al. (1997)
Chaetoceros difficilis	*Calanus pacificus*	Reduced hatching	Uye (1996), Ban et al. (1997)
Chaetoceros gracilis	*Acartia grani*	Reduced fecundity and hatching	Ban et al. (1997)
Cyclotella sp.	*Boeckella triarticulata*	Reduced fecundity and hatching	Ban et al. (1997)
Cylindrotheca closterium	*Acartia clausi*	Reduced fecundity	Ban et al. (1997)
	Calanus helgolandicus	Reduced fecundity	Ban et al. (1997)
	Eurytemora affinis	Reduced fecundity	Ban et al. (1997)
Ditylum brightwellii	*Calanus pacificus*	Reduced hatching	Uye (1996), Ban et al. (1997)
Navicula cryptocephala	*Calanus chilensis*	Reduced hatching	Ban et al. (1997)
Navicula sp.	*Calanus finmarchicus*	Reduced fecundity and hatching	Ban et al. (1997)
Nitzschia palea	*Eucyclops macruroides*	Reduced hatching	Ban et al. (1997)
	Paracyclops affinis	Reduced hatching	Ban et al. (1997)
Phaeodactylum tricornutum	*Acartia grani*	Reduced fecundity and hatching	Ban et al. (1997)
	Calanus helgolandicus	Reduced fecundity and hatching	Ban et al. (1997)
	Centropages typicus	Reduced fecundity and hatching	Ban et al. (1997)
	Eurytemora affinis	Reduced fecundity	Ban et al. (1997)
	Temora longicornis	Reduced fecundity and hatching	Ban et al. (1997)
	Temora stylifera	Reduced fecundity and hatching	Ban et al. (1997)
Skeletonema costatum	*Acartia clausi*	Reduced fecundity and hatching	Ban et al. (1997)
	Calanus helgolandicus	Reduced fecundity	Ban et al. (1997)
	Temora stylifera	Reduced fecundity	Ban et al. (1997)
Synedra acus	*Eucyclops mucruroides*	Reduced hatching	Ban et al. (1997)
Thalassiosira nordenskioeldii	*Calanus finmarchicus*	Reduced hatching	Ban et al. (1997)
Thalassiosira rotula	*Acartia clausi*	Reduced fecundity and hatching	Ban et al. (1997)

	Calanus helgolandicus	Egg abnormalities and mortality Reduced fecundity and hatching	Poulet et al. (1994), Chaudron et al. (1996), Ban et al. (1997)
	Centropages typicus	Reduced fecundity and hatching	Ban et al. (1997)
	Temora stylifera	Lower hatching rate	Ianora and Poulet (1993)
	Thalassiosira weissflogii	*Acartia steueri*	Reduced fecundity and hatching	Ban et al. (1997)
		Calanus pacificus	Reduced hatching	Uye (1996), Ban et al. (1997)
		Centropages hamatus	Reduced fecundity and hatching	Ban et al. (1997)
		Calanus helgolandicus	Reduced fecundity and hatching	Ban et al. (1997)
		Temora longicornis	Reduced fecundity and hatching	Ban et al. (1997)
	Raphidophytes			
	Chattonella antiqua	*Calanopia thompsoni*	No feeding	Uye (1986)
		Labidocera rotundata	No feeding	Uye (1986)
		Tortanus forcipatus	No feeding	Uye (1986)
	Chattonella marina	*Acartia omorii*	Rejected feed and reduced fecundity	Uye and Takamatsu (1990)
	Fibrocapsa japonica	*Acartia omorii*	Rejected feed and reduced fecundity	Uye and Takamatsu (1990)
		Pseudodiapotomus marinus	Rejected feed	Uye and Takamatsu (1990)
	Heterosigma akashiwo (as *Olisthodiscus luteus*)	*Acartia hudsonica*	Reduced feeding	Tomas and Deacon (1981)
		Acartia omorii	Rejected feed and reduced fecundity	Uye and Takamatsu (1990)
		Acartia tonsa	Reduced feeding	Tomas and Deacon (1981)
		Pseudodiapotomus marimus	Rejected feed, reduced fecundity and survival	Uye and Takamatsu (1990)
	Prymnesiophytes			
	Chrysochromulina polylepis	*Acartia* sp.	Reduced fecundity	Nielsen et al. (1990)
		Centropages hamatus	Reduced fecundity	Nielsen et al. (1990)
		Temora longicornis	Reduced fecundity	Nielsen et al. (1990)
	Chrysochromulina spp.	*Acartia tonsa*	Reduced fecundity	Hansen et al. (1995)
	Phaeocystis pouchetii	*Acartia hudsonica*	Reduced feeding and fecundity	Verity and Smayda (1989)
		Acartia tonsa	Reduced feeding and fecundity	Verity and Smayda (1989)
	Prymnesium patelliferum	*Acartia clausi*	No feeding, no reproduction	Nejstgaard and Solberg (1996)
	Pelagophytes			
	Aureococcus anophagefferens	*Acartia tonsa*	Reduced feeding and fecundity	Durbin and Durbin (1989)
	Aureoumbra lagunensis	*Acartia tonsa*	Reduced growth and fecundity	Buskey and Stockwell (1993)
			Reduced development and survival of nauplii	Buskey and Hyatt (1995)

TABLE 10. (continued)

Cyanobacteria			
Anabaena affinis	*Ceriodaphnia dubia*	Reduced feeding	Kirk and Gilbert (1992)
	Daphnia galeata mendotae	Reduced fecundity	Gilbert (1990)
	Daphnia magna	Reduced fecundity	Gilbert (1990)
	Daphnia pulex	Reduced fecundity and mortality	Gilbert (1990)
Anabaena flos-aquae	*Daphnia hyalina*	Feeding inhibition	De Mott et al. (1991)
	Daphnia parvula	Reduced feeding	Fulton (1988b)
	Daphnia pulex	Reduced feeding	Fulton (1988b)
	Daphnia pulicaria	Feeding inhibition	De Mott et al. (1991)
	Diaptomus reighardi	Feeding avoidance	Fulton (1988b)
	Eurytemora affinis	Feeding avoidance	Fulton (1988b)
Anabaena minutissima var. *attenuata*	*Daphnia carinata*	Reduced feeding and survival	Burns et al. (1989)
		Inhibition of appendage beat rate	Forsyth et al. (1992)
Aphanizomenon flos-aquae	*Acartia bifilosa*	Reduced feeding and fecundity	Sellner et al. (1994, 1996)
	Daphnia carinata	Inhibition of appendage beat rate	Haney et al. (1995)
	Diaptomus reighardi	Feeding avoidance	Fulton (1988b)
	Eurytemora affinis	Reduced feeding, avoidance and reduced fecundity	Fulton (1988b), Sellner et al. (1994, 1996)
Microcystis aeruginosa	*Acartia tonsa*	Reduced fecundity	Schmidt and Jónasdóttir (1997)
	Bosmina longirostris	Reduced feeding	Fulton and Paerl (1987)
	Ceriodaphnia quadrangula	Reduced feeding	Fulton and Paerl (1987)
	Daphnia ambigua	Reduced feeding and mortality	Fulton and Paerl (1987)
	Daphnia hyalina	Feeding inhibition	De Mott et al. (1991)
	Daphnia longispina	Reduced growth and depressed clutch size	Stangenberg (1968), Reinikainen et al. (1994, 1999), Hietala et al. (1995)
	Daphnia magna	Feeding avoidance	Yasuno and Sugaya (1991)
	Daphnia parvula	Mortality	Fulton (1988a)
	Daphnia pulex	Reduced growth, depressed reproduction rate and clutch size	De Mott et al. (1991), Reinikainen et al. (1994, 1999), Hietala et al. (1995)
	Daphnia pulicaria	Feeding inhibition	Lampert (1981a, b, 1982), De Mott et al. (1991)
	Diaptomus reighhardi	Reduced feeding	Fulton and Paerl (1987)
	Eucypris virens	Mortality	Stangenberg (1968)
	Moina macrocopa	Feeding avoidance and mortality	Yasuno and Sugaya (1991)

	Moina micrura	Mortality	Fulton (1988a)
	Simocephalus serratulus	Reduced feeding	Fulton and Paerl (1987)
Nodularia sp.	*Eurytemora affinis*	Reduced feeding and fecundity	Koski et al. (1999), Engström et al. (2000)
Nodularia spumigena	*Acartia bifilosa*	Reduced feeding and fecundity	Sellner et al. (1994, 1996)
	Acartia tonsa	Reduced fecundity	Schmidt and Jónasdóttir (1997)
	Eurytemora affinis	Reduced feeding and fecundity	Sellner et al. (1994, 1996)
	Mysis mixta	Reduced feeding	Engström et al. (2001)
Planktothrix agardhii (= *Oscillatoria agardhii*)	*Daphnia pulicaria*	Reduced growth and fecundity	Infante and Abella (1985)
	Daphnia thorata	Reduced growth and fecundity	Infante and Abella (1985)
Trichodesmium sp.	*Acartia tonsa*	Reduced fecundity	Guo and Tester (1994)
		Lethargy and paralysis	Guo and Tester (1994)
	Macrosetella gracilis	Lethargy, mortality	O'Neil and Roman (1994)
	Penaeus merguiensis	Starvation, low survival	Preston et al. (1998)
Trichodesmium thiebautii	*Clausocalamus furcatus*	Reduced feeding	Hawser et al. (1992), O'Neil and Roman (1994)
	Farranula gracilis	No feeding	Hawser et al. (1992), O'Neil and Roman (1994)
	Labidocera sp.	No feeding	O'Neil and Roman (1994)
	Temora turbinata	Reduced feeding	O'Neil and Roman (1994)
	Tigriopus californicus	No feeding	O'Neil and Roman (1994)

TABLE 11. Sublethal or chronic lethal effects of harmful microalgae on plankton (except crustacea)

Microalgal species	Species	Impact	Reference
	Diatoms		
Dinoflagellates			
Alexandrium lusitanicum	*Skeletonema costatum*	Reduced growth	Blanco and Campos (1988)
Karenia mikimotoi (as *Gyrodinium* cf. *aureolum*)	*Chaetoceros gracile*	Reduced growth	Arzul et al. (1993, 1995a)
	Skeletonema costatum	Reduced growth	Gentien and Arzul (1990)
Prorocentrum micans	*Asterionella japonica*	Inhibition of pigment synthesis	Gauthier et al. (1978)
	Chaetoceros didymus	Reduced population growth	Uchida (1977)
	Chaetoceros lauderi	Inhibition of pigment synthesis	Gauthier et al. (1978)
	Skeletonema costatum	Reduced population growth	Uchida (1977)
Raphidophytes			
Heterosigma akashiwo (as *Olisthodiscus luteus*)	*Skeletonema costatum*	Inhibited growth	Pratt (1966), Honjo et al. (1978), Honjo (1992)
Prymnesiophytes			
Chrysochromulina polylepis	*Skeletonema costatum*	Reduced growth	Myklestad et al. (1995)
Phaeocystis pouchetii	*Skeletonema costatum*	Reduced growth	Smayda (1973)
	Dinoflagellates		
Prymnesiophytes			
Chrysochromulina polylepis	*Alexandrium ostenfeldii*	Immobilization	Schmidt and Hansen (2001)
	Alexandrium tamarense	Immobilization	Schmidt and Hansen (2001)
	Ceratium sp.	Moribund	Nielsen et al. (1990)
	Ceratium furca	Immobilization	Schmidt and Hansen (2001)
	Ceratium lineatum	Immobilization	Schmidt and Hansen (2001)
	Ceratium tripos	Immobilization	Schmidt and Hansen (2001)
	Heterocapsa triquetra	Immobilization	Schmidt and Hansen (2001)
	Prorocentrum micans	Immobilization	Schmidt and Hansen (2001)
Pelagophytes			
Aureoumbra lagunensis	*Noctiluca scintillans*	Reduced feeding and fecundity	Buskey and Hyatt (1995)
	Raphidophytes		
Dinoflagellates			
Heterocapsa circularisquama	*Heterosigma carterae*	Growth suppression	Uchida et al. (1996)
	Flagellates		
Dinoflagellates			
Alexandrium lusitanicum	*Isochrysis galbana*	Reduced growth	Blanco and Campos (1988)
	Pavlova lutheri	Reduced growth	Blanco and Campos (1988)
Karenia mikimotoi (as *Gyrodinium* cf. *aureolum*)	*Dunaliella tertiolecta*	Reduced growth	Gentien and Arzul (1990)
	Isochrysis galbana	Reduced growth	Gentien and Arzul (1990)
	Tetraselmis suecica	Reduced growth	Gentien and Arzul (1990)
Prymnesiophytes			
Prymnesium patelliferum	*Pavlova lutheri*	Allelopathic effects	Nejstgaard and Solberg (1996)
	Coccolithophorids		
Prymnesiophytes			
Prymnesium patelliferum	*Emiliana huxleyi*	Allelopathic effects	Nejstgaard and Solberg (1996)
	Ciliates		
Dinoflagellates			
Alexandrium ostenfeldii	*Favella ehrenbergii*	Backwards swimming and death	Hansen et al. (1992)
Alexandrium tamarense	*Favella ehrenbergii*	Backwards swimming and death	Hansen (1989)

TABLE 11. (continued)

Karenia mikimotoi (as *Gyrodinium aureolum*)	*Favella ehrenbergii*	Growth inhibition and decreased survival	Hansen (1995)
Heterocapsa circularisquama	*Favella azorica*	Reduced growth	Kamiyama (1997)
	Favella taraikaensis	Reduced growth and mortality	Kamiyama (1997)
Raphidophytes			
Heterosigma carterae (as *Olisthodiscus luteus*)	*Favella* sp.	Reduced growth	Verity and Stoecker (1982)
	Tintinnopsis tubulosoides	Reduced growth	Verity and Stoecker (1982)
Prymnesiophytes			
Chrysochromulina polylepis	*Favella ehrenbergii*	Reduced feeding and growth	Carlsson et al. (1990)
Pelagophytes			
Aureococcus anophagefferens	Tintinnids	Reduced growth	Lonsdale et al. (1996)
	Strombidium sp	Lowered population growth	Mehran (1996) cited in Bricelj and Lonsdale (1997)
Aureoumbra lagunensis	*Strombidiniopsis* sp.	Reduced feeding and growth	Buskey and Hyatt (1995)
	Heliozoa		
Dinoflagellates			
Alexandrium tamarense	*Heterophrys marina*	Reduced growth	Tobiesen (1991)
Prymnesiophytes			
Prymnesium parvum	*Heterophrys marina*	Reduced growth	Tobiesen (1991)
Chrysochromulina polylepis	*Heterophrys marina*	Reduced growth	Tobiesen (1991)
	Rotifers		
Diatoms			
Pseudonitzschia multiseries	*Brachionus plicatilis*	Reduced feeding and fecundity	Whyte et al. (1996)
Cyanobacteria			
Anabaena flos-aquae	*Asplanchna girodi*	Reduced fecundity	Gilbert (1994)
	Brachionus calyciflorus	Feeding avoidance and reduced fecundity	Fulton (1988b), Gilbert (1994)
	Keratella cochlearis	Reduced fecundity	Gilbert (1994)
	Synchaeta pectinata	Reduced fecundity	Gilbert (1994)
Aphanizomenon flos-aquae	*Brachionus calyciflorus*	Feeding avoidance	Fulton (1988b)
Microcystis aeruginosa	*Keratella cochlearis*	Inhibition?	Smith and Gilbert, unpubl. in Gilbert (1994)
	Keratella crassa	Inhibition?	Smith and Gilbert, unpubl. in Gilbert (1994)
	Keratella mixta	Inhibition?	Fulton and Paerl (1987)
Raphidophytes			
Heterosigma akashiwo (as *Olisthodiscus luteus*)	*Brachionus plicatilis*	Reduced feeding	Chotiyaputta and Hirayama (1978)
	Synchaeta cecilia	Reduced feeding and fecundity	Egloff (1986)
Pelagophytes			
Aureoumbra lagunensis	*Brachionus plicatilis*	Reduced feeding and growth	Buskey and Hyatt (1995)
	Polychaetes		
Pelagophytes			
Aureoumbra lagunensis	*Streblospio benedicti*	Reduced growth and swimming speed	Ward et al. (2000)

Surprisingly little information is available on the effects of HABs on reptiles, particularly sea turtles, alligators, and crocodiles, that are often exposed to toxins. Several cases of such effects have been documented (Tables 2 to 7), and it is likely that many more such mortality or disease events will be linked to HABs as pathobiological examinations incorporate biotoxin analyses. Both aquatic and terrestrial birds are potential victims of HAB events. Numerous bird kills have been reported in which the majority of deaths are associated with the consumption of toxic prey, for example, fish or molluscs that have consumed or otherwise bioaccumulated microalgal toxins. In other cases, birds can succumb to toxins after drinking contaminated water, particularly after ingesting toxins from cyanobacterial blooms in freshwater systems. Recently, biotoxins have been linked to marine mammal mortalities (Tables 2 to 7), but as was the case with reptile mortalities, biotoxins were for many years overlooked as possibly being the cause of marine mammal deaths. In those cases in which an infectious pathogen was implicated, immunosuppression and increased susceptibility to disease as a result of chronic toxin stress may not have been considered. When microalgal biotoxins are not included as a factor in mortality investigations, final diagnoses may be compromised.

Terrestrial organisms (e.g., bears, raccoons, otters, birds) that are associated with freshwater, marine, or estuarine food webs may also be at risk of toxin exposure from preying on toxic aquatic prey. However, by far the largest terrestrial group affected by HABs are those animals drinking toxic freshwater in which cyanobacterial blooms are occurring (Falconer, 1993). Animal mortalities caused by cyanobacteria have been reported since the late 1800s in Australia (Francis, 1878) and occur worldwide. Essentially, however, any animal can be at risk because even a chance encounter with contaminated systems can result in illness or death. Selected examples of terrestrial wildlife and domestic animal intoxications are provided in Table 7. This list is not exhaustive, and extensive reviews are provided in Carmichael (1992), Ressom *et al.* (1994), Yoo *et al.* (1995), and Duy *et al.* (2000). Some of the more unusual reports of animal mortalities associated with cyanobacterial toxins include wildfowl, honeybees, bats, and rhinoceros (Table 7).

The overall effects of HABs on food webs and ecosystems are probably the least understood of all impacts. Not only are the pathways of algal-toxin transmission complex and incompletely known, long-term implications of sublethal, chronic effects (e.g., recruitment failure and the subsequent loss of species from an ecosystem, reduced filtration of water masses, and the subsequent effects on benthic-pelagic coupling) are virtually unknown. Long-term effects (e.g., toxin accumulation) on higher-level consumers also need to be investigated. In many habitats (e.g., coral reefs), there have been increased nutrient inputs and associated increases in macroalgal cover in recent years (Lapointe, 1989). An increase in macroalgal or macrophyte cover used as substrate by toxic benthic microalgae can lead to increases in the abundance of these toxic species. The increased substrate cover may also increase the distribution of toxic microalgal species, which would increase the likelihood they will be ingested by herbivores browsing through the substrate. Potential effects of some microalgae upon herbivores include tumor promotion (Landsberg *et al.*, 1999) (see section on okadaic acid). Persistent algal blooms can cause severe shading, which ultimately can lead to the decimation of seagrass beds (critical habitat for a multitude of species) (Dennison *et al.*, 1989). Such sublethal, chronic effects have farreaching impacts on animal and plant communities.

V. TOXINS AND HARMFUL MECHANISMS

Harmful microalgae can produce a suite of toxic or noxious bioactive compounds (secondary metabolites or phycotoxins) that can adversely affect other organisms or ecosystems. These secondary metabolites are distinct from those involved in primary and intermediate metabolism, because they have no key role in the basic functioning of the cell (Wright and Cembella, 1998). The role of secondary metabolites may be intrinsic (e.g., protection from UV light, intracellular nutrient storage, or a differentiation signal) or extrinsic (e.g., toxic to predators, an allelopathic substance, a promoter of symbiotic relationships, a metal scavenger such as a siderophore [Plumley, 1997], or as plankton "pheromones" that promote mating of gametes [Wyatt and Jenkinson, 1997]). Extrinsic compounds may have the potential to harm other organisms. In many cases, the ecological or evolutionary significance of these products is unclear, especially when the "target" organisms (e.g., humans) are those that are not normally part of the same ecological framework as the toxin-producing organism. The ecological role of these byproducts and the apparent increase in toxic species or strains around the world has been much discussed (e.g., Van Dolah, 2000, and references therein). Numerous environmental and genetic factors regulate the production of microalgal toxins (see, e.g., Bomber, 1991; Wright and Cembella, 1998; Sivonen and Jones, 1999) and are not discussed here. The recognized role of bacteria in the ability of some species to produce toxins (Doucette, 1995; Doucette *et al.*, 1998) is important but is mentioned only when such bacterial-algal interactions pertain to possible effects on aquatic organisms (see section on HABs as potential vectors).

In general, the major producers of toxins are the dinoflagellate and diatom groups in the marine environment and cyanobacteria in fresh and brackish water. Toxins are usually classified (1) by the level of activity, which can range from the biochemical level to the ecosystem level, and (2) by their effects on humans or other mammals. At the biochemical level, microalgal toxins are genotoxic and affect DNA adducts (Huynh *et al.*, 1998). At the cellular level (cytotoxic), toxins can be cytolytic, hemolytic, antineoplastic, or tumor promoters. At the organ level, toxins can be neurotoxic, hepatotoxic, or dermatotoxic. At the phylum level, toxins can adversely affect certain groups of organisms, for example, they are antimicrobial (bacteria, virus, fungi), antialgal (algae), or ichthyotoxic (fish) (Table 1). In addition, some of these same toxins can be tumorigenic in the long term (Table 1). Microalgal toxins are usually distinguished either as cytotoxins or biotoxins; biotoxins are able to affect whole organisms (usually rodents) in bioassays, whereas cytotoxins are not (Carmichael, 1992). In certain cases, depending on their mode of action, some biotoxins can affect a range of vertebrate and invertebrate organisms, whereas others may influence only certain groups. Some bioactive compounds produced by microalgae may have minimal effects on mammalian systems, but they may more seriously affect aquatic organisms because of their mode of activity in an aqueous medium. For example, toxins from several dinoflagellate, prymnesiophyte, or raphidophyte species may affect fish (ichthyotoxic), but they apparently have no known effect on other organisms. At the ecosystem level, toxins or high concentrations of cells alone may have large-scale effects, but these effects are not usually so well defined as in narrower settings. In addition to the production of toxins, microalgae can harm

aquatic organisms in other ways. Other metabolic byproducts, such as enzymes or fatty acids, can affect cell membranes or particular organ systems and, although not necessarily lethal, can affect animal health, perhaps ultimately causing disease or other sublethal effects. In other cases, anatomical structures such as setae, spines, or barbs can mechanically damage other organisms. Often in these cases, the physiological or pathological responses of the organisms exposed to the microalgae may result in pathology, disease, sublethal effects, or mortality. Organisms documented to harm aquatic organisms through nontoxic mechanisms are included in Table 1.

In some cases, a toxic effect caused by a particular microalgal species may have been only demonstrated experimentally by using whole cells rather than purified toxin. Therefore, in a mortality investigation involving the presence of an experimentally proven toxic species, scientists may often infer that mortality was caused by that known toxin. Many species produce multiple toxins, which means that the mortality associated with these species can be caused by an individual toxin, by a combination of toxins, or by other uncharacterized toxic compounds. In terms of studying experimental impacts, a suite of tests using whole cells, cell extracts, and purified toxins should be conducted whenever possible.

In this review, the secondary metabolites that are discussed are those that have been documented, or are strongly suspected, to cause harm to aquatic organisms or to terrestrial organisms that may be exposed to aquatic systems. Some secondary metabolites will not be discussed, but the species producing them are identified in Table 1. Those metabolites fall into the following categories: (1) those causing only cytotoxic effects (e.g., Nagle and Gerwick,1995; Hasui *et al.*, 1995b, 1996; Sogawa *et al.*, 1998), (2) those having antimicrobial or antineoplastic properties (Patterson *et al.*, 1991, 1993; Hasui *et al.*, 1995a; Mundt *et al.*, 1997), (3) those having minimal organismal effects that have been demonstrated only experimentally (Table 1), or (4) those acting as enzyme inhibitors (Namikoshi and Rinehart, 1996). Terrestrial toxic microalgae are not included. In many cases, there may be unexplained mortalities or disease events that could well be attributable to toxins acting at the suborganismal level, but there is currently no field documentation of their possible effects. However, possible correlations should certainly be investigated. Certain toxins that are currently classified as cytotoxic may have chronic impacts at the organismal level, but again this is unknown. Although lethality is often used to determine the level of toxicity, these tests are often made in short-term rodent bioassays and therefore may not necessarily be correlated with effects on aquatic organisms.

Harmful algal blooms are often considered to be directly responsible for observed aquatic mortality events, but in many cases such events may be indirectly due to the presence of the bloom rather than to direct toxicity. Changes in water chemistry as a result of a bloom may lead to mortalities, but these changes are usually directly associated with increased levels of ammonia, nitrite, or hydrogen sulphide toxicity, or anoxia caused by depleted oxygen levels (Mackenthun *et al.*, 1948; Prescott, 1948). Fish or invertebrate kills have been attributed to the low levels of dissolved oxygen associated with nontoxic, high-biomass plankton blooms such as *Ceratium* or *Noctiluca* (Mahoney and Steimle, 1979; Adnan, 1989) (Table 2) (see section on water quality).

Principally because of their effects on human health, toxins rather than the HAB species are usually considered according to their involvement in particular poisoning events (e.g., saxitoxins in paralytic shellfish poisoning, brevetoxins in neurotoxic shellfish poisoning). Because microalgal species may produce multiple toxins, because the same toxins can be produced by numerous species, and because numerous harmful species can be implicated in one event, descriptions of the effects of many of these species are identical or very similar. Table 1 lists microalgal species alphabetically by microalgal (dinoflagellates, diatoms, raphidophytes, prymnesiophytes, silicoflagellates, pelagophytes, and cyanobacteria) or ciliate group and describes the toxins produced by individual species and the toxins' potential effects on human or animal health. This table provides a comprehensive list of the currently known harmful or toxic species; it also includes those species whose toxins have been demonstrated experimentally to have activity at the cellular level, but further discussion of these species is not provided unless they have documented effects on aquatic organisms in the wild. In the following section, species are grouped by the toxins or bioactive compounds that they produce. Species that produce multiple toxins are discussed under each appropriate section, as outlined in Table 1. Where possible, the description of these toxins follows the order of the groups outlined in Table 1, except when multiple species are involved.

A. SAXITOXINS

Neurotoxic paralytic shellfish toxins (PST) are produced by dinoflagellates — approximately 11 *Alexandrium* species, *Gymnodinium catenatum*, and *Pyrodinium bahamense* var. *compressum* — and by the cyanobacteria *Anabaena circinalis*, *Aphanizomenon flos-aquae*, *Cylindrospermopsis raciborskii*, *Lyngbya wollei*, and *Planktothrix* sp. (Table 1). The taxonomy of *Alexandrium* has been in flux, but recently both morphospecies and genospecies have been studied (Costas *et al.*, 1995; Scholin, 1998). For the purposes of this discussion and in documenting previous mortality reports associated with *Alexandrium*, the species are discussed here using the currently accepted taxonomy (Balech, 1995); they are listed in Table 1 with their synonyms.

Most humans who experience paralytic shellfish poisoning (PSP) have consumed toxic bivalves (Shumway, 1990), but occasionally toxic gastropods and crustaceans (Shumway, 1995), and rarely toxic fish (Maclean, 1979; Adnan, 1984), can also cause this sickness. Numerous fatal cases of PSP have been reported globally (Kao, 1993), but the recent successful implementation of programs monitoring the presence of PST-producing microalgae in many countries has helped to minimize the risks to humans. Thus far, all human cases of PSP have been caused by toxic dinoflagellates, and the geographical distribution of these cases is related to the global distribution of the various PST-producing species and their toxigenic strains. PST are highly lethal, having an LD_{50} in mice (intraperitoneally [i.p]) of 10 μg/kg (when compared with an LD_{50} for sodium cyanide at 10 mg/kg (Oshima *et al.*, 1989c). PST are potent neurotoxins that bind to site 1 on the voltage-dependent sodium channel, block the influx of sodium into excitable cells, and restrict signal transmission between neurons. Symptoms of PSP are paresthesia and numbness, first around the lips and mouth and then involving the face and neck; muscular

weakness; sensation of lightness and floating; ataxia; motor incoordination; drowsiness; incoherence; progressively decreasing ventilatory efficiency; and in high doses, respiratory paralysis and death (Catterall, 1985; Kao, 1993).

PST are present in a wide range of aquatic organisms, and they have been documented to occur when dinoflagellates were apparently absent (Sakamoto *et al.*, 1992). Knowledge of the widespread distribution of PST and results of a series of experimental studies have led to the conclusion that in many cases dinoflagellates are not the only source of PST (Doucette *et al.*, 1998). A bacterial origin for PST has been demonstrated, and bacteria also play a significant (but not exclusive?) role in the production of PST in certain dinoflagellate species (Kodama *et al.*, 1988b, 1990a, 1990b; Ogata *et al.*, 1990; Doucette *et al.*, 1998) (see section on HABs as vectors).

PST comprise the saxitoxins (STX) and at least 21 derivatives (Oshima, 1995) that in various combinations and concentrations have been associated with PSP. No natural toxigenic dinoflagellate or cyanobacteria population has been found to contain all naturally occurring PST derivatives, so the toxin profile (i.e., the toxin components produced) is considered to be characteristic of the microalgal strain or species (Cembella *et al.*, 1993; Onodera *et al.*, 1996). Some of the PST derivatives are highly toxic (as sodium channel-blocking agents in mammals) and include the carbamate toxins, saxitoxin (STX), neosaxitoxins (NEO), and the gonyautoxins (GTX1-4). The decarbamoyl analogues (dcSTX, dcNEO, dcGTX1-4) and the deoxydecarbamoyl analogues (doSTX, doGTX2, doGTX3) are of intermediate toxicity. The least toxic derivatives are the *N*-sulfocarbamoyl toxins B1 (GTX5), B2 (GTX6), and C1-C4 (Sullivan, 1993; Oshima, 1995). Although not usually associated with PSP, *Cochlodinium polykrikoides* (as *Cochlodinium* type '78) has been shown to produce two unique, zinc-bound, neosaxitoxin-like compounds (Onoue and Nozawa, 1989b) (see multiple toxins/*Cochlodinium*). In 1977, *Cochlodinium* sp. was implicated in PSP outbreaks in Venezuela (Reyes-Vasquez *et al.*, 1977), but corroborative evidence is lacking.

Even though numerous microalgal species have been documented to produce PST and all are potentially dangerous to aquatic organisms, the majority of mortality reports have been associated with the dinoflagellates *Alexandrium tamarense* and *A. catenella* (Table 2). The fact that PST are produced by several species of cyanobacteria in freshwater systems suggests that aquatic and terrestrial animals also have a good chance of being exposed to these toxins. Toxin composition can vary among microalgal species and strains; with geographical location, with environmental factors, and under different experimental conditions (Cembella *et al.*, 1988; Anderson, 1990; Anderson *et al.*, 1990, 1994). Because the toxin profiles of PST-producing dinoflagellate species differ the exposure dose and the proportion of highly toxic PST derivatives to which animals are exposed will differ (Landsberg, 1996).

The transport of PST through the food chain and the accumulation of toxins in zooplankton have been identified as important mechanisms by which toxins become available to higher trophic levels (White, 1979, 1981a; Turriff *et al.*, 1995; Teegarden and Cembella, 1996a; Turner *et al.*, 2000). Exposing euphausiid, lobster, and crab larvae to PST did not produce any apparent effects in two studies (Yazdandoust, 1985; Robineau 1991a), yet in other studies short-term adverse effects were reported. Exposure to PST may be lethal (Bagøien *et al.*, 1996), produce sublethal effects (Tables 10 and 11), or cause active avoidance (Turriff *et al.*, 1995), yet many species

of zooplankton accumulate PST and act as vectors in transferring toxin up the food chain (White, 1981a, 1981b; Turriff *et al.*, 1995; Teegarden and Cembella, 1996a; Turner *et al.*, 2000). When copepods were exposed to toxic and nontoxic strains of *A. tamarense*, a range of responses was noted. Physiological reactions of some copepods included paralysis (Ives, 1985, 1987), whereas other copepods experienced no obvious adverse effects (Teegarden and Cembella, 1996a). Toxic strains of *Alexandrium* were rejected by copepods (Huntley *et al.*, 1986; Turriff *et al.*, 1995), ingested at lower rates in response to increasing toxicity (Ives, 1985, 1987), or ingested at a high rate similar to the rate at which nontoxic strains are ingested (Teegarden and Cembella, 1996a). This range of responses suggests that susceptibilities of copepod species to *Alexandrium* toxins is species specific. Copepods have highly sensitive and specific chemoreceptive and selective abilities; they are capable of selecting preferred prey from mixed algal populations, and the presence or absence of PST is not necessarily a factor in grazing selectivity (Teegarden and Cembella, 1996a, 1996b). The differential response of copepods to *Alexandrium* species may also be due in part to the presence of other bioactive compounds (Turriff *et al.*, 1995; Bagøien *et al.*, 1996) (see section on uncharacterized toxins and *A. tamarense*).

Regardless of the level at which zooplankton feed on or are exposed to toxic algae, the accumulation of saxitoxins in zooplankton and the subsequent transference of the toxins by zooplankton into the food web are well documented (White, 1981a, b; Turriff *et al.*, 1995; Teegarden and Cembella, 1996a; Turner *et al.*, 2000). Although the rates at which copepods feed on PST-producing dinoflagellates may vary, copepods can still bioaccumulate PST (Boyer *et al.*, 1985b; Turriff *et al.*, 1995; Bagøien *et al.*, 1996; Teegarden and Cembella, 1996a). When the copepods *Tigriopus californicus* were fed *Alexandrium catenella*, they accumulated toxin readily over a 3-day period and reached a saturation of 12 μg PST/g dry weight. The toxin profile of the copepods showed higher levels of GTX2 and GTX3 than originally found in *A. catenella*, indicating some toxin transformation (Boyer *et al.*, 1985b). In experimental exposures of the copepods *Eurytemora herdmani* and *Acartia tonsa* to *A. tamarense*, profiles of the toxins accumulated by these copepods were dramatically different from the toxin profiles of the dinoflagellates and had patterns more consistent with metabolic transformation than differential retention. Concentrations of up to 2332.3 μgSTXeq/100 g were measured in *E. herdmani* tissues after 12 h. That such high levels of PST were accumulated reinforces the hypothesis that zooplankton act as toxin vectors (Teegarden and Cembella, 1996a). Recently, such a finding was confirmed in the field where PST concentrations were disproportionately high in the copepods *Calanus finmarchius* and *Centropages typicus* when compared with other taxa in the zooplankton community (Turner *et al.*, 2000).

Because most outbreaks of PSP result from eating shellfish, most studies on PST concern those vector species that are consumable, economic resources. Globally, the presence of PST has been documented in numerous species of molluscs. Several extensive reviews are available on the occurrence, exposure, biotransformation, and effects of PST in molluscs, especially in bivalves and gastropods (Shumway, 1990; Shumway *et al.*, 1990; Shumway and Cembella, 1993; Bricelj and Shumway, 1998a, 1998b); therefore, only a brief survey of PST effects will be provided here. STX was first isolated from toxic Washington butterclams, *Saxidomus gigantea* (Schantz *et al.*, 1957; Schantz, 1960). Because STX and its derivatives block only voltage-gated

sodium channels, which function in mammalian nerves as well as in skeletal and cardiac muscle fibers (Kao, 1993), researchers formerly thought that bivalves were not affected by PST because their neuromuscular functions operate mainly by voltage-gated calcium channels. High levels of STX were not typically considered to be lethal or pathogenic to bivalves (Prakash *et al.*, 1971). Only in recent years have researchers focused on the fact that these toxins can and do affect molluscs in various ways and that they have been responsible for many mortalities and harmful effects.

Of the known PSP-producing microalgae, documented mass mortalities of molluscs have thus far been associated only with *Alexandrium catenella* and *A. tamarense* (Table 2). These molluscan mortalities also usually occur in conjunction with other marine animal mortalities and sometimes with PSP outbreaks (Table 2) (see below). The potential effects of different HAB species and their toxins on bivalves may vary, depending on a series of species-specific or individual responses. Some species may initially avoid exposure by behavioral or physiological mechanisms or by their individual response to ingested toxins. Because microalgae can produce toxic benthic cysts and/or vegetative planktonic stages, bivalves may be differentially exposed to toxins because of their feeding modes. Some species feed on resuspended particulate matter from sediments, whereas others filter plankton from the water. Bivalve feeding behavior may be one of the principal controlling factors that initially limit the extent to which toxins are ingested. Some bivalves may immediately respond behaviorally to avoid the consumption of toxic dinoflagellates (Shumway and Cucci, 1987; Gainey and Shumway, 1988a; Shumway, 1990). For example, in the presence of *Alexandrium*, northern quahogs, *Mercenaria mercenaria*, close the shell valves (Shumway, 1990); softshell clams, *Mya arenaria*, may retract the siphon (Shumway and Cucci, 1987); and Pacific oysters, *Crassostrea gigas*, reduce pumping rates (Dupuy and Sparks, 1968). Bivalves that are exposed for short periods to *Alexandrium* spp. and PST can respond by a variety of mechanisms. Such mechanisms include increasing mucus and pseudofeces production, modifying valve activity and changing filtration rate, reducing feeding or burrowing behavior, altering the rate of byssus production, and changing cardiac activity or oxygen consumption (Table 9) (Cucci *et al.*, 1985; Shumway *et al.*, 1985, 1987; Shumway and Cucci, 1987; Gainey and Shumway, 1988a, 1988b; Shumway, 1990; Marsden and Shumway, 1992; Bricelj *et al.*, 1996; Lassus *et al.*, 1999).

The fate and distribution of PST in bivalves varies according to HAB bloom characteristics; environmental conditions; prior history of exposure; species, intrapopulation, and individual variability; uptake dynamics and detoxification mechanisms; anatomical localization and retention; physiological breakdown or biotransformation mechanisms; and differences in initial toxicity of dinoflagellates (Shimizu and Yoshioka, 1981; Maruyama *et al.*, 1983; Beitler and Liston, 1990; Bricelj *et al.*, 1990, 1991, 1996; Kitts *et al.*, 1992; Chebib *et al.*, 1993; White *et al.*, 1993; Cembella *et al.*, 1993, 1994; White *et al.*, 1993; Shumway *et al.*, 1994; Bricelj and Cembella, 1995; Cembella and Shumway, 1995; Lassus *et al.*, 1996; Bricelj and Shumway 1998a, 1998b; Curtis *et al.*, 2000; Smith *et al.*, 2001). In more tolerant species, if PST are not lethal or usually cause only short-term responses, then suboptimal conditions may allow sublethal effects to occur. Differences between bivalve species in the ability to accumulate PST have been correlated with each species' *in vitro* nerve sensitivity to STX and ability to continue actively feeding during toxic blooms (Twarog *et al.*,

1972; Bricelj *et al.*, 1996). For example, STX-resistant blue mussels, *Mytilus edulis*, that had been experimentally fed a toxic isolate of *A. fundyense* for $4\ ^1/_2$ weeks had growth rates similar to, but a condition index lower, than those in mussels that were fed a nontoxic diet of the diatom *Thalassiosira weissflogii* (Bricelj *et al.*, 1993).

Bivalves store PST for different lengths of time, and the toxic components retained vary. Some species are able to depurate toxins rapidly, whereas others are slow to detoxify. A range of PST toxicity levels is found in different bivalves. Extremely high PST concentrations have been found in the mussels *Mytilus trossulus* and *M. edulis*, in softshell clams and Washington butterclams, and in the scallops *Patinopecten yessoensis* and *Placopecten magellanicus*. In other bivalves — such as northern quahogs, *Mercenaria mercenaria*, and oysters, *Crassostrea* spp. — PST are at low levels or are absent (Shumway, 1990; Landsberg, 1996; Bricelj and Shumway, 1998 and references therein). Depuration times also vary between species. Most species can eliminate PST within weeks (Shumway, 1990). Pacific oysters, *C. gigas*, are able to depurate toxins from their tissues in less than nine weeks (Shumway *et al.*, 1990), whereas Washington butterclams, sea scallops (*Placopecten magellanicus*), and Atlantic surfclams (*Spisula solidissima*), are known to retain high levels of toxins for long periods of time (from months to more than 5 years) (Shumway and Cembella, 1993; Shumway *et al.*, 1994). Populations of bivalves and species of bivalves may also vary in their susceptibility to effects of PST. Mussels from populations with a history of exposure to PSP toxins appear to have a lower toxin sensitivity than do mussels from unexposed populations. Wild blue mussels from a region chronically contaminated with PST accumulated twice as much toxin on a weight-normalized basis as did cultured mussels from a pristine zone when subjected to identical *A. tamarense* (as *A. excavatum*) bloom conditions (Chebib *et al.*, 1993). Such species-specific and intraspecific differences at least partly explain the variations in toxicity profiles reported in molluscs.

The toxin profiles of bivalve populations vary depending on the toxigenicity of the dinoflagellate to which each population is exposed. For example, in general, bivalves exposed to *Alexandrium tamarense, A. catenella*, and *A. minutum* accumulate high GTX levels, whereas bivalves exposed to *Pyrodinium bahamense* var. *compressum* and *G. catenatum* accumulate very low levels of GTX (Landsberg, 1996). Bivalve toxin profiles also vary by geographic region, by season, and by the distribution of toxic components in different tissues (Beitler and Liston, 1990; Martin *et al.*, 1990; Cembella *et al.*, 1993; Shumway and Cembella, 1993; Cembella *et al.*, 1994; Shumway *et al.*, 1994; Bricelj and Cembella, 1995). The location and deposition weight of toxin components in the various bivalve organs varies between species. For example, in the scallops *Placopecten magellanicus* and *Patinopecten yessoensis* the majority of the toxins are concentrated in the digestive gland, and toxicity levels in the gills, gonads, and adductor muscles are typically less than 80 μg STXeq/100 g (Shumway and Cembella, 1993). Because toxins are accumulated and then transformed in the gonad, kidney, and adductor muscle of the great scallop, *Pecten maximus*, these three tissues contained almost no GTX1 and GTX4 15 days after the scallop was experimentally exposed to *Alexandrium tamarense*. The digestive gland still contained GTX1-4 and NEO after 35 days (Lassus *et al.*, 1992). Toxins are not readily accumulated in the adductor muscle of scallops, and because this is the only part of the shellfish usually consumed, they are normally safe for public consumption (Shumway and Cembella, 1993).

Because they naturally ingest a variety of dinoflagellate species and strains, bivalves are exposed to a variety of toxic components. Knowledge of which toxins are deposited in which tissues may be critical for determining the effects of each toxin on shellfish health. For example, Atlantic surfclams and sea scallops are naturally exposed in New England to PST associated with *Alexandrium* spp. STX toxins are typically stored in the tissues of these species, whereas other potentially carcinogenic substances such as the carbamate-derivative gonyautoxins are converted to less toxic compounds. The ability to convert carbamate toxins to their corresponding nontoxic decarbamoyl derivatives has been demonstrated in a few bivalves, such as Atlantic surfclams; Pacific littleneck clams, *Protothaca staminea*; and the Japanese clams *Peronidia venulosa* and *Mactra chinensis* (Sullivan *et al.*, 1983; Bricelj and Cembella, 1995; Oshima, 1995; Bricelj *et al.*, 1996). However, it is unclear how the health of those species that do not convert toxins into milder forms is affected by long-term exposure to toxic components.

Although the acute effects of PST exposure on behavioral and physiological responses have been demonstrated, other effects of PST on bivalve health are generally unknown. Because of public health concerns and the development of safety protocols, it has been critical that we understand the dynamics of toxin distribution in different species, particularly in edible tissues. In general, although PST are widely distributed among shellfish, it is not usually thought that there might be negative health effects associated with long-term toxin deposition, and, in general, shellfish are thought to be immune from such effects. Yet some consideration of possible effects is appropriate, especially in cases where the etiology of certain diseases is still unknown. For example, a possible association between HABs, toxin deposition, and the incidence of neoplasia in shellfish was hypothesized recently (Landsberg, 1996).

Limited information is available on the short-term responses of shellfish to cyanobacterial exposure. Under experimental conditions, the freshwater mussel *Alathyria condola* accumulated high levels of PST when fed *Anabaena circinalis* (10^6 cells/ml). Total PST concentration reached 1580 μg/g dry weight, with the toxin profile comprising mostly C toxins and significant levels of GTX2 and GTX3. The majority of toxins (96%) were contained in the viscera. Mussels exposed to very high concentrations tended to filter feed for a few hours and then cease feeding. Feeding resumed from 1 to 3 days later. The mussels' erratic feeding behavior when cell concentrations were high was not observed when animals were exposed to low concentrations of cells. The reduction in feeding rate associated with exposure to high concentrations of *A. circinalis* therefore may suggest a potential for sublethal deleterious effects in mussel populations (Negri and Jones, 1995).

In the short term, there are no documented effects associated with PST exposure in other invertebrates. Crustaceans, echinoderms, and (rarely) polychaetes accumulate PST apparently without any ill effects (Daigo *et al.*, 1988; Nagashima *et al.*, 1998). PST have been found most commonly in xanthid crabs (Noguchi *et al.*, 1969, 1985; Koyama *et al.*, 1981; Yasumoto *et al.*, 1981; Raj *et al.*, 1983; Daigo *et al.*, 1985; Llewellyn and Endean, 1989; Arakawa *et al.*, 1994, 1995a, 1995b; Tsai *et al.*, 1995, 1996; Negri and Llewellyn, 1998), and in some cases were derived from the calcareous alga *Jania* sp., consumed by the crabs (Kotaki *et al.*, 1983). PST have also been found in the crabs *Cancer* spp. (Foxall *et al.*, 1979; Shumway 1995); the horseshoe crab *Carcinoscorpius rotundicauda* (Fusetani *et al.*, 1982), the kelp crab

Pugettia producta; the shore crabs *Hemigraspus oregonensis*, *H. nudus*, *Metopograspus frontalis* (Jonas-Davies and Liston, 1985; Negri and Llewellyn, 1998), *H. sanguineus*, and *Pachygrapsus crassipes* (Sato *et al.*, 1993); the blue manna crab, *Portunus pelagicus* (Sang and Ming, 1984; Negri and Llewellyn, 1998); the lobsters *Homarus americanus* (Desbiens and Cembella, 1995) and *Panulirus* spp. (Sang and Ming, 1984); the crayfish *Procambrus clarkii* (Sato *et al.*, 1993); penaeid shrimp (Sang and Ming, 1984); barnacles *Balanus* spp. (Jonas-Davies and Liston, 1985); and other crustacean species (in Shumway, 1995, and Negri and Llewellyn, 1998). Other invertebrates that accumulate PST include the tubeworms *Eudistylia* sp. (Jonas-Davies and Liston, 1985) and the starfish *Asterias amurensis*, *Astropecten scoparius*, *A. polyacanthus*, and *Pisaster ochraceus* (Noguchi *et al.*, 1982; Jonas-Davies and Liston, 1985; Asakawa *et al.*, 1997; Lin *et al.*, 1998). Some predatory invertebrates accumulate toxins through the consumption of toxic bivalves (Shumway, 1995).

It has been suggested that lobsters exposed to high PST concentrations do not survive (Yentsch and Balch, 1975), but it appears that many macrocrustaceans, including lobsters, are able to tolerate extremely high levels of PST. Concentrations of up to 1512 μgSTXeq/100g in the hepatopancreas of the American lobster, *Homarus americanus*, apparently did not cause any significant health problems. Lobsters can accumulate PST by preying on blue mussels, among others, which can have maximum toxicities of up to 23,000 μgSTX eq/100 g (Desbiens and Cembella, 1995). Xanthid crabs can harbor toxins in their tissues at concentrations that would be fatal to other animals (Llewellyn, 1997). When some xanthid crabs are handled, they release PST, which suggests that these toxins are used as a defense mechanism (Noguchi *et al.*, 1985). Maximum toxin levels of more than 16,000 μgSTX eq/100 g were found in the xanthid crab *Atergatis floridus* in Australia, even though the majority of samples contained less than 80 μg PST/100 g (Negri and Llewellyn, 1998). In Japan, an individual *Zosimus aeneus* contained nearly 16,500 Mouse Units (MU) per g (Koyama *et al.*, 1983), which is equivalent to 300,000 μgSTX eq/100 g (1MU = 0.18 μgSTX; Schantz *et al.*, 1957; Negri and Llewellyn, 1998). The nerves of *A. floridus* are 1000-fold less sensitive to PST than are the nerves of *Daira perlata*, a xanthid not known to carry PST (Daigo *et al.*, 1988), and presumably neural sodium channels in *A. floridus* have a very low affinity for toxins (Llewellyn, 1997). Several species of xanthid crabs produce a hemolymph protein, saxiphilin, that can bind with STX and thus confer some resistance to possible toxic effects (Llewellyn, 1997). This mechanism may explain why some species appear to tolerate exceptionally high levels of toxin (Llewellyn, 1997). When saxitoxins were injected into xanthid crabs, the rate of dissipation within the crab was fairly high and suggested that high concentrations of toxin are not accumulated (Arakawa *et al.*, 1998).

As they did historically with shellfish, researchers believed that cold-blooded vertebrates such as finfish were not negatively affected by PST (Prakash *et al.*, 1971). In recent years, however, several studies have demonstrated the lethality of PST to finfish, and researchers have also begun investigating the distribution of PST in finfish tissues. In July 1976 in the Bay of Fundy, Canada, Atlantic herring, *Clupea harengus harengus*, were observed dead and dying. A bloom of *Alexandrium tamarense* was coincident with the mortality, and shellfish (softshell clams; blue mussels; and northern horsemussels, *Modiolus modiolus*) were confirmed to be contaminated with PST. Stomach contents from dead fish contained the pteropods *Limacina retroversa* and algal remnants. In this case, the pteropods acted as vectors

for transmitting the PST to the fish. In laboratory experiments, 28 herring were exposed by gavage to crude extracts of *A. tamarense*, and within several minutes all treated fish displayed similar symptoms. Fish swam in an irregular, jerky manner; lost equilibrium and swam on their sides; became paralyzed, some swimming in tight circles; and began breathing slowly. Within 1 to 2 days after treatment 79% of them died. The fish died with their mouths gaping widely, as they had in the field, which is suggestive of asphyxiation (White, 1977). White (1981b) suggested that fish may be as sensitive as homeotherms are to PST and has provided further corroborative evidence for the role of zooplankton as vectors of PST up the food chain (White 1979, 1980, 1981a, 1981b, 1984; White *et al.*, 1989). Fish kills associated with *Alexandrium* spp. have been reported in numerous geographical locations (Table 2). In some cases, these kills may have been caused by toxins other than PST (see section on uncharacterized toxins and *Alexandrium* spp.).

Experimental ingestion of *A. tamarense* (reported as *A. excavata*) by first-feeding larvae of red sea bream, *Pagrus major*, resulted in high mortalities and, eventually, debilitation of first-feeding larvae of Japanese anchovy, *Engraulis japonica* (White *et al.*, 1989). After 4 days, 95% of the red sea bream larvae exposed directly to *Alexandrium* had died, and moribund larvae lay paralysed on the tank bottom. Within 1 to 2 h after feeding on *Alexandrium*-fed zooplankton, some (22 to 38%) older (4 to 6 weeks) larvae of both species lost their equilibrium and swam on their sides, upside down, or in circles. Most larvae died within a few hours (White *et al.*, 1989). Several studies have demonstrated further that exposing fish larvae to *Alexandrium* species, either directly or via toxic zooplankton vectors, results in mortality or reduced growth. Vulnerability to toxins depends on the age and feeding behavior of the fish, toxigenicity of *Alexandrium* strains, mode of exposure to toxin, and the susceptibility of the fish to the toxins (Mills and Klein-MacPhee, 1985; Huntley *et al.*, 1986; Gosselin *et al.*, 1989; Robineau *et al.*, 1991a, 1991b). The level of mortality caused by the toxins was invariably less when the fish were exposed to toxins via vectors than when the fish were exposed to the toxins directly (Gosselin *et al.*, 1989; White *et al.*, 1989; Robineau *et al.*, 1991a, 1991b). With increased strain toxicity, mortality from vectoral intoxication tended to increase, but not as rapidly as mortality from direct intoxication. These results are consistent with the observations that zooplankton eliminate the toxins and that the saturation of the tissues results in reduced variability in the final toxicity. Thus, in nature, first-feeding larvae that readily feed on dinoflagellates will be at a higher risk of intoxication than carnivorous postlarvae (Robineau *et al.*, 1991b). When bluebanded gobies, *Lythrypnus dalli*, were experimentally exposed to *A. catenella*-toxic crab larvae, mortalities were observed within 24 to 60 h. When exposed directly to *A. catenella* cultures, gobies exhibited erratic swimming, loss of balance and buoyancy, rapid darting prior to death, and death within 13 to 14 h (Yazdandoust, 1985). First-feeding winter flounder, *Pseudopleuronectes americanus*, larvae exposed to concentrations of *A. tamarense* above 1×10^2 cells/ml died sooner than those exposed to lower concentrations or than larvae on control diets did (Mills and Klein-MacPhee, 1985).

Preliminary results on the codistribution of fish larvae and *A. tamarense* (as *A. excavatum*) in the estuary and Gulf of St. Lawrence showed that capelin, *Mallotus villosus*, could not detect the presence of a toxic bloom and confirmed laboratory observations that these fish cannot discriminate between toxic and nontoxic strains. In addition, local survival of fish larvae appeared to be determined by the density

of *Alexandrium*, and no larvae were found when cell densities exceeded 1.3×10^1 cells/ml. The presence of toxic dinoflagellates therefore can compromise the survival of larval cohorts and recruitment to local populations (Robineau *et al.*, 1993).

Recently, PST were implicated in chub mackerel, *Scomber japonicus*, mortalities in Argentina. In August 1993, cell counts of *Alexandrium tamarense* were reported to be 3.45×10^2 cells/ml when mortalities were reported. Dying fish were gasping at the surface, and swimming on their sides or upside down (loss of equilibrium). Mackerel stomach contents included *A. tamarense* cells that were found both free or within mucus strands from ingested salps. A mouse bioassay confirmed the presence of PST in stomach contents, liver, intestine, and gills. The highest values of 2800 μg STXeq/100 g were detected in the stomach, but no PST was detected in the muscle of the fish. The most abundant toxins in the stomach were GTX1 and GTX4. The toxin profile of the liver included GTX2 and GTX3 and minor amounts of STX and NEO. Mackerel did not appear to ingest *A. tamarense* cells directly but rather were exposed by preying on toxic salps that had fed on *A. tamarense*. Although toxins were principally transmitted to the mackerel through the diet, the presence of a significant amount of toxin in the gills may also suggest other exposure mechanisms (Montoya *et al.*, 1996). The PST profile of fish differed from that of the Argentinian *A. tamarense* strain (Montoya *et al.*, 1998).

As they are in bivalves, the toxic profiles of PST that accumulate in fish are likely to be partially determined by species-specific differences in the bioconversion process or to be dependent upon the variety of toxic prey species — and of the toxins they contain — consumed by the fish. During July 1988, a small bloom of *Alexandrium fundyense* occurred in southwestern Bay of Fundy, New Brunswick, Canada. The highest concentration in a surface-water sample was 7.5 cells/ml. Concentrations of PST in Atlantic mackerel, *Scomber scombrus*, liver extracts were measured by mouse bioassay and ranged from 40 to 209 μg STXeq/100 g wet weight. By far the dominant component in mackerel liver was STX except in a few fish, where NEO was also dominant. GTX2 and GTX3, and rarely B2, were also detectable. The difference between the toxic profiles of the fish and *A. fundyense* was attributed to the variety of toxic prey consumed by the fish. The fact that mackerel accumulate PST demonstrates the transfer of PST up the food chain (Haya *et al.*, 1990).

Although not usually targeted, PST have been incidentally found in numerous species of fish. Several marine species have been identified with low concentrations of PST in the liver or intestine: shark, *Lamna ditropis* (STX, GTX); salmon, *Oncorhynchus keta* (NEO, STX); skipjack, *Katsuwonus pelamis* (GTX); filefish, *Navodon modestus* (GTX, STX); cod, *Gadus macrocephalus* (GTX, NEO); and parrotfish, *Ypsiscarus ovifrons* (GTX, NEO, STX) (Sato *et al.*, 1993, 1997). It is unclear if or to what extent these toxins may contribute to chronic health effects. As part of a study for TTX (see below), STX and GTX were also found in the freshwater puffer fish *Chelonodon patoca* and *Tetraodon cutcutia* in Bangladesh (Zaman *et al.*, 1997), in *Tetraodon suvatii* and *T. leiurus* (Kungsuwan *et al.*, 1997) and *T. fangi* (Sato *et al.*, 1997) in Thailand, and in the marine puffer fish, *Takifugu poecilonotus*, *T. vermicularis*, and *T. pardalis* in Japan (Kodama *et al.*, 1984; Nakamura *et al.*, 1984) and in the Philippines (Sato *et al.*, 2000).

Even though PST can be toxic to fish, it appears that fish are not usually vectors for PST transfer if humans only eat fish muscle. The accumulation of toxins is usually

confined to the fish's gut, and either certain species perish before detectable amounts of toxin appear in the muscle (White, 1980, 1984) or negligible concentrations of toxins accumulate in the muscle. Several fish species challenged with oral (LD_{50} = 400 to 750 μg/kg body weight) or i.p. (intraperitoneal) (4 to 12 μg/kg body weight) doses of PST showed similar symptoms: loss of equilibrium; gasping; reduced locomotor activity; short, irregular, hyperactive periods; and death within 1 h. Heavy accumulation of PST was confined to the gut (340 to 840 μg per 100 g tissue); PST occurred in the muscle tissues at a level an order of magnitude lower than in the gut (White, 1984).

Because PST does not appear to accumulate in fish muscle, humans who consume only the muscle are unlikely to become intoxicated, whereas those who eat the viscera are likely to become sick. In 1976 in Brunei, 14 nonfatal PSP cases were associated with the consumption of the planktivorous fish *Rastrelliger* sp. during a bloom of *Pyrodinium bahamense* var. *compressum* (Maclean, 1979). One PSP incident in 1983 in Indonesia involved 191 cases and four human fatalities due to the consumption of the planktivorous clupeoid fish *Sardinella* spp. and *Selaroides leptolepis*. In a second incident in November 1983, 45 people became ill after consuming fish and suffered numbness, dizziness, and tingling sensations of the lips, tongue, and throat. Although no known toxic dinoflagellate was associated with the event (Adnan, 1984), PSP was highly suspected (Maclean and White, 1985). PST with toxin profiles similar to *Pyrodinium bahamense* var. *compressum* have been confirmed in gut contents of *Sardinella* sp. from Brunei (Oshima *et al.*, 1990) and in PSP incidents involving *Pyrodinium*, toxic shellfish, and fish that were reported from the Philippines (Gonzalez *et al.*, 1989). These incidents likely occurred because it is customary in southeast Asia to eat small fish whole, including any potentially toxic viscera (Maclean and White, 1985; Gonzalez *et al.*, 1989). During these *Pyrodinium* blooms, mortalities of invertebrates, fish, turtles, and dolphins were also reported (Table 2) (see below).

Turtles are not typically reported to be affected by PST in areas of *Alexandrium* or *Gymnodinium* blooms, but there have been a few reports of turtles in both Asia and Mexico that were affected by blooms of *Pyrodinium bahamense* var. *compressum*. From the mid 1950s until the early 1970s, several dead turtles were reported concurrent with *Pyrodinium* red tides, fish kills, and PSP outbreaks (Maclean, 1973). During a winter (1995) *P. bahamense* var. *compressum* bloom in southwest Mexico — more than 145 turtles (species not specified) stranded on the beaches — along with fish and hundreds of lobsters (Orellana-Cepeda, 1998). Whether the fish and invertebrate strandings were due to anoxic or hypoxic conditions associated with the bloom is unknown. In neither the Asian nor Mexican incidents was examination made for the presence of PST or for possible vectors of toxin exposure.

If PST are ingested by fish or other secondary producers and the toxins are not lethal to those organisms (unlike several of the previously cited examples in which fish mortalities occurred), then there is the possibility that the toxin ingested will be bioaccumulated and passed up the food chain. Mass mortality events involving PST and birds have been documented occasionally (Table 2). In most cases, piscivorous birds were affected after consuming fish contaminated by PST. In May 1942, at least 2000 dead sea birds were observed along the coastal beaches of Washington State, USA. The mortality was coincident with an *Alexandrium catenella* bloom (Table 2). At the same time, six human cases of fatal PSP had been reported, three from the

Olympic Peninsula and three from Vancouver Island, British Columbia. Cats and chickens that had consumed razor clam viscera were also dying along the Washington beaches. At least eight species of birds (Table 2) were found dead with crustaceans and clams in their stomachs and inflamed intestines. The peak occurrence of dead birds was about 2 weeks after the crest of the red tide, and about 2 weeks after the disappearance of the bloom, the numbers of dead birds seen on the beaches began to decline. Based on the available information, McKernan and Scheffer (1942) suggested that the birds were killed by feeding on toxic fish and crustaceans that had ingested *A. catenella* cells.

In May 1968, dying sea birds and dead sand eels, *Ammodytes* sp., were reported around the Farne Islands, northeast England. When several humans were admitted to a hospital with symptoms of PSP and the reports of dead fish continued, a possible connection with the presence of a red tide bloom was investigated. Large numbers of striped Venus, *Venus striatula*; edible cockles, *Cardium edule*; and Baltic macomas, *Macoma balthica*, were found in a moribund state along the shore. Although blue mussels were found to be highly toxic, there were no mortalities observed in this species. The first deaths of sand eels were recorded about a week after the peak of an *Alexandrium tamarense* bloom in the same area (Adams *et al.*, 1968). The amount of toxin in mussels ranged from 10,062 to 20,800 Mouse Units (MU) per 100 g tissue. (One MU was defined as the amount of toxin that when injected intraperitoneally, causes typical neurotoxic signs and kills a 20 g mouse in 15 min [Ingham *et al.*, 1968.] Although no sick individuals were reported, a total of 636 birds (species listed in Table 2) were found dead along 65 miles of the northeast coast. Many of the birds had been feeding shortly before they died. The majority of the dead birds were shags, cormorants, terns, and fulmars. Within a few days, 82% of the breeding shag population had died. Dying shags found on the Farne Islands exhibited a loss of equilibrium, lack of motor coordination, paralysis, restriction of pupils, excess vomiting, abnormal green-brown faeces, intestinal hemorrhage, failure of the circulatory system, and congestion of organs, including the lungs. All these symptoms were remarkably similar to those observed in humans and domestic chicks affected by PSP. Seventy-eight cases of PSP in humans caused by eating toxic mussels occurred almost simultaneously during this May 1968 period (Coulson *et al.*, 1968). From May to June 1975, a similar incident occurred in the same area, and an estimated 500 shags were affected (Table 2) (Armstrong *et al.*, 1978).

The first red tide bloom that led to a major PSP outbreak in the USA occurred in September 1972 from southern Maine to Cape Ann, Massachusetts. Blue mussels and softshell clams were the bivalves most susceptible to PST accumulation and were the most toxic. Paralyzed softshell clams were reported. Northern quahogs did not accumulate toxins, even in areas where blue mussels and softshell clams had high toxin levels. Eastern oysters, *Crassostrea virginica*, had very low STX levels (Twarog and Yamaguchi, 1975). In a few isolated areas, softshell clams and blue mussels remained toxic until April 1973 (Hartwell, 1975), but this may have been attributable to a reocurrence of dinoflagellate cells (S. Shumway, personal communication). This outbreak also coincided with several reports of disseminated neoplasia in softshell clams, but whether there is a connection with PST remains unconfirmed (Landsberg, 1996). Birds were affected during this red tide, with reported mortalities of at least 620 waterfowl, gulls, and shorebirds, representing 13 species, and 1600 black ducks. Representative samples of gut contents showed the presence

of small, filter-feeding bivalves such as blue mussels and the Atlantic jacknife, *Ensis directus*. Many other birds apparently perished after feeding on toxic shellfish, but these were not recovered (Bicknell and Walsh, 1975; Sasner *et al.*, 1975).

A classic case of transfer of PST up the food chain and subsequent mortality at a higher trophic level involved humpback whales in New England, USA. During a 5-week period beginning in late November 1987, 14 humpback whales, *Megaptera novaeangliae*, died in Cape Cod Bay after eating Atlantic mackerel, *Scomber scombrus*, containing STX. The absence of STX in New England waters and shellfish during the episode suggested that the mackerel accumulated toxins farther north in the Gulf of St. Lawrence, and that the whales were exposed to STX after consuming toxic fish that had migrated south. Animals were in good condition, there were no significant lesions, and at least six of the whales had partially digested mackerel in their stomachs, suggesting that they had been feeding just prior to death. STX was present in the viscera, especially the liver (mean of 153 μg STX eq./100 g), of mackerel caught where the whales had been feeding. Extracts from kidney, liver, and stomach contents of the whales were lethal to mice in a standard bioassay, and the mice showed the classic signs of STX toxicity. This was the first case demonstrating the transfer of PST through a commercially important fish and the first one documenting that PST were involved in a marine mammal mortality event (Geraci *et al.*, 1989).

Recently, from May to July 1997, at least 117 Mediterranean monk seals, *Monachus monachus*, died along the coast of the western Sahara, Africa. The seals were in a good nutritional state and had no obvious gross lesions, but their lungs were congested and filled with fluid. Terminally ill animals were lethargic, lacked motor coodination, and were paralyzed in the water; animals floated horizontally and were incapable of effective movement. The period between the onset of clinical signs and the death of the seals was short. Water samples indicated the presence of the known PST producers *Alexandrium minutum* and *Gymnodinium catenatum*. Mouse bioassays yielded 30 to 40 μg STX eq/100 g tissues in six seal samples and in two fish (blacktail, *Diplodus sargus*, and spotted seabass, *Dicentrarchus punctatus*). Symptoms in the mice were consistent with those usually seen after exposure to PST. Variable levels of PST (dcSTX, NEO, and GTX1) were found in all seal samples (liver, kidney, skeletal muscle, and brain), in all fish (Hernández *et al.*, 1998; Reyero *et al.*, 1999), and a few mussel samples. Results were confirmed by high-performance liquid chromatography (HPLC) and mass spectrometry (MS) (Reyero *et al.*, 1999). The evidence suggested that PST were a likely cause for these mortalities (Hernández *et al.*, 1998). The mortality affected mainly adults, which is not consistent with the demographics of recent morbillivirus outbreaks in aquatic mammals, where juveniles are more severely affected (Hernández *et al.*, 1998). A morbillivirus (MSMV-WA) different from that of the closely related dolphin morbillivirus was found (Osterhaus *et al.*, 1998), so other epizootiological factors in this mortality may be relevant. The potential immunosuppressive role of PST and associated increased susceptibility of marine mammals to virus infections should also be considered, along with other potential interactive causal factors.

Other examples have been documented of marine mammals having been affected or suspected of having been affected by PST, but the evidence has often been unavailable or inconclusive or the appropriate tests have not been conducted. As with other kinds of contaminants, the finding of microalgal toxins in tissues alone

does not necessarily imply a direct cause and effect. A strongly circumstantial case was made for the involvement of PST in sea otter, *Enhydra lutris*, mortalities in the Kodiak Archipelago, Alaska, USA, during the summer of 1987. At least 60 animals had died between June and October, but in many cases, dead animals were in such an extreme state of decomposition that it was impossible to obtain samples suitable for analysis. Necropsies of four otters showed no obvious pathology, but they had foam in the lungs, which suggests aspiration of water prior to drowning. There were three reports of sick otters and one of a moribund animal that was able only to dive feebly. Coincident with the discovery of the dead otters, two cases of human PSP on Kodiak Island resulting from the consumption of toxic blue mussels were documented. One mussel sample collected from the site contained > 5800 μg PST/100 g mussel meat (80 μg STX/100 g tissue is considered the regulatory limit for human consumption). Consequently, De Gange and Vacca (1989) suggested that PSP could have been the cause of the sea otter mortalities.

One interesting, but unconfirmed, example from Hawaii indicated that a potent Na^+ channel inhibitor, characteristic of TTX (tetrodotoxin) (see below) or STX, may have been involved in the death of two Atlantic dolphins living in an artificial lagoon (Hokama *et al.*, 1990). Necropsy examination revealed no significant findings except for hypersensitivity-type inflammatory changes in the intestinal tract. Testing of fish present in the same lagoon by stick enzyme immunoassay (S-EIA) confirmed the presence of ciguatoxin (CTX) (see ciguatoxins), with high levels present in the viscera of the mullet *Neomyxus chaptalli*. Fish such as capelin (imported from Newfoundland), herring, and mackerel (imported from California) that were usually fed to the dolphins were negative for CTX by S-EIA as were extracts from dolphin livers and stomach contents. In a mouse bioassay, symptoms, including wobbly walk, cyanosis, slow irregular breathing, and paralysis in the hind legs resulted from injections of the viscera of mullet; the manini, *Acanthurus triostegus sandvicensis*; the wrasse *Cheilinus rhodochrous*; the aholehole, *Kuhlia sandvicensis*; and the livers and gastric contents of two dolphins. In the guinea pig atrium assay, strong and moderate Na^+ channel inhibition was shown after injections of extracts of mullet viscera and dolphin livers, respectively. It was suggested that the dolphins died from toxins present in the gut contents of mullet, wrasse, and aholehole, but that these toxins were not CTX. That the toxin was a Na^+ channel inhibitor could implicate PST, which would be unusual in this area (Hokama *et al.*, 1990).

Although dinoflagellates have been implicated in most of the documented cases in which PST have affected animals, other organisms are now known to produce similar effects. Recently, and for the first time, PST from an *Anabaena circinalis* bloom were implicated in sheep mortalities in Australia. Although previous livestock mortalities associated with *A. circinalis* blooms were recognized to be due to neurotoxic exposure, the neurotoxins involved were not identified. Affected sheep showed symptoms of trembling, recumbency, and crawling; necropsies and histopathology showed no significant lesions. Except at the lowest dose, *Anabaena circinalis* extract injected i.p. into mice caused death within 4 to 7 min. Symptoms included staggering at low doses, followed by gasping, leaping, and death from respiratory failure; salivation was not observed (Negri *et al.*, 1995). Two extensive surveys of Australian *A. circinalis* blooms showed that approximately half the samples were neurotoxic to mice and two-thirds contained detectable concentrations of PST (Negri *et al.*, 1998). Interestingly, although there is a worldwide distribution

of *A. circinalis*, it appears that there is a geographical segregation of neurotoxin production. American and European isolates of *A. circinalis* produce only anatoxin-a (see later in text), whereas Australian isolates produce exclusively PST (Beltran and Neilan, 2000).

B. TETRODOTOXIN

Another type of fatal human poisoning with characteristics similar to those of PSP is attributed to exposure to tetrodotoxin (TTX) through the consumption of the fish delicacy fugu' (puffer fish) (Mosher and Fuhrmann, 1984). TTX has also been found in molluscs such as the Japanese scallop, *Patinopecten yessoensis* (Kodama *et al.*, 1993), and at least eight species of gastropods (see Shumway, 1995; Lin and Hwang, 2001); these organisms represent another potential source for human toxicity. Although poisoning events associated with eating fugu usually occur in Asia, cases in Florida, USA (Mosher and Fuhrmann, 1984), and in Europe (Kao, 1993) have also been reported. TTX acquired through consumption of puffer fish, along with other ingredients, is also largely responsible for the human "zombie" state associated with the vodoun religion (Davis, 1985).

TTX has been found in numerous other species of aquatic organisms, including the goby *Gobius criniger*; the shark *Lamna ditropis*; the salmon *Oncorhynchus keta*; the conger eel *Conger myriaster*; the saury *Cololabis saira*; the cod *Gadus macrocephalus*; the parrotfish *Ypsiscarus ovifrons*; the skipjack *Katuwonus pelamis*; the filefish *Navodon modestus*; the salamanders *Taricha torosa*, *T. rivularis*, and *T. granulosa*; the octopus *Hapalochlaena maculosa*; the xanthid crab *Atergatis floridus*; the horseshoe crabs *Carcinoscorpius rotundicauda* and *Tachypleus gigas*; the Taiwanese crab *Lophozozymus pictor*; the crayfish *Procambarus clarkii*, the starfish *Astropecten polyacanthus* and *A. scoparius*; and the flatworm *Planocera multitentaculata* (Noguchi *et al.*, 1982, 1983; Mosher and Fuhrmann, 1984; Miyazawa *et al.*, 1986; Kungsuwan *et al.*, 1987; Tamplin, 1990; Sato *et al.*, 1993; Shumway, 1995; Tsai *et al.*, 1995; Lin and Hwang, 2001).

Chemically, TTX is very different from STX, but it produces similar symptoms in mammals because they both act on site 1 of the voltage-dependent sodium channel. Like PST, TTX exerts its toxic action by specifically blocking the voltage-sensitive sodium channels in nerve and muscle membranes (Kao, 1993). The biogenetic origin of TTX has been linked to bacteria such as the widely distributed genera *Vibrio* and *Aeromonas* (Noguchi *et al.*, 1986; Tamplin, 1990). Recently, TTX was also shown to be produced by *Alexandrium tamarense*, or at least by bacteria associated with this dinoflagellate (Kodama *et al.*, 1993, 1996). Although TTX is present in a wide range of aquatic organisms, it is not known to what extent the toxin originates from dinoflagellates. High concentrations of TTX, which are fatally toxic to other organisms, are known to occur in puffer fish and xanthid crabs (Mosher and Fuhrmann, 1984; Yamamori *et al.*, 1988), which appear to be immune to its effects. Rainbow trout, *Oncorhynchus mykiss*, and Arctic char, *Salvelinus alpinus*, can detect extremely low levels of TTX via specialized gustatory receptors. Some other fish species have been shown to reject toxic puffer livers and artificial food pellets containing TTX (Yamamori *et al.*, 1988). Although TTX acts in a manner similar to PST, it is currently unclear what effects TTX has on aquatic organisms.

C. SPIROLIDES

Spirolides are a group of macrocyclic amines that have recently been confirmed in shellfish from aquaculture sites in Nova Scotia, Canada. Although the human or animal health significance of these toxins is unknown, when injected into mice, spirolides caused rapid death due to neurointoxication. The bioorigin of spirolides has been determined to be *Alexandrium ostenfeldii* (Cembella *et al.*, 2000; Hu *et al.*, 2001).

D. BREVETOXINS

Brevetoxins are potent neurotoxins and hemolysins produced by the dinoflagellate *Karenia brevis* (= *Gymnodinium breve*) Hansen and Moestrup (Daugjberg *et al.*, 2000) and the raphidophyte *Chattonella* cf. *verruculosa* (Table 1). Brevetoxin-like compounds have been found in the dinoflagellate *Karenia* sp. and the raphidophytes *Chattonella antiqua*, *C. marina*, *Heterosigma akashiwo* (= *H. carterae*), and *Fibrocapsa japonica* (Table 1). Brevetoxins can cause serious health effects and significant animal mortalities (Table 2). In terms of their frequency and the range of species affected, *Karenia* blooms (Table 2) that produce brevetoxins are far more devastating than blooms of raphidophytes (Table 5). Thus far raphidophytes (with the exception of one case [Table 5], and an unconfirmed case [Section T.3]) have been reported to be ichthyotoxic only (Table 5).

Brevetoxins are complex, polycyclic ethers, which are differentiated into two main types according to their backbone structure (PbTx-1 type 10 rings; PbTx-2 type 11 rings). Nine brevetoxins (PbTx-1 to PbTx-3, PbTx-5 through PbTx-10) have been isolated thus far from *K. brevis* (Baden, 1989; Schulman *et al.*, 1990). PbTx-1 is the most potent brevetoxin described (Shimizu *et al.*, 1986). Dominant brevetoxin components are PbTx-2 (4.93 to 12.6 pg/cell), PbTx-3 (0-2.31 pg/cell), and PBTx-1 (0.07-1.72 pg/cell) in *K. brevis* cultures (Shimizu *et al.*, 1986; Baden and Tomas, 1989) and are PbTx-2 and PbTx-3 in bubble-generated aerosols (Pierce, 1986; Pierce *et al.*, 1990). PbTx-3 is the primary toxin responsible for respiratory irritation (Baden and Mende, 1982).

Five neurotoxic components (FjTx-I, FjTx-II, FjTx-IIIa, FjTx-IIIb, and FjTx-IV) corresponding to brevetoxins PbTx-1, PbTx-2, PbTx-9, PbTx-3, and oxidized PbTx-2, respectively, were identified by HPLC from cultures of *F. japonica* strains originally isolated from the Dutch part of the North Sea (Khan *et al.*, 1996b). Four toxins have been isolated from *C. marina* (CmTx) and *H. akashiwo* (HaTx) that correspond to PbTx-2, oxidized PbTx-2, PbTx-3, and PbTx-9, and three toxins from *C. antiqua* (CaTx) that correspond to PbTx-2, oxidized PbTx-2, and PbTx-3 (Ahmed *et al.*, 1995; Khan *et al.*, 1995, 1996a, 1996c). Further chemical characterization is required to definitively show that FjTx, CmTx, CaTx, and HaTx are the same as brevetoxins, as recently confirmed for *C.* cf. *verruculosa* (Bourdelais *et al.*, 2002)

By binding to specific sites on the voltage-sensitive channels, brevetoxins alter membrane properties of excitable cells. Both brevetoxins and ciguatoxins bind to sodium channel site 5 to shift activation to more negative potentials, resulting in subsequent membrane depolarisation (Huang *et al.*, 1984; Catterall, 1985; Poli *et al.*, 1986; Lombet *et al.*, 1987). The effects and toxicokinetics of brevetoxins in mamma-

lian models (Templeton *et al.*, 1989; Cattet and Geraci, 1993) and the chemistry, pharmacology, and toxicology of brevetoxins in experimental systems (see Baden, 1983, 1989) have been studied. Mice administered brevetoxins i.p. show an irritability immediately after injection, followed by hind-quarter paralysis, dyspnea, salivation, lachrymation, urination, defecation, and death from respiratory paralysis. Whole LD_{50} for brevetoxins in mice ranges from 0.05 mg/kg body weight for i.v. (intravenously) administration to 0.5 mg/kg for oral and i.p. administration (Baden and Mende, 1982; Baden, 1989).

Karenia brevis is one of the oldest reported HABs. Fish kills have been reported since 1844 (Ingersoll, 1882) (Table 2), but the causative dinoflagellate was not identified and named until the 1946 to 1947 outbreak (Davis, 1948; Steidinger, 1993). *Karenia brevis* is principally distributed throughout the Gulf of Mexico, with occasional red tides occurring along the mid and south Atlantic coast of the USA (Steidinger, 1993). Although shellfish poisonings from eating bivalves in Florida, USA, have been known since the 1880s (Walker, 1884), the cause was not identified until the 1960s (McFarren *et al.*, 1965; Steidinger, 1993). Neurotoxic Shellfish Poisoning (NSP) is caused by the consumption of shellfish contaminated by brevetoxins or brevetoxin analogs and, thus far, has been associated only with bivalves. The first written report of respiratory irritation caused by a Florida red tide was made in 1917 (Taylor, 1917a). People can suffer from respiratory effects when brevetoxins become aerosolized through the disruption of *K. brevis* cells by breaking waves, surf, or onshore winds (Pierce, 1986; Pierce *et al.*, 1990). In humans, NSP is characterized by paresthesia, reversal of hot-cold temperature sensation, myalgia, vertigo, ataxia, abdominal pain, nausea, diarrhea, burning pain in the rectum, headache, bradycardia, and dilated pupils (Hemmert, 1975; Steidinger *et al.*, 1973; Baden, 1983, 1988; Morris *et al.*, 1991). Exposure to *K. brevis* aerosols can also cause conjunctival irritation, rhinorrhea, and nonproductive cough; asthmatics may also experience wheezing (Music *et al.*, 1975). Occasionally there are reports of skin irritation and itching when people swim in waters affected by red tides. Experimentally, there was some evidence of *in vitro* skin penetration of PbTx-3 (< 3% of dose) in guinea pigs 2 h after the initial exposure (Kemppainen *et al.*, 1992).

NSP cases have been associated principally with brevetoxins produced by *Karenia brevis* (Baden, 1989) and *Karenia* sp. (Haywood *et al.*, 1996; Chang *et al.*, 1998; A. Haywood, personal communication). Thus far, no human fatalities have been attributed to NSP, and there have been no documented cases of NSP caused by raphidophytes. New NSP cases may occur when people consume unregulated shellfish species or shellfish illegally harvested. Until 1987, NSP incidents in humans were limited to the Gulf of Mexico (Steidinger, 1993). In 1987 to 1988, 145,280 hectares of shellfish-growing waters along the Atlantic coast were closed to harvest because of an entrained *K. brevis* red tide that originated off the west coast of Florida and was transported to North Carolina coastal waters by the Gulf Stream. There were 48 documented cases of people contracting NSP by eating toxic shellfish; 35 cases occurred before harvesting bans could be implemented by state officials (Fowler and Tester, 1989; Tester and Fowler, 1990; Morris *et al.*, 1991; Tester *et al.*, 1991; Steidinger, 1993). From December 1992 to January 1993, a large-scale NSP incident occurred for the first time in New Zealand (Bates *et al.*, 1993; Chang *et al.*, 1995; Satake *et al.*, 1996a). Toxic shellfish were detected in the Bay of Plenty, northeast North Island, and 186 people met the case definition of NSP, having symptoms that

included systemic and general CNS, gastrointestinal, neurosensory, neurocerebellar, and neuromuscular effects (Bates *et al.*, 1993). The dinoflagellate implicated in this event was tentatively identified as *K.* cf. *brevis* (as *Gymnodinium* cf. *breve*) (Chang, 1995; Haywood *et al.*, 1996) but is now being classified as a new species (Haywood *et al.*, in preparation).

There have been several documented cases in which *K. brevis* blooms have killed invertebrates in the field (Simon and Dauer, 1972; Steidinger *et al.*, 1973). Except for five benthic species of polychaetes and a brachiopod, at least 17 invertebrate species normally present in Tampa Bay, Florida, USA, were absent immediately after a red tide. Dominant species killed included the polychaetes *Onuphis emerita* and *Travisia* sp. and several amphipod species, including *Acanthohaustorius* sp. The cephalochordate *Branchiostoma caribbaeum* was also affected (Simon and Dauer, 1972). Several experimental studies have investigated the differential susceptibility of invertebrate species to *K. brevis* exposure. When the copepods *Calanus pacificus* were fed *K. brevis*, there was a noticeable increase in heart rate and loss of motor control (Huntley *et al.*, 1986; Sykes and Huntley, 1987). Unaffected by exposure to varying concentrations of *K. brevis* were eastern oysters, *Crassostrea virginica*; hooked mussels, *Ischadium recurvum* (as *Brachidontes recurvus*); the annelid *Polydora websteri*; the barnacle *Balanus eburneus*, the crab *Eurypanopeus depressus*; blue crabs, *Callinectes sapidus*; and stone crabs, *Menippe mercenaria* (Ray and Aldrich, 1967; Sievers, 1969; Roberts *et al.*, 1979). Other species have been acutely affected by exposure to *K. brevis*. The molluscs *Fasciolaria lilium hunteria* (banded tulip), *Melongena corona* (crown conch), and *Oliva sayana* (lettered olive) lost muscle control and could not right themselves; mortalities varied from 55.5% to 69.0%. Gross pathology and histopathology of internal tissues did not reveal any differences between exposed and control animals. Crabs did not retain toxins when fed toxic shellfish (Roberts *et al.*, 1979).

The recruitment of bay scallops, *Argopecten irradians*, was significantly affected by the North Carolina red tide of 1987 (Summerson and Peterson, 1990). Bay scallops are a potential health risk, but they are usually safe if people eat only the adductor muscle, which does not accumulate brevetoxins. Cases of NSP in the southeastern USA have been associated with the consumption of eastern oysters, *Crassostrea virginica*; quahogs, *Mercenaria campechiensis* and *M. mercenaria*; Atlantic surfclams, *Spisula solidissima raveneli*; sunray venus, *Macrocallista maculata*; variable coquinas, *Donax variabilis*; cross-barred venus, *Chione cancellata*; and other filter feeders. Brevetoxins accumulate in the gut and hepatopancreas in these species (McFarren *et al.*, 1965; Steidinger *et al.*, 1973, 1993; Hemmert, 1975; Roberts *et al.*, 1979; Baden *et al.*, 1982; Tester and Fowler, 1990; Steidinger *et al.*, 1998a). The persistence of toxicity is species dependent and varies according to the concentration of the bloom and the bivalves' rates of feeding and elimination (Baden, 1983). When Pacific oysters, *Crassostrea gigas*, were exposed to between 10 to 25 million *K. brevis* cells/oyster over a 24 h period, NSP levels were 25 to 100 MU per 100 g of drained oyster meat. After 3 days of depuration, brevetoxin concentrations in oysters were considerably reduced and almost at acceptable regulatory limits for human consumption of 20 MU per 100 g (Fletcher *et al.*, 1998). In coquinas that have accumulated the toxin, the proportions of PbTx-2 and PbTx-3 are different from the proportions present in *K. brevis*. PbTx-3 predominates in coquinas, but it forms only about 28% of the toxic component in *K. brevis* (Baden, 1988). Analysis of shellfish

extracts from an NSP outbreak in June 1996 in Florida demonstrated the likely metabolic conversion of the parent brevetoxin PbTx-2 into PbTx-3. No PbTx-2 was detected in the shellfish (Poli *et al.*, 2000). Although there is some information on the toxin deposition of brevetoxins in a few molluscs, there is no information on potential chronic health effect to these molluscs.

Several brevetoxin analogs have been described from New Zealand shellfish. BTXB1 (brevetoxin B1) was found in the cockles *Austrovenus stutchburyi* (Ishida *et al.*, 1994, 1995) and was lethal to mice (i.p.) at a dose of 0.05 mg/kg. Mice showed irritability immediately after injection, followed by hind-quarter paralysis, severe dyspnea, convulsions, and death by respiratory paralysis (Ishida *et al.*, 1995). BTXB2 (brevetoxin B2), BTXB3 (brevetoxin B3), and BTXB4 (brevetoxin B4) were isolated from greenshell mussels, *Perna canaliculus*, collected at the time of the NSP event. BTXB4 extracted from the hepatopancreas of toxic mussels was lethal to mice by i.p. injection at a dose of 0.1 mg/kg. Symptoms observed in mice were similar to those caused by BTXB2: paralysis of limbs, diarrhea, dyspnea, and convulsions. In greenshell mussels, BTXB4 was the most toxic brevetoxin metabolite and accounted for two-thirds of the mouse toxicity (Morohashi *et al.*, 1995, 1999; Satake *et al.*, 1996a; Murata *et al.*, 1998). Of the two major brevetoxins, PbTx-2 (= BTXB) and PbTx-3, PbTx-2 was not detected in green mussels (Morohashi *et al.*, 1999) or in cockles (Ishida *et al.*, 1994, 1995), while PbTx-3 was detected in cockles (Ishida and Tsuji, 1999) in New Zealand waters. PbTx-2 and PbTx-3 were also detected in Pacific oysters, *Crassostrea gigas*, collected from Tiki Road in January 1993 and Rangaunu Harbour (northern North Island) in February 1994 and June 1995 (Ishida *et al.*, 1996a, 1996b).

Brevetoxins are potent ichthyotoxins and have been responsible for the deaths of billions of fish over the years. Fish mortalities associated with *Karenia brevis* events are very common, widespread, and affect hundreds of species (Steidinger *et al.*, 1973; Quick and Henderson, 1975) (Table 2) and some life-history stages may be more susceptible than others (Riley *et al.*, 1989; Warlen *et al.*, 1998; Kimm-Brinson and Ramsdell, 2001). In July-September 2000, brevetoxins produced by *Chattonella* cf. *verruculosa* were implicated in a mortality of 1 to 2.5 million Atlantic menhaden, *Brevoortia tyrannus*, in Delaware, USA (Bourdelais *et al.*, 2002).

Brevetoxin is thought to be absorbed directly across the gill membranes of fish (Abbott *et al.*, 1975), although ingestion is another documented route (Tester *et al.*, 2000). Fish kills are postulated to originate with the lysis of toxic *K. brevis* cells and the subsequent liberation of toxin and passage across the gills (Baden, 1988). Intoxication begins with binding of PbTx to specific receptor sites in excitable tissues of fish (Baden and Mende, 1982); toxin binds with high affinity, for example, to *Tilapia* brain synaptosomes (Stuart and Baden, 1988). Signs of intoxication in fish include violent twisting and corkscrew swimming, defecation and regurgitation, pectoral fin paralysis, caudal fin curvature, loss of equilibrium, quiescence, vasodilation, and convulsions, culminating in death due to respiratory failure. Chronically neurointoxicated fish show little pathology aside from slight precipitate hemolysis (Steidinger *et al.*, 1973; Quick and Henderson, 1975; Baden and Mende, 1982; Baden, 1989). There is also some indication that there are hemolytic components, but these are not toxic to mice (Trieff *et al.*, 1975 in Baden, 1983). Evidence for in situ ichthyotoxicity related to the hemolytic fraction is fragmentary, although several species of fish collected during red tides in 1973 to 1974 displayed signs of chronic

tissue damage and hemopathy. Chronic hemolysis was detected via evidence of anemia, cyanosis, hyperviscous blood, splenomegaly, hepatic hemosiderosis, and dehydration (Quick and Henderson, 1974, 1975; Baden, 1983).

In some instances, mortalities caused by red tides are not immediate but may occur over a period of days or weeks of exposure to subacute concentrations of toxins. Mortalities typically occur at a cell concentration of 2.5×10^2 *K. brevis* cells/ml which is often considered to be a lethal concentration (Quick and Henderson, 1974). However, it is known that fish can die at lower cell concentrations (Morton and Burklew, 1969; Quick and Henderson, 1974) and can also apparently survive in much higher concentrations (at 3×10^3 cells/ml) (Landsberg *et al.*, unpublished data). Some of these differences in toxicity level will depend on the susceptibility of each fish species to exposure; the *K. brevis* strains involved, the component toxins, and cell concentrations; the stability of extracellular toxins; and the exposure routes. If *K. brevis* produces 11 pg/cell, then 4.85×10^5 cells are required to yield 6 n*M* of toxin (Stuart and Baden, 1988), which is sufficient to kill fish. In ichthyotoxicity assays of mosquitofish, *Gambusia affinis*, *Karenia brevis* Type 2 brevetoxins (PbTx-1, PbTx-7) are more potent than Type 1 brevetoxins (PbTx-2, PbTx-3, PbTx-8, PbTx-9). Lethal concentrations for 50% of the test population within 24 h were 3 to 5 n*M* for Type 2 toxins and 10 to 37 n*M* for Type 1 toxins (Baden, 1989; Baden *et al.*, 1989) (see also Lewis, 1992, section on ciguatoxins).

Unlike brevetoxins, thus far there is no evidence that brevetoxin analogs are ichthyotoxic. Brevetoxin analogs isolated from New Zealand shellfish were not toxic to fish (100 ng/ml of BTXB1 for zebrafish, *Danio rerio* [Ishida *et al.*, 1995], or 0.1 ppm of BTXB4 for white cloud mountain minnow, *Tanichthys albonubes* [Morohashi *et al.*, 1999]).

In order to examine differential brevetoxin-like production, juvenile red seabream, *Pagrus major*, were exposed to raphidophytes in different phases of the raphidophyte's growth cycle. From mid-logarithmic to early stationary phases, *Chattonella marina* and *C. antiqua* were intensely toxic to these fish (Khan *et al.*, 1996a). *Fibrocapsa japonica* was the most toxic during the mid-logarithmic phase and the least toxic during the stationary phase. In 2-day cultures (1.68×10^3 *F. japonica* cells/ml), fish showed abnormal movements for about half an hour, and then recovered gradually. Early-logarithmic-phase cultures (4.1 to 6.5×10^3 cells/ml) killed the fish in 2 to 4 h, whereas 6-, 8-, and 10-day cultures (1.06×10^4 cells/ml, 1.67×10^4 cells/ml, and 2.23×10^4 cells/ml) killed the fish within 66, 37, and 30 min, respectively. When red sea bream were exposed to *C. marina* neurotoxins, a significant decrease in heart rate was noted (Endo *et al.*, 1989), probably due to depolarization of the vagus nerve. Exposure to neurotoxic fractions caused minor alterations in the gill lamellar epithelium (Endo *et al.*, 1992) instead of the significant pathology caused by reactive oxygen species (ROS) (see section on ROS).

Brevetoxins from *K. brevis* were traced through experimental food chains from dinoflagellates, through copepod grazers, to juvenile fish. The generality of this food chain transfer was demonstrated by using three different combinations of copepods (*Temora turbinata*, *Labidocera aestiva*, *Acartia tonsa*) and various juvenile fish (spotted mojarra, *Eucinostomus argenteus*; striped killifish, *Fundulus majalis*; pinfish, *Lagodon rhomboides*; spot, *Leiostomus xanthurus*) during different seasons. Juvenile spot were fed toxin-laden copepods so that vectorial intoxication could be examined. Toxins were shown to move from fish viscera to muscle tissue within

periods from 2 to 6 h to 25 h (Tester *et al.*, 2000). When gulf toadfish, *Opsanus beta*, were experimentally exposed to PbTx-3 by injection, the toxin was found principally in the liver, bile, muscle, kidney, gill, stomach, and intestinal tract. The concentration of PbTx-3 in the blood declined exponentially with time, and the deposition of toxin in tissues was rapid (1 h following intravenous administration). No brevetoxin metabolites were found in the blood after 6 h. With time, high levels of PbTx-3 were found in the gill and kidney, suggesting that both renal and branchial routes may be important in the excretion of brevetoxin or its metabolites (Kennedy *et al.*, 1992). When PbTx-3 was given orally to gulf toadfish in a fish-meal slurry, 40% of the total PbTx-3 body burden was concentrated in the hepatobiliary system, 27% in muscle, and 25% in the gastrointestinal tract. The hepatobiliary system therefore is the key route for metabolizing and excreting brevetoxin in fish, regardless of the method of toxin administration. Significant amounts of toxin were also associated with the gastrointestinal tract, another important site for detoxification (Washburn *et al.*, 1994). The use of different exposure protocols in experimental settings is critical to understanding brevetoxin toxicokinetics. Because experimental exposures do not necessarily mimic natural exposures, care should be taken in extrapolating the results. For example, some experimental studies may misleadingly indicate that toxin accumulates in the muscle, which would have important implications for public health. However, in natural exposures to *K. brevis*, there is no evidence that brevetoxins are deposited in the muscles of fish; it has been determined that neither PbTx-2 nor PbTx-3 is found in the muscle — both are principally concentrated in the intestinal tract (Landsberg *et al.*, unpublished data).

During the Florida west coast *K. brevis* red tide of October 1973 to May 1974, in addition to the usual reports of dead fish, large numbers of birds were found moribund or dead, particularly double-crested cormorants, *Phalacrocorax auritus*; red-breasted mergansers, *Mergus merganser*; and lesser scaup, *Aythya affinis*. During an 8-week period, several thousand lesser scaup died. All scaup examined had substantial subcutaneous fat and normal breast muscles, which indicates that the birds died quickly. Most of the ducks had fed recently, and the proventriculi contained turritellid, pyramidellid, and opisthobranch gastropods, and amethyst gemclams, *Gemma gemma*. Clinical signs included weakness, reluctance to fly, slumping of the head, clear nasal discharge, viscous oral discharge, oil gland dysfunction, excessive lacrimation, chalky yellow diarrhea, dyspnea, tachypnea, tachycardia, decreased blood pressure, depressed body temperature, diminished reflexes, and dehydration. To expose white Pekin ducklings to red tide toxins, they were force fed with toxic northern quahogs, *Mercenaria mercenaria* (assayed at 48 MU per 100 g tissue), or red tide water containing 2.2×10^4 *Karenia brevis* cells/ml. The ducklings showed signs of toxicity 2 days after exposure, appearing lethargic. On day three, the ducklings showed signs of ataxia, spastic movements of the head, and a tendency to droop the head to one side. Over the next few days the ducks died and showed signs similar to those noted in field observations of moribund birds (Quick and Henderson, 1974; Forrester *et al.*, 1977). Anecdotal reports of dead birds during red tide events are not unusual but are not always documented in the scientific literature.

During 1946 to 1947 and 1953 to 1955, two of the largest *K. brevis* red tide events on record, in both geographical distribution and longevity, occurred in central and southwest Florida, USA (Gunter *et al.*, 1948; Rounsefell and Nelson, 1966). Cata-

strophic mortalities of marine animals were recorded from Tarpon Springs to Key West (some 150 miles of coastline). During these events, there were reports of dead bottlenose dolphins (*Tursiops truncatus*), sea turtles, and numerous fish species (Gunter *et al*., 1948; Rounsefell and Nelson, 1966). Mass mortalities of dolphins were reported recently in north Florida (August to December 1999) when more than 100 animals stranded and brevetoxins were confirmed in dolphin tissues (B. Mase and T. Leighfield, NOAA, personal communications). In other years, there have been numerous reports of individual dolphin strandings. By far the largest *K. brevis*-associated dolphin mortality involved more than 740 bottlenose dolphin strandings along the Atlantic coast from June 1987 to May 1988. In the fall of 1987, in an unusual event, a Florida red tide was transported to North Carolina (see above), therefore exposing a wider range of dolphins and fish to toxins than are exposed when red tide is restricted to Florida. Dolphins migrating south in the fall encountered the bloom off North Carolina and fed there on contaminated fish. It has been estimated that more than 50% of the coastal migratory stock between New Jersey and Florida, USA, died during this period. Brevetoxin was considered to be the proximate cause of the mortality. Although infectious agents (*Vibrio*, virus) were found in numerous individuals, these were likely secondary to brevetoxicosis. The spatial and temporal patterns of mortality also lacked the hallmark patterns of infectious disease. Contaminant loadings (PCBs) were not considered to be abnormal during this event. Eight of 17 stranded dolphins collected during the mortality were positive for brevetoxins, and brevetoxin was found in the viscera of menhaden, *Brevoortia tyrannus*, taken from one dolphin stomach. No brevetoxin was detected in any of the control prey taken from dolphins that had died in captivity or prior to this event. Brevetoxin concentrations in dolphin livers ranged from 80 to 16,000 ng/g. Dolphins were sublethally exposed to brevetoxins by ingesting toxic fish and then succumbed to a range of chronic disorders, including fibrosis of the liver and lung, adhesions of the abdominal and thoracic viscera, and secondary microbial infections associated with immunosuppression (Geraci, 1989).

Karenia brevis was implicated in mortalities of the endangered Florida manatee, *Trichechus manatus latirostris*, in 1963 (Layne, 1965), 1982 (O'Shea *et al*., 1991), and 1996 (Bossart *et al*., 1998), when 7, 39, and 149 animals, respectively, died in southwest Florida, USA, during the winter-spring. In 1963, in addition to manatee deaths, newspapers (Sarasota Herald Tribune, March 31, 1963) reported red tide in the region for 6 months, and strandings of turtles, mortalities of cormorants and fish, and neurotoxic symptoms in sick raccoons occurred coincidentally. The large-scale mortalities of manatees in 1982 and 1996 were attributed to a set of unusual environmental conditions (Landsberg and Steidinger, 1998). *Karenia brevis*, which typically develops 18 to 74 km offshore at low concentrations, usually comes inshore during the fall-winter and then dissipates (Tester and Steidinger, 1997). Red tides do not usually appear inshore during the winter-spring months, when manatees are congregated in low or zero salinity areas, in the warmer waters of the coastal power plants, at warm-water spring refugia, or in residential canals (Reynolds and Wilcox, 1986). In the winter-spring periods of 1982 and 1996, red tide made unusual appearances inside the barrier islands of southwest Florida. High-salinity areas (above 24 ppt) allowed persistently high concentrations of *K. brevis* cells ($>1 \times 10^2$/ml) to be maintained. In the spring, as the water temperature warms up, manatees usually disperse downstream into the inshore bays. If red tide has come inshore

during this period (as occurred in 1982 and 1996), then the likelihood of manatees being exposed to red tide during their post-winter movements is fairly high, depending on which areas the manatees move to and their proximity to the red tide bloom.

Several aspects of the manatee mortality events in 1982 and 1996 were different. In 1982, there was a lag of 3 weeks between the time that the red tide cell counts had decreased to below 1×10^2 cells/ml (Steidinger, unpublished data) and the time that the last manatee died (O'Shea *et al.*, 1991). In 1982, it was suspected that filter-feeding tunicates accumulated brevetoxins and that they were still toxic to manatees some 3 weeks after the dissipation of the bloom. Manatees normally consume seagrass but were also exposed to toxic tunicates that were attached to the seagrass. Sick and dying manatees were observed throughout the red tide event (O'Shea *et al.*, 1991). In 1996, the duration of the mortality event was coincident with the duration of the red tide bloom that occurred in the same inshore areas where manatees were affected. There was no significant lag time between the last manatee mortality and the dissipation of the red tide (Landsberg and Steidinger, 1998). At the gross level of examination, severe nasopharyngeal, pulmonary, hepatic, renal, and cerebral congestion were present in all manatees examined. Nasopharhyngeal and pulmonary edema and hemorrhage were seen. Microscopic lesions consisted of catarrhal rhinitis, pulmonary hemorrhage and edema, multiorgan hemosiderosis, and nonsuppurative leptomeningitis. Immunohistochemical staining with a polyclonal antibody to brevetoxin showed intense positive staining of lymphocytes and macrophages in the lung, liver, and secondary lymphoid tissues. Additionally, lymphocytes and macrophages associated with inflammatory lesions of the nasal mucosa and meninges were also positive for brevetoxin. These findings implicated brevitoxicosis as a component of and the likely primary etiology for the epizootic (Bossart *et al.*, 1998): brevetoxins were confirmed in manatee tissues, brevetoxin shows high affinity for binding to manatee brain nerves (Trainer and Baden, 1999), and manatee tissue extracts were toxic to mice in bioassays (Baden, unpublished data). The coincidence of the mortality with the red tide bloom would suggest that manatees were exposed to high levels of brevetoxins through inhalation. Residual toxin bound up in the food web, water, or substrate would persist after the bloom had dissipated, but aerosolized brevetoxin that manatees could inhale would disperse relatively quickly (Landsberg and Steidinger, 1998). The presence of brevetoxins in nasal and lung tissue implicate the aerosol, and lesions of the upper respiratory tract were the only severe and consistent inflammatory lesions seen in the manatees from the epizootic (Bossart *et al.*, 1998).

Although acute exposure to lethal doses of brevetoxin results in massive animal mortalities, effects from low-level exposure to brevetoxins are harder to interpret. Chronic dietary exposure to brevetoxins could exert lethal or sublethal effects at all trophic levels, leading to impaired feeding, bloom avoidance behavior, physiological dysfunction, impaired immune function, reduced growth and reproduction, pathological effects, or mortality. There is some evidence for immunosuppressive effects associated with persistent chronic exposure to brevetoxins and suggests an influence on manatee health in the long term (Bossart *et al.*, 1998). The chronic mortalities of dolphins in 1987 together with numerous secondary health effects in dolphins are also suggestive of longer-term toxicity exposure (Geraci, 1989).

E. GYMNODIMINE

In 1994, screening of contaminated dredge oysters, *Tiostrea chilensis*, from Foveaux Strait, New Zealand (South Island), led to the discovery of a novel toxic compound — gymnodimine (Seki *et al.*, 1995, 1996; Mackenzie *et al.*, 1996a). The examination of phytoplankton samples showed that high numbers of *Karenia* sp. (A. Haywood and K. Steidinger, personal communications) (as *Gymnodinium* sp.) (Seki *et al.*, 1995, 1996; Mackenzie *et al.*, 1996a) were associated with this toxicity. *Karenia* sp. (as *Gymnodinium* sp.) bears a close morphological relationship to *Karenia mikimotoi* (= *Gymnodinium mikimotoi* Hansen and Moestrup [Daugjberg *et al.*, 2000]) (Haywood *et al.*, 1996; A. Haywood and K. Steidinger, personal communications). Mouse bioassay using crude extracts of either *Karenia* sp. (as *Gymnodinium* sp.) cultures or oysters fed with *Karenia* sp. (as *Gymnodinium* sp.) were lethal to mice. The minimum lethal dose of gymnodimine injected i.p. into mice was 450 μg/kg (Mackenzie *et al.*, 1996a; Seki *et al.*, 1996). Mice died in 5 to 15 min and presented with neurological symptoms, curled tail, jumping, and paralysis (Seki *et al.*, 1996). These symptoms were identical to those shown by mice that had been exposed to shellfish naturally contaminated with gymnodimine from a *Karenia* sp. (as *Gymnodinium* sp.) bloom (Mackenzie *et al.*, 1996a). Thus far, there is no evidence that there are human health risks associated with the consumption of gymnodimine-contaminated shellfish (Mackenzie *et al.*, 1996a) but the potential public health threats still need to be considered.

When dredge oyster larvae were exposed to whole cells, culture filtrates, or sonicated cell extracts of *Karenia* sp. (as *Gymnodinium* sp.), debilitating and lethal effects occurred. Within 30 min of exposure, the larvae shed the primary swimming cilia and their mantle margins gradually disintegrated; death occurred 7 to 24 h after exposure (Mackenzie *et al.*, 1996a). Gymnodimine was also a potent ichthyotoxin to a freshwater fish, the white cloud mountain minnow (= red fin), *Tanichthys albonubes*, at 250 to 500 ppb (pH 7) or 50 to 100 ppb (pH 8) (Seki *et al.*, 1996). When *T. albonubes* were exposed to 2 m*M* gymnodimine, the toxin targeted and damaged both the gill lamellar epithelial cells and the chloride cells. The severity of lesions was not calcium dependent (Terao *et al.*, 1996). Gymnodimine showed no hemolytic activity or cytotoxicity (Seki *et al.*, 1996). It is not yet clear what the mechanism of gymnodimine toxicity is nor what impact the toxin has under natural conditions.

From September to October 1999, wide-scale mortalities of cultured fish, principally sobiaty (*Acanthopagrus cuvieri*) and wild largescale mullet (*Liza macrolepis*), were reported in Kuwait Bay, Arabian Sea. The mortalities coincided with a bloom of the dinoflagellate *Karenia* sp. (A. Haywood and K. Steidinger, personal communications) (as *Gymnodinium* sp.) (Heil *et al.*, 2001) present at maximum concentrations of $> 6.0 \times 10^3$ cells/ml. This *Karenia* sp. is the same species as the *Karenia* sp. known to produce gymnodimine in New Zealand (A. Haywood, personal communications). Although the Kuwait strain has not yet been tested for toxicity it is quite likely that gymnodimine was associated with the fish kills.

F. OKADAIC ACID AND DERIVATIVES (DINOPHYSISTOXINS)

Diarrheic (diarrhetic) shellfish poisoning (DSP) in humans (Yasumoto *et al.*, 1978, 1979b) results from the consumption of toxic shellfish containing okadaic acid (OA)

and the OA derivatives dinophysistoxins (DTX1-4) (Aune and Yndestad, 1993). Together these toxins can be referred to as DST (diarrheic shellfish toxins). DTX and OA are the major toxins produced by the planktonic dinoflagellates *Dinophysis* spp. and the epibenthic dinoflagellate *Prorocentrum lima* (Table 1). *Dinophysis* spp. are typically temperate in distribution, and *P. lima* is cosmopolitan. DSP cases usually occur in temperate climates (Aune and Yndestad, 1993). OA and DTX are also produced by a few benthic *Prorocentrum* species found in tropical regions (Table 1), but these species are not known to be involved in DSP. Some of the benthic OA-producing *Prorocentrum* are suspected in incidences of ciguatera (Table 1) (see section on ciguatoxins) or as possibly promoting tumor development (see below).

In the short term, when humans consume DST, they can experience gastrointestinal distress, diarrhea, nausea, and vomiting (Aune and Yndestad, 1993; Quilliam and Wright, 1995). Monitoring programs strive to minimize DST exposure to protect public health and have developed action plans to estimate exposure levels in shellfish either by monitoring counts of *Dinophysis* spp. or *P. lima* cells in the water, by determining DST levels in the meats, or both (Shumway *et al.*, 1995). When mice were experimentally exposed to OA, DTX-1, and DTX-3 either orally or by i.p. administration, short-term effects on the digestive tract were similar (Terao *et al.*, 1993). OA induces rapid changes in the small and large intestine of the rat, resulting in hypersecretion, selective shedding of the enterocytes at the top of the villi, and accumulation of goblet cells (Edebo *et al.*, 1988a; Lange *et al.*, 1990). DTX-1 causes excessive fluid accumulation in the intestines of suckling mice (Hamano *et al.*, 1985). Within 15 min of exposure to the toxin, marked destruction of the absorptive epithelium of the ileum villi accompanied by severe diarrhea occurred. Potent effects of DTX-3 in the liver led to degeneration of the hepatocytes within 24 h (Terao *et al.*, 1990, 1993).

Okadaic acid inhibits protein phosphatases types 1 and 2A, thus increasing protein phosphorylation that (1) affects intracellular processes, including metabolism, membrane transport and secretion, contractility, gene transcription, maintenance of cytoskeletal structure, receptor-mediated signal transduction, and cellular division; (2) stimulates the expression of certain proto-oncogenes; (3) activates H1 kinase *in vitro*; and (4) induces various mitosis-specific events (Bialojan and Takai, 1988; Fujiki *et al.*, 1989; Haystead *et al.*, 1989; Herschmann *et al.*, 1989; Yamashita *et al.*, 1990; Sakai and Fujiki, 1991; Fujiki and Suganuma, 1993; Rossini, 2000). OA probably causes diarrhea by stimulating the phosphorylation of proteins that control sodium secretion by intestinal cells or by enhancing phosphorylation of cytoskeletal or junctional elements that regulate permeability to solutes, thereby resulting in passive loss of fluids (Aune and Yndestad, 1993).

There are few reports implicating DST in animal mortalities or as having sublethal effects. Although numerous studies have been made on the potential threats of DSP to human health through shellfish consumption, the potential effect of DST on molluscs has not been well investigated. DST have been found in numerous species of bivalves (Shumway, 1990). In separate DSP outbreaks in Europe, Japan, and North America, the principal toxins have been either OA, DTX-1, or DTX-3. Dominant toxins in the shellfish will vary depending on the species of microalga to which the molluscs are exposed and the toxins each microalga produces. For example, in Japan, *Dinophysis fortii* is the primary source of DTX-1, whereas in Europe *D. acuta* and *D. acuminata* produce mainly OA. When bivalves

feed on microalgae containing OA or DTX, the toxins are accumulated mainly in the hepatopancreas (Edebo *et al.*, 1988b; Alvito *et al.*, 1990; Aune and Yndestad, 1993), but only a few studies have investigated their potential effects on aquatic organisms.

As with PSP, different bivalve species accumulate varying concentrations of DST (Alvito *et al.*, 1990; Suzuki and Mitsuya, 2001), can be seasonally toxic (Sato *et al.*, 1996), and may remain toxic for different periods of time. Blue mussels, *Mytilus edulis*, in Swedish waters remained toxic for up to 5 months after toxin accumulation (Shumway, 1990). Although high concentrations of OA are found in Swedish mussel populations for several months every year, the toxins are not associated with any known health effects. When blue mussels were exposed to high concentrations of *Prorocentrum lima*, filtration rates decreased after 1 h, most likely because of the toxicity associated with inhibitory or cytotoxic effects (Pillet and Houvenaghel, 1995). Blue mussels that were experimentally exposed to *P. lima* accumulated OA and DTX1 in the hepatopancreas. A slow buildup of toxin, from 1.2 to 2.0 μg/g wet weight occurred in the hepatopancreas by day 14, with a peak of 3.8 μg/g on day 16. Further accumulation was not documented, and no mortality was associated with exposure (Pillet *et al.*, 1995). Blue mussels appear to have some protective mechanism whereby the activity of certain enzymes, such as glycogen synthase, are not affected by OA (Svensson and Förlin, 1998). Mussels can also have rapid clearance mechanisms; in one report, concentrations of OA declined from 7.2 to 1.8 μg OA/g hepatopancreas within 1 week (Edebo *et al.*, 1988b). When bay scallops, *Argopecten irradians*, were exposed to *Prorocentrum lima* (8×10^1 cells/ml for 2 days) total DSP toxin concentrations (including OA, DTX-1 and okadaic acid diolester) were approximately 1 μg/g in visceral and gonadal tissues and less than 0.1 μg/g in the gills, mantle, and adductor muscle. There were no observed detrimental physiological effects or mortalities during the exposure period of 13 days (Bauder *et al.*, 2001).

Toxins are also modified by bivalves. After experimental exposures to *Dinophysis fortii*, Japanese scallops *Patinopecten yessoensis* transformed DTX-1 into DTX-3 (Suzuki *et al.*, 1999).

There is little information regarding the distribution of OA in fish. In tropical reef systems, where OA is produced by benthic dinoflagellates such as *Prorocentrum lima* and *P. concavum*, there is a strong likelihood that fish are exposed to these toxins through the diet (see ciguatera). Few studies have investigated the presence of DST in fish, unless the studies were conducted in combination with ciguatoxin assays. There has been one report of OA in a carnivorous fish, the barracuda *Sphyraena barracuda*, but this has not been confirmed since its original isolation by Gamboa *et al.* (1992).

As with other aquatic groups, there is little information on the potential effects of DST on zooplankton. A potentially lethal effect of OA on zooplankton has been extrapolated from experimental *Artemia franciscana* bioassays using *Prorocentrum lima* cultures. Demaret *et al.* (1995) found that more than 50% of 1-day-old *Artemia* larvae died after they were exposed to 5.0×10^1 to 1×10^4 cells/ml. Adult *Artemia* were also rapidly affected, with 77% mortality in 5 h. *Prorocentrum lima* cells also rapidly killed *Artemia* nauplii and metanauplii. Therefore, Demaret *et al.* (1995) concluded that DSP toxins were potentially highly toxic to zooplankton.

In the summer of 1993 and lasting into 1994, a large bloom of *Dinophysis caudata*, with maximum cell concentrations of 1.5×10^3 cells/ml was reported in Tuticorin Bay, on the east coast of India. Except for a few species of tintinnids, there

was a total absence of zooplankton as well as a general decline in the number of diatoms and fish during the bloom (Santhanam and Srinivasan, 1996). A similar situation was also recorded during a bloom of *D. acuminata* in the Galician Rias Bajas in northwestern Spain. Maneiro *et al.* (2000) determined that several zooplankton species could ingest and transfer toxins through the pelagic food web. Grazing experiments indicated that some copepods (*Temora longicornis* and *Oithona nana*) and the tintinnid *Favella serrata* fed on *Dinophysis* spp., whereas other copepods (*Acartia clausi* and *Euterpina acutifrons*) did not. During the bloom, populations of tintinnids noticeably increased, whereas densities of *T. longicornis* and *O. nana* declined dramatically. Okadaic acid content found in seston size fractions 100 to 200, 200 to 300, and 300 to 1000 μm showed a close correlation with *F. serrata*. The results suggest that tintinnids can play a significant role in the transfer of okadaic acid toxins to higher trophic levels in the food web (Maneiro *et al.*, 2000).

In addition to the involvement of OA in acute human shellfish poisoning events, there is an increasing awareness of the potential role of OA and OA derivatives as tumor promoters. In two-stage carcinogenesis experiments, OA has been shown to induce skin papillomas and carcinomas in mice and adenomatous hyperplasia and adenocarcinomas in the glandular stomach of rats (Fujiki *et al.*, 1989; Suganuma *et al.*, 1990; Sakai and Fujiki, 1991; Fujiki and Suganuma, 1993). DTX has also been to shown to induce tumors in mice (Fujiki *et al.*, 1988). An epidemiological study of digestive-tract cancer mortality in relation to the distribution of DSP was recently conducted in France, and although there appeared to be a very tentative positive association between the two, Cordier *et al.* (2000) recognized the need for more extensive surveys and in-depth research before any link can be definitively proven. The potential role of microalgal toxins in tumor development in marine animals has also been discussed recently (Landsberg, 1995, 1996; Landsberg *et al.*, 1999). Fibropapillomatosis (FP) in green turtles is a debilitating neoplastic disease that has reached epizootic levels worldwide. The etiology of FP is unknown, but FP has been linked to oncogenic viruses (Herbst, 1994). Toxic benthic dinoflagellates (*Prorocentrum* spp.) are not typically considered tumorigenic agents, but they have a worldwide distribution and produce tumor-promoting OA (Fujiki and Suganuma, 1993). Benthic *Prorocentrum* spp. are epiphytic on the macroalgae and seagrasses that are normal components of green turtle diets. In the Hawaiian Islands, green turtles consume *Prorocentrum*, and high-risk FP areas are linked to areas where *P. lima* and *P. concavum* are both widespread and abundant. The presence of OA in the tissues of Hawaiian green turtles indicates exposure and that this tumor-promoter may have a potential role in the etiology of FP (Landsberg *et al.*, 1999).

G. PECTENOTOXINS

For many years, researchers have been aware of the presence of pectenotoxins (PTX) in toxic shellfish poisoning events, and PTX were implicated in some cases of DSP (Yasumoto *et al.*, 1985; Murata *et al.*, 1982, 1986). The bioorigin of pectenotoxins has just recently been confirmed to be *Dinophysis* species (Table 1). Because both PTX and DTX have often co-occurred in shellfish, the potential specific impacts of PTX on the health of these organisms has not been clearly defined. PTX1-7 and PTX-10 have been isolated from shellfish and at least 10 PTXs have been chemically

defined thus far (Draisci *et al.*, 2000). PTX-2 is converted into PTX-1, PTX-3, PTX-6, PTX-2 seco acid (PTX-2SA) and other derivatives by shellfish, such as scallops, greenshell mussels, *Perna canaliculus*, and Mediterranean mussels, *Mytilus galloprovincialis* (Draisci *et al.*, 2000; Suzuki *et al.*, 2001).

H. CIGUATOXINS

Ciguatera is a type of human food poisoning caused by the consumption of tropical fish that are contaminated with ciguatoxins (P-CTX or C-CTX) (Pacific or Caribbean origin respectively) (Lewis and Holmes, 1993; Swift and Swift, 1993; Lewis *et al.*, 2000). There are a suite of ciguatera toxins that originate from the benthic dinoflagellate *Gambierdiscus toxicus* (Table 1), which inhabits reefs and hard grounds in subtropical and tropical regions (Anderson and Lobel, 1987). Ciguatoxin precursors and maitotoxin (MTX) originating from *G. toxicus* (Table 1) pass up the food chain when herbivorous fish browse on substrates or on primary consumers that have been exposed to *Gambierdiscus* cells or toxins. When toxic herbivorous fish are consumed by carnivorous fish such as barracuda or grouper and the ciguatoxins are bioaccumulated in their muscles, they pose a risk to human consumers (Lewis and Holmes, 1993; Swift and Swift, 1993). Although ciguatoxin per se (P-CTX-1) has not been isolated from wild or experimental cultures of *G. toxicus* (Holmes *et al.*, 1991), other ciguatoxins (P-CTX-3C, P-CTX-4A, and P-CTX-4B) (Satake *et al.*, 1993a, 1993c; Yasumoto *et al.*, 1993b; Lewis *et al.*, 2000), maitotoxin (MTX1-3), gambierols, and gambieric acids (Table 1) have been detected in certain strains (Holmes *et al.*, 1991). CTX-4A (scaritoxin) has been confirmed recently in both *G. toxicus* and the heavybeak parrotfish, *Chlorurus gibbus* (as *Scarus gibbus*), further supporting a food-chain link (Satake *et al.*, 1997c). At least two types of maitotoxin (MTX-1 and MTX-2) have been isolated from Australian *G. toxicus* (Holmes *et al.*, 1990), and additional water-soluble toxins have been isolated from Caribbean strains (Miller and Tindall, 1988). *Gambierdiscus toxicus* strains from the same areas can produce precursors of varying toxicities in experimental bioassays (Bomber *et al.*, 1989; Holmes *et al.*, 1991).

Although several other *Gambierdiscus* species have been described recently (Faust, 1995; Holmes, 1998; Chinain *et al.*, 1999); some of which have been demonstrated to produce cigua-like toxins (Table 1), it is unclear at this stage what role they may have in ciguatera. Also known to be part of the tropical benthic dinoflagellate community (Tindall and Morton, 1998) and often implicated in ciguatera are *Ostreopsis*, *Coolia*, and *Prorocentrum* species, each of which produce their own unique toxins and toxin derivatives (Table 1). CTX has not been isolated from any other species of benthic dinoflagellate except for *G. toxicus* (Table 1), and thus far *Gambierdiscus* is the only genus that has been definitely implicated as an origin of ciguatera (Lewis and Holmes, 1993). Benthic *Prorocentrum* species are common in tropical communities; those producing okadaic acid were discussed previously (see okadaic acid). In addition to OA and its derivatives, *Prorocentrum* spp. have also been shown to produce the fast-acting toxins prorocentrolide, which is lethal to mice in experimental assays (Torigoe *et al.*, 1988; Hu *et al.*, 1996) and hoffmanniolide (Table 1), but it is currently unclear how these toxins may affect animal health in the wild. Although additional benthic *Prorocentrum* species have

been described recently, these have not all been tested for toxicity (Faust, 1990, 1993a, 1993b, 1994). Recently, *Prorocentrum borbonicum* was shown to produce borbotoxins that block postsynaptic nicotinic acetylcholinesterase receptors (Ten-Hage *et al.*, 2002). *Coolia monotis* produces toxins that are lethal to mice (Tindall *et al.*, 1984; Holmes *et al.*, 1995), *Artemia*, and molluscan larvae (Rhodes and Thomas, 1997), but there is no indication that this species is involved in ciguatera (Holmes *et al.*, 1995). Some *Ostreopsis*, such as *O. lenticularis*, are also suspected in ciguatera cases in the Caribbean (Tosteson *et al.*, 1998), are toxic to mice (Tindall *et al.*, 1990), and have been demonstrated to have neurotoxic effects on chick embryo neurons (Rivera Rentas *et al.*, 1995). Two neuroactive compounds isolated from *O. lenticularis* were demonstrated to interact with nicotinic cholinergic receptors (Type-I extracts) and voltage-dependent sodium channels (Type-II extracts) (Mercado *et al.*, 1995). Several *Ostreopsis* species produce hemolysins, ostreotoxins, ostreocin, and other uncharacterized toxins (Table 1). Recently, ostreocin D isolated from *O. siamensis* was characterized as a palytoxin analog, which implicates *Ostreopsis* species as a likely biogenetic origin for palytoxin (one of the most lethal marine toxins known) (Usami *et al.*, 1995; Ukena *et al.*, 2001). Palytoxin or its analogs were recently implicated in a fatal human poisoning caused by the consumption of toxic sardines, *Herklotsichthys quadrimaculatus*, in Madagascar (Yasumoto, 1998). Consequently, palytoxin has been inferred to be the possible toxin source in clupeotoxism, a fatal human intoxication caused by ingestion of clupeoid fish (Onuma *et al.*, 1999). Palytoxin is also a potent tumor promoter (Fujiki *et al.*, 1984b), and so the potential role of *Ostreopsis* spp. as tumor promoters in aquatic systems should also be considered. Other *Coolia* and *Ostreopsis* species have been described (Faust, 1995, 1999; Faust and Morton, 1995), but have not been tested for toxicity. Currently, the potential harmful effects of *Coolia* and *Ostreopsis* species on aquatic organisms are unknown. Although it is not currently considered that *Prorocentrum*, *Ostreopsis*, and *Coolia* are necessarily involved in ciguatera, there is a potential for their toxins to reach human consumers via toxic fish. Because tropical benthic dinoflagellate communities include numerous toxic genera, reef-dwelling organisms have the potential to be exposed to numerous toxins. Most of the benthic dinoflagellates inhabit a variety of substrates, such as corals, macroalgae, and sand (Carlson and Tindall, 1985; Anderson and Lobel, 1987), and are inadvertently consumed by benthic browsers such as herbivorous fish. Therefore, the combinations of toxins that are potentially available to higher trophic levels are considerable.

Because top-level carnivorous fish may have consumed a variety of herbivorous fish species during the course of their lifetime, the CTX complex toxins that have been biotransformed, bioaccumulated, and deposited in the muscle of the fish may be present in different proportions and combinations. The presence of different families of ciguatoxins in ciguateric fish from the Caribbean Sea and the Pacific Ocean probably underlies the clinical differences in the ciguatera syndrome as reported in the two regions (Vernoux and Lewis, 1997). Because the ciguatoxin complex comprises multiple toxic components in fish, their effects on humans can be varied (>175 symptoms have been identified [Swift and Swift, 1993]), even though only a few of the toxins have been identified or characterized from toxic fish. Human consumption of toxic herbivorous fish is usually associated with gastrointestinal illness or neurological symptoms, whereas consumption of toxic carnivorous fish is

more often associated with cardiovascular and neurological disorders (Bagnis, 1968). Symptoms include paresthesia, arthalgia, myalgia, diarrhea, asthenia, chills and headache, nausea, pruritus, abdominal pain, vomiting, perspiration, tearing, and giddiness (Swift and Swift, 1993). In fatal cases, there are no remarkable gross or histological changes (Tonge *et al.*, 1967; Bagnis *et al.*, 1979). When mice are injected with lethal doses of acetone-extracted or methanol-extracted ciguatoxins, ciguatera symptoms observed are loss of activity, diarrhea, gasping, penile cyanosis and/or transitory and incomplete erection, ataxia, and very labored choking-gasping breathing. Respiratory failure is the cause of death because the heart is still beating after respiratory arrest (Vernoux *et al.*, 1985). Ciguatoxins are potent activators of voltage-dependent sodium channels in a variety of tissues, especially nerves. Activation results from binding of the ciguatoxins to site 5 on the sodium channel (see Lewis and Holmes, 1993), a site also attacked by the brevetoxins (Baden, 1989). There is a wealth of information on the history, epidemiology, pharmacology, pathology, and toxicology of ciguatera and ciguatera-associated benthic dinoflagellates (see Withers, 1988; Bomber and Aikman, 1989; Miller, 1991; Lewis and Holmes, 1993; Swift and Swift, 1993; Lewis *et al.*, 2000; Terao, 2000), and except for references pertinent to potential harmful effects on aquatic organisms, ciguatera will not be discussed further.

For many years, it was generally assumed that ciguatera toxins were sublethal or lethal to the humans at the top of the food chain because they are exposed to high doses of bioaccumulated toxin and organisms at lower trophic levels were unlikely to be affected by lower concentrations of toxin. Randall (1958) proposed a hypothesis to link ciguatera transfer via the food chain. Three corollaries were established to support the hypothesis: (1) fish acquire CTX via their diet, (2) consumption of toxin has no effect on fish, and (3) CTX is stored within the bodies of fish in an unaltered state (Helfrich and Banner, 1963). For the most part, the second assumption has been accepted, although even now the potential effects of ciguatera toxins (other than CTX) from benthic dinoflagellates on fish have been investigated minimally. Ciguatera toxins have been reported to have no effect on fish in the wild (Banner *et al.*, 1966; Swift and Swift, 1993). Earlier studies (Helfrich and Banner, 1963; Banner *et al.*, 1966) suggested that there was no effect because when herbivorous surgeonfish, *Acanthurus xanthopterus*, were fed toxic red snapper, *Lutjanus bohar*, no overt pathology was detected. It was assumed that herbivorous fish would remain behaviorally asymptomatic and would carry the toxin without any adverse effects (Helfrich and Banner, 1963). However, the method of toxin administration, that is, carnivory by a herbivore, would not be a normal mechanism of toxin exposure in the wild. Guppies exposed to purified MTX and CTX (from wild *G. toxicus*) in the water with a dose of 17 MU per ml died within two hours (MTX) and 60 to 70 minutes (CTX) (Bagnis *et al.*, 1980). The relevancy of these earlier tests to field conditions was questioned by Capra *et al.* (1988), who suggested that a dietary exposure route would be more appropriate.

Recent experiments have shown that CTX can be lethal to fish when administered orally, by intraperitoneal injection, or when dissolved in aquarium water in which fish were swimming (Davin *et al.*, 1986, 1988; Capra *et al.*, 1988; Lewis, 1992). In fish bioassays with mosquitofish, *Gambusia affinis*, pure CTX-1, CTX-2, or PbTx-2 added to water induced similar signs, including pronounced opercular movement (suggestive of respiratory distress), inactivity, darkening of the skin, bursts of

uncoordinated swimming activity when disturbed, and loss of righting reflex preceding death. The estimated LD_{50} (48 h) to mosquitofish for CTX-1, CTX-2, and PbTx-2 were 0.5, 2.1, and 10 n*M*/l, respectively, indicating that in this assay the ciguatoxins were up to 20-fold more potent than the brevetoxins were (Lewis, 1992). In experiments, pathological changes took place in the livers of carnivorous fish that ingested *Gambierdiscus toxicus* (Capra *et al.*, 1988; Gonzalez *et al.*, 1994), but carnivores would not necessarily be expected to have direct contact with benthic dinoflagellates. Behavioral changes have been observed in crustaceans, herbivorous, or carnivorous fish after these organisms were allowed to feed either on ciguatoxic flesh or directly on *G. toxicus* cells or were exposed to lethal doses of CTX dissolved in aquarium water. Fish behaved abnormally, exhibiting erratic movement, disorientation, inactivity, and loss of equilibrium as well as experiencing physiological distress such as blanching or darkening of the skin and loss of appetite (Davin *et al.*, 1986, 1988; Kohler *et al.*, 1989; Kelly *et al.*, 1992; Lewis, 1992; Magnelia *et al.*, 1992; Durand-Clement *et al.*, 1987, cited in Gonzalez *et al.*, 1994; Goodlett *et al.*, 1994). Sublethal doses of CTX-1 or CTX-2 induced signs of respiratory distress and a loss of righting reflex in mosquitofish, *Gambusia affinis*, that persisted for the 5-day duration of the experiment (Lewis, 1992). Tilapia juveniles fed four different strains of *Gambierdiscus toxicus* showed responses ranging from death within 24 h (LD_{50}s between 16 and 30 *G. toxicus* cells) to abnormal swimming behavior, quiescence, loss of equilibrium, and loss of appetite. Fish showing minimal intoxication recovered 21 days after the one-time dose was administered (Kelly *et al.*, 1992). Pathological changes in fish fed *G. toxicus* were not studied (Durand-Clement *et al.*, 1987, cited in Gonzalez *et al.*, 1994). In addition to behavioral effects, CTX increases the efflux rate of Na^+ and produces other electrophysiological changes in fish nerves (Capra *et al.*, 1987; Flowers *et al.*, 1987). This effect appears to be similar to the CTX effect on mammalian tissues (Capra and Cameron, 1985). When ciguatoxins were microinjected into the egg yolk of Japanese rice fish (*Oryzias latipes*) embryos, those exposed to 0.1 to 0.9 pg/egg (ppb) had cardiovascular, muscular, and skeletal abnormalities, and those injected with 1 to 9 pg/egg (ppb) had reduced hatching success. Edmunds *et al.* (1999) suggested that the sensitivity of embryonic fish to CTX via direct oocyte exposure may indicate that maternal transfer of low levels of ciguatoxin is an unrecognized threat to the reproductive success of reef fish.

The specific effects of each of the toxic components originating in benthic dinoflagellate species are not well characterized. Because multiple toxins are produced by tropical benthic dinoflagellate species (Table 1) and because these are transformed through the food chain, fish may be exposed to a variety of toxins in various combinations. Ciguatoxins can be transformed at each trophic level, and the suite of toxins referred to as ciguatoxins thus may be somewhat modified from their original structure in *Gambierdiscus*. Of all the toxins known to be produced by *G. toxicus* (Table 1), only CTX and CTX analogs have been identified repeatedly in carnivorous fish (Murata *et al.*, 1990; Legrand *et al.*, 1992; Yasumoto *et al.*, 1993b; Satake *et al.*, 1997c). Recently, a new toxic component, C-CTX-1, was isolated from horse-eye jack, *Caranx latus* (Marquais *et al.*, 1998). Scaritoxin (SCTX = CTX4A), MTX, and CTX analogs have been isolated from herbivorous fish (Yasumoto *et al.*, 1976; Chungue *et al.*, 1977; Satake *et al.*, 1997c; 1998a). Because it is water soluble, MTX is not found concentrated in carnivorous fish muscle (Endean *et al.*, 1993) and

apparently has no direct role in ciguatera (Holmes *et al.*, 1991). However, MTX is one of the most lethal nonproteinaceous toxins known (Yokoyama *et al.*, 1988), and fish are routinely exposed to this toxin.

At least 400 fish species have been implicated in ciguatera (Halstead, 1967). Aspects of the mechanisms of toxin transfer, of modification of the precursors to CTXs through the food chain, and of accumulation of toxin in carnivorous fishes are still unclear. The fate and deposition of the various ciguatoxin derivatives in fish tissues is not well defined. How the toxins are accumulated, sequestered, excreted, or chemically biotransformed by fish is currently unknown. Knowledge of the chemical structure of the ciguatera toxins is incomplete, and many of the toxins are present in only very low concentrations in fish tissue (Anderson and Lobel, 1987), which makes purification and identification of these toxins difficult and expensive. Also, in many cases only CTX is tested for in tissues. In acanthurids that had consumed heavy concentrations of *G. toxicus*, which resulted in dramatic behavioral changes that indicated a toxic effect, CTX could not be detected in muscle or liver tissues (Magnelia *et al.*, 1992). Abnormal neurological behavior was reported in herbivorous fish that were exposed to a *G. toxicus* bloom in a coral reef microcosm, but CTXs were not detected in the muscle tissue (Goodlett *et al.*, 1994). One study demonstrated that CTX was present in all tissues (liver, ovary, skin, muscle, gills, bones, and viscera [other than liver and ovary]) of the jacks *Caranx latus* and *C. bartholomaei* and the yellowtail *Seriola dumerili*. The highest concentration of toxin was 14 MU per g/tissue in the liver of a 3.6-kg *C. latus* (Vernoux *et al.*, 1985). Up to 1000 MU per g/tissue in the liver of a parrotfish has been reported (Yasumoto *et al.*, 1977). Fish can retain CTX for long periods of time — ciguatoxic fish maintained in nontoxic water and fed a nontoxic diet maintained toxicity for up to 30 months (Banner *et al.*, 1966). By definition, ciguateric fish can accumulate sufficiently high levels of CTX (estimated at > 0.1 n*M* CTX-1/kg fish) to cause human intoxication (Lewis, 1992). Selected reports of the levels of CTX extracted from the flesh of highly toxic ciguateric fish (see references in Lewis, 1992) indicate that CTX (assuming all toxicity stems from CTX-1) can be present at levels of up to at least 1.3 n*M*/kg in the giant moray eel, *Gymnothorax javanicus* (as *Lycodontis javanicus*); 1.9 n*M*/kg in the chinaman fish, *Symphorus nematophorus* (as *Glabrilutjanus nematophorus*); 1.5 n*M*/kg in the heavybeak parrotfish, *Chlorurus gibbus* (as *Scarus gibbus*); 1.5 n*M*/kg in the narrow-barred Spanish mackerel, *Scomberomorus commersoni*; 1.0 n*M*/kg in the pickhandle barracuda, *Sphyraena jello*; and 3.1 n*M*/kg in the yellow-edged lyretail, *Variola louti*. These levels are lower than the level of CTX-1 shown to be lethal to mosquitofish (4.7 n*M* CTX-1/kg) (Lewis, 1992). Because CTX can be highly toxic and lethal to fish, Lewis (1992) suggested that there may be an upper limit to the CTX levels fish can have before the toxins kill them, and that this factor may contribute to the low incidence of human fatalities associated with ciguatera. Given the generally infrequent occurrence of ciguateric fish and the fact that those found were no more than moderately toxic, it was not considered surprising that fish kills attributed to the ciguatoxins have not been reported (Lewis, 1992).

Thus far, there is minimal but compelling evidence that CTX can affect fish health and, under certain circumstances, may also be responsible for fish mortalities. There is little information regarding the effects of other ciguatera toxins on fish, although it has been demonstrated recently that MTX is lethal to fish (Terao *et al.*,

1996; Igarashi *et al.*, 1999). When the freshwater fish white cloud mountain minnow, *Tanichthys albonubes*, was exposed to water containing MTX (0.58 n*M*), chloride cells in the epithelium of the gills were affected after 10 to 30 min. Marked vacuolations appeared in the cytoplasm of the chloride cells, and the cell organelles were eventually destroyed. Blood cells in the capillaries of the gill lamellae showed marked apoptosis after 4 h exposure (Terao *et al.*, 1996). The mode of action of MTX is an increased influx of Ca^{2+} ions into the cells (Takahashi *et al.*, 1983), which can then lead to cell apoptosis (Terao *et al.*, 1996). In both hemolysis and ichthyotoxicity assays, MTX required Ca^{2+} to exert its activity. Ca^{2+} entry into the cells triggers a series of events that lead to hemolysis. Ca^{2+} entry into the cells activates calmodulin, which in turn promotes phospholipase A2 activity, which finally leads to the destruction of the cell membrane through the hydrolysis of membrane lipids (Igarashi *et al.*, 1999). The entry and subsequent accumulation of Ca^{2+} in mitochondria or intracellular vacuoles can result in a decrease in ATP and other nucleotides, eventually causing cytolysis and cell death (Hassan *et al.*, 1991). The severity of cellular damage in fish gills was proportional to increased concentrations of Ca^{2+} and a higher pH (Terao *et al.*, 1996). At a pH of 8.0 and a concentration of 2 m*M* Ca^{2+}, MTX was 2000 times more toxic than PbTx-3 (Igarashi *et al.*, 1999). Such experimental information needs to be extended to field situations in order to evaluate potential mechanisms by which fish may be affected by MTX.

Recently, Landsberg (1995) discussed the possibility that CTX or other benthic microalgal toxins could be involved in tropical reef fish kills. She postulated that a reef fish disease and mass mortality event was triggered by immunosuppression due to the consumption by fish of ciguatera-associated toxins (see also page 289). The species of fish implicated in the ciguatera food chain in Florida (de Sylva, 1994) were similar to those reef fish species that were affected during the 1980 and 1993 to 1994 mortalities in the same area. The behaviors and signs demonstrated by fish experimentally exposed to CTX (see above) were similar to those of diseased tropical fish during the 1993 to 1994 event. Pathological changes in diseased fish included fluid accumulation and sloughing and detachment of the intestinal epithelium down to the basal lamina (Landsberg, 1995). Capra *et al.* (1988) noted degeneration of the lamina propria, swelling of the villi tips, and an absence of the brush border in the intestine of barrier reef chromis, *Chromis nitida*, exposed to CTX via intraperitoneal injection. These pathological changes in the intestines of reef fish may be likened to both the intestinal pathology and the diarrhetic symptoms in mice associated with exposure to either CTX (Coombe *et al.*, 1987) or DTX-1 (Terao *et al.*, 1990).

The potency or activity of lipid-soluble toxins, such as CTX, that accumulate in carnivorous fish, may be expected to differ from the potency or activity of water-soluble toxins, such as MTX and SCTX, that are concentrated in herbivorous fish. Although MTX is routinely excreted (Magnelia *et al.*, 1992), could high doses of MTX or particularly toxic *G. toxicus* strains be sufficient to cause pathological changes in the intestine before these toxins can be excreted from fish? If so, the fish could become more susceptible to disease. Theoretically, the range of responses of fish to different benthic dinoflagellate strains (presumably due to the effects of different toxic components of various potencies) could explain the difference between acute, toxic mortalities and the mortalities caused by chronic toxicity that leads to pathological effects and subsequent invasion by opportunistic pathogens (Landsberg, 1995) (see also page 289).

The potential effects of benthic dinoflagellate toxins on fish need to be critically evaluated through experimental and field studies. It may be that the methods currently used to test for known ciguateric toxins are not able to detect the broad spectrum of toxins that may affect or accumulate in fish or to evaluate the potential interactions of these toxins. The effect of CTX on the top predators of the food web, that is, humans, has been studied, but the potential effect on aquatic organisms needs to be examined.

I. YESSOTOXINS

Yessotoxin (YTX) and two analogs, 45-hydroxyyessotoxin (45-OHYTX) and 45,46,47-trinoryessotoxin (norYTX), were first isolated from Japanese scallops, *Patinopecten yessoensis*, in Mutsu Bay, Japan, where DSP incidents were frequent (Murata *et al.*, 1987; Satake *et al.*, 1996b; Yasumoto and Tazikawa, 1997). Because YTX occurred together with DTX-1 and DTX-3, it was tentatively included in the DSP family (Yasumoto and Satake, 1998). Although it has been reported from shellfish in Japan (Murata *et al.*, 1987), Norway (Lee *et al.*, 1988), Chile, New Zealand (Yasumoto and Tazikawa, 1997), and Italy (Ciminiello *et al.*, 1997; Draisci *et al.*, 1999), its biogenetic origin was discovered only recently. YTX, a disulfated polyether toxin, was isolated from the dinoflagellate *Gonyaulax grindleyi* (= *Protoceratium reticulatum*) (Table 1) (Satake *et al.*, 1997a; Draisci *et al.*, 1999). The biological effects of YTX are different from those of DTX and OA. YTX did not cause intestinal fluid accumulation in mice, whereas OA and DTX-1 (associated with DSP) did (Ogino *et al.*, 1997). When administered i.p., YTX shows a potent mouse lethality, but the toxicologic effects on human health are virtually unknown (Terao *et al.*, 1990; Satake *et al.*, 1997b). In *in vitro* studies with human lymphocytes, YTX appears to interact with calcium channels in a way similar to maitotoxin (de la Rosa *et al.*, 2001). Orally administered YTX was not lethal to mice at 1.0 mg/kg, and did not appear to cause hemolytic effects or to inhibit protein phosphatase 2A. None of the Japanese rice fish, *Oryzias latipes*, exposed to 0.5 and 1.0 ppm YTX died during a 24-h exposure, but three fish exposed to bisdesulphated YTX died after 6 h. Ichthyotoxicity due to YTX was not considered to be significant (Ogino *et al.*, 1997).

Other analogs of YTX — homoyessotoxin (homoYTX), 45-hydroxyhomoYTX, and carboxyhomoyessotoxin — were isolated recently from Mediterranean mussels, *Mytilus galloprovincialis*, in the Adriatic Sea (Satake *et al.*, 1997b; Ciminiello *et al.*, 1998, 2000; Tubaro *et al.*, 1998; Yasumoto and Satake, 1998), and 1-desulfoyessotoxin was isolated from mussels *M. edulis* in Norway (Daiguji *et al.*, 1998b). Mussel extracts contaminated by homoYTX induce neurological symptoms in mice similar to those provoked by YTX. No evidence of diarrheogenicity of homoYTX was obtained at the doses tested (Tubaro *et al.*, 1998). YTX and homoYTX were confirmed recently to be present in the dinoflagellate *Lingulodinium polyedrum* (= *Gonyaulax polyedra*) (Draisci *et al.*, 1999).

Both *Gonyaulax grindleyi* and *Lingulodinium polyedrum* have been implicated in marine animal mortalities (Table 2), but little is known about their possible toxic mechanisms and the potential role of YTX and its analogs on the health of aquatic organisms. One incident in 1966 suggests that under certain situations *G. grindleyi* can be lethal to marine fauna. During December 1966, in South Africa, a red tide

caused by *Gonyaulax grindleyi* extended through St. Helena Bay to about 50 miles north. Maximum cell counts were 5.0 to 6.7 × 10^3 cells/ml, and dissolved oxygen levels were above 5.0 ppm. There was no evidence of oxygen depletion associated with a decaying bloom. This bloom resulted in the death of thousands of white mussels, *Donax serra*, a large number of black mussels, *Chloromytilus meridionalis*, and numerous species of invertebrates (Table 2). Almost no fish species were involved, and only a few sucker fish, *Chorisochismus dentex*, were washed ashore. Dead mussels from the affected area had many *Gonyaulax* cells on the gills but no identifiable cells in the gut contents, although unidentified red-pigmented material was present. Toxicity tests carried out on both the white and black mussels revealed that they were highly toxic. That no cases of human shellfish poisoning occurred was attributed to the fact that mussels were not a popular source of food in the area and to warnings that were issued over the radio and in the press. Although at the time there was no information on toxin production by *G. grindleyi*, this species was considered highly suspect (Grindley and Sapeika, 1969; Grindley and Nel, 1970).

Both cells and cell-free filtrate of *G. grindleyi* suppressed feeding in *Calanus pacificus*. Copepods exposed to *G. grindleyi* for a prolonged period were starving. In addition to the high mortality rate and absence of egg production, copepods produced very few fecal pellets and became conspicuously lethargic after about 10 days. When Californian anchovy, *Engraulis mordax*, larvae were exposed to *G. grindleyi*, very low rates of feeding, growth, and survival were observed, rates that were lower than those in the control larvae that were in seawater without dinoflagellate food sources (Huntley *et al*., 1986; Sykes and Huntley, 1987). When these original studies were conducted, the production of YTX by *G. grindleyi* was unknown.

Blooms of *L. polyedrum* have been recorded along the southern California, USA, coast for many years (Sweeney, 1975), but rarely have mass mortalities have been noted. One of the earliest reports described the mortality of numerous marine species (Table 2) four days after the "red streak" had reached the shore (Torrey, 1902). No evidence was found to suggest that the California *L. polyedrum* blooms were toxic (Torrey, 1902; Sweeney, 1975), but organisms were not tested for toxins. Similar blooms have also been associated with marine mortalities of demersal organisms in the Adriatic Sea along the coast of Croatia (Table 2).

Although no direct evidence was available, Huntley (1989) hypothesized that the recruitment of northern anchovy in 1976, which was the worst year during 1962-1977, followed a large-scale *L. polyedrum* bloom in 1975. In 1975, *L. polyedrum* was the dominant food organism in the south California Bight, and Lasker (1981) concluded that its poor nutritional quality was primarily responsible for the poor year-class of 1976 (Huntley, 1989). Experimental studies confirmed that fish exposed to *L. polyedrum* showed no growth (Huntley, 1989). *Lingulodinium polyedrum* blooms in Los Angeles–Long Beach Harbor caused mechanical damage to the gills of mussels, *Mytilus* sp., that had settled on pilings. The gills became clogged, the mussels smothered, and the animals fell to the bottom and decayed (Oguri *et al*., 1975).

J. AZASPIRACID

In 1995, a shellfish poisoning event in the Netherlands was caused by the consumption of toxic mussels, *Mytilus edulis*, and resulted in gastrointestinal illness in eight

people. Symptoms included nausea, vomiting, severe diarrhea, and stomach cramps — all symptoms similar to DSP. The mussels had originated from Killary Harbor, Ireland (McMahon and Silke, 1996), where toxicity persisted in the shellfish for at least 8 months. The toxin was identified recently and characterized as azaspiracid (Satake *et al.*, 1998b, 1998c; Ofuji *et al.*, 1999a, 1999b; Draisci *et al.*, 2000; James *et al.*, 2000). In October 1997, a second shellfish poisoning event in Arranmore, along the northwest coast of Ireland, affected 12 people. Now recognized as a serious risk to human health the shellfish poisoning syndrome has been termed azaspiracid poisoning or AZP (Ofuji *et al.*, 1999a).

When mice were injected with acetone-extracted hepatopancreas from toxic mussels, the clinical symptoms in mice were clearly different from those caused by DSP. Mice experienced neurological symptoms, including respiratory distress, limb paralysis, and death within 20 min at higher doses. Unlike DSP, which only targets the digestive tract, pathological changes in mice included necrosis of the lamina propria in the small intestine, fat accumulation in the liver, and lymphocyte necrosis in the thymus, spleen, and Peyer's patches of the small intestine (Ito *et al.*, 1998a, 2000; Satake *et al.*, 1998a).

The bioorigin of azaspiracid is associated with *Protoperidinium crassipes* (Gribble, 2002). It is unclear at this stage what, if any, effects this toxin may have on the health of aquatic organisms.

K. HEMOLYSINS

Experimentally, the hemolytic properties of bioactive compounds are determined by their ability to lyse mammalian (or other animal) erythrocytes in *in vitro* tests (Yasumoto *et al.*, 1990). Most of the hemolysins produced by harmful microalgae are fatty acids (Table 12). Many species have a specific fatty acid profile, with the numerous fatty acids occurring in different proportions in each species, and not all of these fatty acids are necessarily hemolytic. Hemolytic fatty acids tend to be the longer-chain polyunsaturated fatty acids and lipids (such as octadecapentaenoic acid [C:18:5n3]), which appear to act by altering the membrane function of target aquatic species. Octadecapentaenoic acid is rarely encountered in algal species and is more potent than the fatty acids 20:5n3 or 22:6n3 (Arzul *et al.*, 1995a; Bodennec *et al.*, 1995). Therefore, hemolytic activity, depends on the production of high concentrations of specific fatty acids, and like toxins, their production may vary according to environmental conditions and genetic factors (Bodennec *et al.*, 1995). Several other species also produce toxins that are hemolytic, but the toxins' mode of action are different from the fatty acids. For example, MTX produced by *Gamberdiscus toxicus* causes lysis of cells due to the influx of calcium (see ciguatoxins).

Several species of microalgae produce hemolysins that can adversely affect aquatic organisms. Species reported to produce hemolysins include the dinoflagellates *Alexandrium catenella*, *A. monilatum*, *A. tamarense*, *Amphidinium carterae*, *A. operculatum*, *Cochlodinium polykrikoides*, *Gambierdiscus toxicus*, *Heterocapsa circularisquama*, *Karenia brevis*, *Karenia mikimotoi* (= *Gymnodinium mikimotoi* = *G. nagasakiense* = *Gyrodinium aureolum* in part), *Gymnodinium pulchellum*, *Gymnodinium aureolum* (= *Gyrodinium aureolum*), *Ostreopsis ovata*, and *O. siamensis*; the diatom *Nitzschia* sp.; the prymnesiophytes *Chrysochromulina*

TABLE 12. Hemolytic lipids reported from microalgae

Lipids	Species	Reference
C18:4n3	*Amphidinium carterae*	Yasumoto et al. (1990)
	Prymnesium parvum	Kozaki et al. (1982)
C18:5n3	*Karenia mikimotoi* (reported as *Gyrodinium aureolum*)	Yasumoto et al. (1990)
	K. mikimotoi	Parrish et al. (1998)
	Gymnodinium sp.	Parrish et al. (1998)
	Gymnodinium sp.	Arzul et al. (1995b)
	K. mikimotoi (reported as *Gymnodinium* cf. *nagasakiense*)	Arzul et al. (1995a)
	Chrysochromulina polylepis	Yasumoto et al. (1990)
	Prymnesium parvum	Kozaki et al. (1982)
C20:4n6	*K. mikimotoi* (reported as *Gymnodinium* cf. *nagasakiense*)	Arzul et al. (1995a)
C20:5n3	*Cochlodinium polykrikoides*	Lee (1996)
	K. mikimotoi (reported as *Gymnodinium* cf. *nagasakiense*)	Arzul et al. (1995a)
	Ostreopsis lenticularis	Carballeira et al. (1998)
C22:6n3	*C. polykrikoides*	Lee (1996)
	K. mikimotoi (reported as *Gymnodinium* cf. *nagasakiense*)	Arzul et al. (1995a)
	O. lenticularis	Carballeira et al. (1998)
MGDG	*K. mikimotoi* (reported as *Gyrodinium aureolum*)	Yasumoto et al. (1990)
	K. mikimotoi	Parrish et al. (1998)
	Gymnodinium sp.	Parrish et al. (1998)
	Chrysochromulina polylepis	Yasumoto et al. (1990)
	Microcystis aeruginosa	Bury et al. (1998a)
DGDG	*K. mikimotoi*	Parrish et al. (1998)
	Gymnodinium sp.	Parrish et al. (1998)
	M. aeruginosa	Bury et al. (1998a)
	Synechococcus sp.	Mitsui et al. (1987)
Glycolipid	*Alexandrium monilatum*	Bass et al. (1983)

polylepis and *Prymnesium parvum*; the raphidophyte *Chattonella marina*; and the cyanobacterium *Synechococcus* sp. (Table 1). Numerous fish kills associated with blooms of these hemolysin-producing species have been documented world-wide, and like other HAB species they appear to have been increasing in frequency in the last 30 years (Tables 2 to 7). In some cases where species produce multiple toxins, for example, *Karenia brevis* and *Gymnodinium pulchellum*, these toxins may have different actions — the major toxic derivatives are neurotoxic, whereas other components are hemolytic. Species producing multiple toxins that include hemolytic activity are discussed in other sections (see Table 1). The following section provides examples of the major species currently known to produce hemolysins.

1. Dinoflagellates

a. Alexandrium monilatum

Although most toxic *Alexandrium* species produce PST, *A. monilatum* has not been demonstrated to produce these toxins. *Alexandrium monilatum* has been associated with fish kills principally in the Gulf of Mexico and along the Atlantic coast of Florida (Table 2). Although recorded frequently 20 to 50 years ago in these areas, there have been few reports of *A. monilatum*-associated fish kills in the last few years (K. Steidinger, personal communication).

Whole cells and crude extracts of *A. monilatum* have been shown experimentally to be lethal to mice, rats, fish, and cockroaches (Gates and Wilson, 1960; Aldrich *et al.*, 1967; Clemons *et al.*, 1980a,b; Erker *et al.*, 1985). The extracts contained a water-soluble glycosidic substance that was not STX or GTX. The extract was administered i.p. to young adult mice, and it produced sedation, abdominal constriction, fecal clumping in the perianal area, ataxia, tremors, cyanosis, loss of reflexes, convulsions, and death. Gross and microscopic pathology included an acute active hyperemia of the viscera, multifocal areas of necrosis of the musculature of the intestinal wall and diaphragm, and the presence of cytoplasmic vacuoles in cells in the peripheral margins of the acinar portion of the pancreas (Erker *et al.*, 1985). Rats exposed to extracts from mussels contaminated by *A. monilatum* toxins showed increased disaccharidase activity in the intestine (Taboada *et al.*, 1995).

The hemolytic compound identified from this species was thought to be a nonaromatic glycolipid (Bass *et al.*, 1983), but the hemolysin has still not been characterized. When experimentally exposed to *A. monilatum* cells at 10^7 cells/ml, there were significant mortalities of eastern oysters, *Crassostrea virginica*, and hooked mussels, *Ischadium recurvum* (as *Brachidontes recurvus*). At lower concentrations, byssus production was inhibited in bent mussels, and oysters closed the shell valves. Crustaceans were resistant to the extracts' effects (Sievers, 1969). When striped mullet, *Mugil cephalus*, were exposed to *A. monilatum*, the fish first showed distress, then frenzied activity, loss of equilibrium, turning upside down or horizontally, and a final violent burst of activity just prior to death (Gates and Wilson 1960).

b. Amphidinium carterae and *A. operculatum*

Although *Amphidinium* spp. have been demonstrated to produce ichthyotoxic hemolysins (Table 1), reports of their effects in natural environments are rare. Because of their benthic habitat and the lack of human presence in remote reef areas, it is possible that many mortality events associated with these species are not reported until some time after the events have occurred. Additionally, because of their small size (< 20 μm) and the difficulties of obtaining samples of them, it will require a concerted effort to investigate the extent to which *Amphidinium* may be involved in unexplained fish kills.

Hemolytic activities of a fatty acid (C18:4n3), hemolysin-1, and hemolysin-2 of *A. carterae* were estimated to be 1.9, 0.8, and 0.24 SU/mg, respectively, where one SU (saponin unit) stands for the hemolytic potency of 1 mg of Merck's saponin (Yasumoto *et al.*, 1990). The minimum concentrations of C18:4n3 and hemolysin-1 required to kill killifish were 10 and 7 to 18 ppm, respectively (Watanabe, 1986, in Yasumoto *et al.*, 1990). Ichthyotoxicity of hemolysin-2 has not been tested. In fish killed by hemolysin-1, congestion in the gills occurred first, the opercula stayed open, the scales began to peel off, and death occurred in 24 to 50 min after vigorous convulsive movements (Yasumoto *et al.*, 1990).

An active compound isolated from *A. operculatum* (reported as *A. klebsii*) inhibited the growth of the fungus *Aspergillus niger* and was eight times more potent than amphotericin B (Nagai *et al.*, 1990). The compound hemolyzed mouse blood cells at 84 ng/ml, indicating that it was 120 times more potent than commerical saponin (Merck) (Nagai *et al.*, 1990). Seven bioactive compounds, amphidinols 2 to 8, were characterized recently from *A. klebsii* (Paul *et al.*, 1995, 1996, 1997).

Amphidinol 1 was originally reported to be an antifungal agent with hemolytic activity by Satake *et al.* (1991). Amphidinols are active against the fungus *A. niger* and the diatom *Nitzschia* sp. and cause hemolysis of human erythrocytes (Paul *et al.*, 1996, 1997). The mode of action of amphidinols mimics that of the antimycotic amphotericin B. The formation of a complex at the cell membrane results in channel formation, increased ionic exchange, and increased permeability of the cell membrane, which can lead to hemolysis (Paul *et al.*, 1996). Amphidinols bind to sterols in plasma membranes of target cells, ergosterol in fungi, and cholesterol in animal cells, thus disturbing the arrangement of the lipid bilayer structure by nullifying its barrier function and/or deactivating enzymes (such as Na^+/K^+ATPase) bound therein (Paul *et al.*, 1997). Amphidinols were detected in the culture medium of *A. operculatum*, and because of their potent antidiatom activity, it was suggested that they function as allelopathic compounds against other benthic microbes (Paul *et al.*, 1997).

c. Gymnodinium aureolum and *Karenia mikimotoi*

Species in the *Gymnodinium aureolum* Hansen in Hansen *et al.* (2000) (= *Gyrodinium aureolum* Hulburt) and *Karenia mikimotoi* Hansen and Moestrup in Daugbjerg *et al.* (2000) (=*Gymnodinium mikimotoi* Miyaki and Kominami ex Oda [= *G. nagasakiense* Takayama and Adachi]) complex have been variously confused or synonymized, so some taxa may have been reported under an incorrect name. Because of uncertain identifications, in addition to *G. aureolum* and *K. mikimotoi* some fish and invertebrate mortalities (Table 2) have been attributed to *Gyrodinium* cf. *aureolum, Gymnodinium* cf. *mikimotoi*, *G. nagasakiense*, *G.* cf. *nagasakiense*, or *Gymnodinium* type '65 (Iizuka and Irie, 1969; Partensky and Sournia, 1986; Partensky *et al.*, 1988; Takayama and Adachi 1984; Takayama and Matsuoka, 1991). Some researchers recognized that the European *Gymnodinium aureolum* had closer affinities with the Pacific *Karenia mikimotoi* than with the North American *G. aureolum* (Partensky, 1988; Partensky *et al.*, 1988; Nagasaki *et al.*, 1991; Blasco *et al.*, 1996; Gentien, 1998), whereas others treated the European *Gymnodinium aureolum* as conspecific with *Karenia mikimotoi* (Steidinger *et al.*, 1989; Taylor *et al.*, 1995; Daugbjerg *et al.*, 2000; Hansen *et al.*, 2000), suggesting that the species responsible for fish kills in northern Europe, Australasia, and Japan is *Karenia mikimotoi* (Taylor *et al.*, 1995). Reports of *Gymnodinium aureolum* in North America have indicated that this species is toxic to marine animals (Mahoney *et al.*, 1990; Smolowitz and Shumway, 1996) (Table 2).

At the current state of knowledge, the *Gymnodinium aureolum* described from North America as *Gyrodinium aureolum* (Hulburt, 1957), is morphologically and genetically different from the European *K. mikimotoi* (Taylor *et al.*, 1995; Hansen *et al.*, 2000) (described as *Gyrodinium aureolum*). To further confuse matters, a Danish strain of *Gymnodinium aureolum* identical to the North American strain has also been described (Hansen *et al.* 2000) and *K. mikimotoi* has also been reported in North America (K. Steidinger, personal communication). For the purposes of this discussion, species reported in the *G. aureolum*/*K. mikimotoi* complex to be harmful to marine animals will be referenced together and, unless otherwise stated, will be denoted in Table 2 by their original description. Following Hansen *et al.* (2000), the North American *G. aureolum* will be considered as a separate species from the

species previously referred to as the European *Gyrodinium aureolum* — and are referred to in the text as *K. mikimotoi*.

Since the mid-1960s, when blooms of *Karenia mikimotoi* in Japan (Iizuka and Irie, 1966) and in Norwegian waters (described as *Gyrodinium aureolum*) (Braarud and Heimdal, 1970) became problems, multispecies fish and invertebrate mortalities have been reported from Europe, Australasia, Japan, South America, and North Africa (Table 2). Significant economic losses to fish farms have occurred (Tangen, 1977; Dahl and Tangen, 1993; Honjo, 1994); for example, damage costs from a *Karenia mikimotoi* bloom in 1984 amounted to about 4.4 billion yen. Some human health effects, such as nausea, sore throat, eye irritation, and lung congestion, have been associated with *Gymnodinium aureolum* (Mahoney *et al.*, 1990).

Hemolysins associated with *Karenia mikimotoi* have been identified as exotoxins (Gentien and Arzul, 1990). The presence of a fat-soluble cytotoxin from cultures of *K. mikimotoi* (reported as *Gyrodinium* cf. *nagasakiense*) was demonstrated (Partensky *et al.*, 1989), but only in small quantities that were not considered to be high enough to be lethal. At the organism level, no ichthyotoxin was isolated and preliminary fish bioassays were negative (Tangen, 1977). There were suggestions (Partensky *et al.*, 1989) that fish and invertebrate mortalities were possibly due to other environmental stressors, such as depletion of dissolved oxygen (Helm *et al.*, 1974; Tangen,1977; Heinig *et al.*, 1992). However, field measurements of dissolved oxygen did not indicate this to be the case in southern Ireland (Ottway *et al.*, 1979) or in Scotland (Jones *et al.*, 1982).

A digalactosyl monoacylglycerol (MGDG) and a polyunsaturated fatty acid (PUFA) (octadecapentaenoic acid [C18:5n3]) isolated from *K. mikimotoi* (as *Gyrodinium aureolum*) were shown to be hemolytic (Table 12) and ichthyotoxic (Yasumoto *et al.*, 1990). The origin of both of these hemolysins could have been the more common type of glycolipid, a glycosyl diacylglycerol. Hydrolysis of this type of glycolipid would yield a free fatty acid and a glycosyl monoacylglycerol (Parrish *et al.*, 1998). When the percent lipid compositions of the two species and their hemolytic components were evaluated, *Karenia mikimotoi* contained 7.6% MGDG and 8.9% digalactosyl diacylglycerol (DGDG), and *Gymnodinium* sp. contained 14.2% MGDG and 20.8% DGDG (Parrish *et al.*, 1998). Although the fatty acid components of both the hemolytic MGDG and DGDG were proportionally different in each species, the dominant fatty acid was, as in *K. mikimotoi* (as *Gyrodinium aureolum*) (Yasumoto *et al.*, 1990), C18:5n3 (Parrish *et al.*, 1998). Hemolysis of red blood cells, growth inhibition of the diatom *Chaetoceros gracile*, and reduction of bioluminescence in *Photobacterium phosphoreum* was determined for several different PUFAs produced by *K. mikimotoi* (reported as *Gymnodinium* cf. *nagasakiense*), including C18:5n3 (Yasumoto *et al.*, 1990; Arzul *et al.*, 1995a). The fatty acid C18:5n3 made up 25.1% of the total fatty acids isolated from *K. mikimotoi*. The composition of additional fatty acids from *K. mikimotoi* (as *Gyrodinium aureolum*) that demonstrated hemolytic activity against mouse blood cells and inhibited growth of *Chaetoceros gracile* were C20:5n3, C20:4n6, and C22:6n3 (Arzul *et al.*, 1995a). The exact mode of action of PUFA in the inhibition of diatom growth is still unknown (Arzul *et al.*, 1995a). Takagi *et al.* (1984) classified PUFAs extracted from the toxic hepatopancreas of contaminated scallops according to their toxicity to mice (cited in Arzul *et al.*, 1995a). In October 1994, in the Gulf of Gabè, Tunisia, a *Gymnodinium* sp. (Arzul *et al.*, 1995b), which was also reported as *Gyrodinium aureolum* (Romdhane *et al.*,

1998), was demonstrated to produce C18:5n3 (Arzul *et al.*, 1995b). There is some indication that *K. mikimotoi* (reported as *Gymnodinium* cf. *nagasakiense*) also produces reactive oxygen species (ROS) (Gentien, 1998).

Effects on invertebrates, including plankton, have been documented both in the field (Table 2) and experimentally (Tables 1, 9 to 11) (Widdows *et al.*, 1979; Heinig and Campbell, 1992; Erard-Le Denn *et al.*, 1990; Nielsen and Strømgren, 1991; Dahl and Tangen, 1993; Lesser and Shumway, 1993; Hansen, 1995; Smolowitz and Shumway, 1996; Matsuyama *et al.*, 1998a, b). Several plankton species have also been shown to be adversely affected by *K. mikimotoi* (Tables 10 and 11), including the diatom *Chaetoceros gracile* (Arzul *et al.*, 1995a), whose growth was inhibited. Tintinnid ciliates, *Favella ehrenbergii*, were unable to sustain growth when exposed to high concentrations of *K. mikimotoi*, presumably because of exposure to toxic exudates. However, direct attempts to demonstrate toxic effects of exudates, using filtrates of dense cultures of *K. mikimotoi* failed. Hansen (1995) suggested that lack of toxic effects may have been due to the rapid turnover of the toxin. When *K. mikimotoi* (as *Gyrodinium aureolum*) accounted for about 90% of the total biomass, the growth rate of *F. ehrenbergii* was reduced by less than 25%. Lugworms, *Arenicola marina*, were not adversely affected by exposure to *G. aureolum*, whereas mortalities of Pacific oyster embryos and brine shrimp, *Artemia salina*, nauplii were documented (Helm *et al.*, 1974).

In September 1988, a large mortality event occurred in Maquoit Bay, Maine, USA, when an estimated 30 to 40% of softshell clams, blue mussels, and marine worms were exposed to a *Gymnodinium aureolum* bloom. An offshore bloom of *G. aureolum* was transported shoreward by southerly winds and tidal action. *Gymnodinium aureolum* cells were further concentrated to around 1.4×10^5 cells/ml by onshore winds and weaker-than-normal tidal flushing. The high number of mortalities may have been due to the exposure of the animals to low dissolved oxygen concentrations as well as to the mucus and toxin produced by *G. aureolum* (Heinig and Campbell, 1992).

Blue mussels exposed to *K. mikimotoi* (as *G. aureolum*?) cultures at concentrations of 9×10^3 cells/ml showed a significant reduction in growth rate (Nielsen and Strømgren, 1991), which was probably due to reduced clearance of cells (Widdows *et al.*, 1979). When bivalves were exposed to *G. aureolum* in laboratory tests, species-specific differences in pathological effects were documented. Pathological effects ranged from none (in Atlantic surfclams, *Spisula solidissima*; softshell clams, *Mya arenaria*; and northern quahogs *Mercenaria mercenaria*) to the development of mantle and gill lesions (in eastern oysters, *Crassostrea virginica*) to increased mortalities, decreased height of absorptive cells, and increased lumen diameter in the digestive gland (in bay scallops, *Argopecten irradians*) (Lesser and Shumway, 1993; Smolowitz and Shumway, 1996). When exposed to concentrations of 10^4 *Karenia mikimotoi* cells/ml, two species of abalone showed different responses: after 24 h, all *Haliotis discus* died, whereas *Sulculus diversicolor* were more resistant and demonstrated paralysis only. Avoidance behavior such as contraction of the tentacles and escape locomotion was also exhibited by *Haliotis discus*. Only after a 48-h exposure at concentrations of 10^5 cells/ml were mortalities of *S. diversicolor* noted (Matsuyama *et al.*, 1998a). When Mediterranean mussels, *Mytilus galloprovincialis*, were exposed to *K. mikimotoi* at densities exceeeding 5×10^2

cells/ml, clearance of cells was reduced noticeably. Mussels also retracted their mantle edges, showed intermittent shrinkage of their exhalent siphons, and were unable to completely close their valves during the 10-min experiment. Eighty-five percent mortalities (N = 20) were noted after 5 days' exposure to 1.3 to 2.5×10^5 cells/ml (Matsuyama *et al.*, 1998b). Wild great scallops, *Pecten maximus*, that survived a bloom of *Gyrodinium* cf. *aureolum* showed "stress rings" on the shells that could be used for dating growth inhibition periods. A bloom of up to 8×10^2 cells/ml caused mass mortalities of postlarval (0.25 to 3.0 mm) scallops and growth cessation in juveniles (5 to 30 mm) until the red tide vanished after 1 month. When postlarvae and juvenile scallops were experimentally exposed to *G.* cf. *aureolum* at densities of 5×10^2 to 1.5×10^3 cells/ml, filtration rates were affected and growth was inhibited (Erard-le-Denn *et al.*, 1990).

Young animals and larval stages of many fish and invertebrate species are also susceptible to the presence of *K. mikimotoi* (as *Gymnodinium aureolum*), and naturally occurring blooms may well influence their development and recruitment. After a bloom, declines in the number of individuals of numerous species and stages have been reported (Potts and Edwards, 1987). Fish usually respond to dense populations of *K. mikimotoi (as G. aureolum)* by avoidance (Dahl and Tangen, 1993). In fish farms, adverse effects were observed in salmon, rainbow trout, and cod when algal *K. mikimotoi* densities exceeded 1×10^3 cells/ml. Behavioral effects included reduced feeding and increased surface swimming; a pathological response was a mild sloughing of the gill epithelium (Dahl and Tangen, 1993). During a *K. mikimotoi* (as *G. aureolum*) bloom in a salmonid fish farm in Scotland, distressed fish came to the water's surface and circled around before turning over and sinking. Death appeared to take place within a few hours. At the time of the fish kill, water in the ponds was turbid and viscous, with considerable foaming on the surface (Jones *et al.*, 1982). Concentrations of *K. mikimotoi* (as *G. aureolum*) above 1×10^4 cells/ml may cause acute mortality due to severe sloughing in the primary and secondary gill lamellae and damage to the chloride cells. Damaged gills affect oxygen uptake, osmoregulation, and blood pH. Dahl and Tangen (1993) also suggested that chronic exposure (several weeks) of salmon to low to moderate concentrations of *K. mikimotoi* (as *G. aureolum*) (0.5 to 2×10^3 cells/ml) may cause liver necrosis. When experimentally exposed to up to 10.9×10^3 *K. mikimotoi* (as *G. aureolum*) cells/ml, fish immediately increased their rates of opercular movement. At low concentrations, fish were hyperactive and attempted to leap out of the container. In the highest concentration, the fish became inactive, turned dark in color, and were comatose or dead within 1 h. In all treatments, the fish secreted large quantities of mucus. Negative effects on the gills and digestive tract of salmonids were also associated with *K. mikimotoi* (as *G. aureolum*). Histopathological examination of the gills of moribund fish showed a severe and acute toxic necrosis, sloughing of the epithelial tissues, swelling and pyknosis of the primary lamellar epithelium, lamellar hypertophy, and congestion of the branchial vessels (Roberts *et al.*, 1983; Turner *et al.*, 1987); conditions similar to those observed in natural mortalities of Atlantic salmon, *Salmo salar* (Jones *et al.*, 1982). Pathological examination of affected salmon showed that death was likely to have resulted from asphyxiation and osmotic shock as a result of extensive cellular damage to the gills and intestine. Acidic extracts of gut or gut contents from salmonids killed during a *K. mikimotoi* (as *G. aureolum*) bloom were lethal to mice 24 h after injection, whereas animals injected with flesh extracts

remained healthy. Ether extracts of flesh, liver, and gut from affected fish resulted in sublethal effects on mice within minutes of injection. Mice showed signs of mild paralysis, loss of coordination, hyperactivity, and respiratory problems (Jones *et al.*, 1982).

In laboratory tests, sea bass, *Dicentrarchus labrax*, were exposed to octadecapentaenoic acid (C18:5n3) and other PUFAs produced by *K. mikimotoi* (as *Gymnodinium* cf. *mikimotoi*) (Fossat *et al.*, 1999; Sola *et al.*, 1999). Exposure to octadecapentaenoic acid resulted in inhibition of *in vitro* branchial or intestinal Mg-ATPase activity, but there was no demonstrable change in Na-ATPase or K-ATPase activity in the gills of fish during *in vivo* exposures. Postexposure examination of the fish gills determined that morphologically, there were less mucus and chloride cells, and a reduction in the amount of mucus produced. The presence of fatty acids did not inhibit the production of the enzymes Na-ATPase or K-ATPase in the chloride cells, so enzyme activities related to ionic transport were not influenced, but Sola *et al.* (1999) suggested that other observed morphological changes in the gills may be sufficient to induce gill pathologies and ultimate death in fish.

2. Prymnesiophytes

a. Chrysochromulina spp.

At least eight species of *Chrysochromulina* are currently known or suspected to be toxic (Table 1), but only a few species have been implicated in mortalities of aquatic organisms (Table 4). In early 1988, a *Chrysochromulina polylepis* bloom caused the first known toxic outbreak of a *Chrysochromulina* species to result in mortalities of thousands of fish (800 tons) and invertebrates in Norway (Dahl *et al.*, 1989; Underdal *et al.*, 1989; Lindahl and Dahl, 1990; Eikrem and Throndsen, 1993; Granéli *et al.*, 1993) (Table 4). Economic losses to fish farms were estimated at $4.5 million. Salmon that were kept in water with concentrations of 4 to 8×10^3 *C. polylepis* cells/ml and a salinity of 30 ppt were killed within 4 h. There was evidence of gill epithelial damage that would have increased permeability and resulted in osmoregulatory failure (Underdal *et al.*, 1989; Lindahl and Dahl, 1990). Effects on marine fauna (Table 4) ranged from extreme to slight. Numerous symptoms, including discoloration, changes in behavior patterns, and "loosening" of organs were noted. Sea urchins, *Echinus esculentus*, were severely affected and to a large extent, gastropods. In some areas, the Atlantic dogwinkles (*Nucella lapillus*), common periwinkles (*Littorina littorea*), waved whelks (*Buccinum undatum*), dog whelks (*Nassarius reticulatus*), and pelican's foot (*Apporhais pespelicani*) were completely eradicated (Underdal *et al.*, 1989). In other areas, dogwinkle mortalities were as high as 98 to 99%, which reduced dogwinkle distribution, local population sizes, and reproduction levels (due to the high mortality rates of 1 and 2 year olds, 3 years of recruits were lost) (Robertson, 1991). Mortality rates were also high among the bivalves Arctic rock borer, *Hiatella arctica*, and saddle oysters, *Anomia ephippium*. Numerous mortalites occurred among the fish groups Labridae and Gobiidae and in the tadpole fish *Raniceps raninus* (Underdal *et al.*, 1989; Lindahl and Dahl, 1990). Sea anemones, *Metridium senile*, had retracted their tentacles and were losing mucus (Lindahl and Dahl, 1990). Unusually, and rarely reported with HABs, several species of macroalgae were affected by the bloom; dead and dying macroalgae, such as red

seaweed, *Delesseria sanguinea*, was common. Adverse affects such as frayed and discolored thalli were reported, particularly amongst benthic rhodophyceans (Underdal *et al.*, 1989). Laboratory experiments showed that in water containing *C. polylepis*, *D. sanguinea* changed color from red to orange to green, indicative of pigment breakdown (Lindahl and Dahl, 1990). Empty thecae of the dinoflagellate *Ceratium* were also noted inside the bloom area (Dahl *et al.*, 1989). At the height of the bloom, when *Chrysochromulina polylepis* densities reached 6 to 7 $\times$ 10^4 cells/ml, no potential grazers were present in the subsurface bloom, and bacterial production was extremely low. Field and laboratory experiments showed that *C. polylepis* inhibited the activity of planktonic bacteria, ciliates, and copepods (Tables 10 and 11). Two weeks after the height of the bloom, the normal pelagic food web structure was reestablished (Nielsen *et al.*, 1990).

In laboratory experiments, toxicity of *Chrysochromulina* spp. has been difficult to demonstrate (Granéli *et al.*, 1993; Edvardsen and Paasche, 1998). At minimum concentrations of 5 $\times$ 10^4 cells/ml, *C. polylepis* reduced the growth of blue mussels, and concentrations of 1.1 $\times$ 10^8 cells/ml reduced growth by up to 60% when compared with controls (Nielsen and Strømgren, 1990). Experiments conducted during the 1988 *C. polylepis* bloom demonstrated that toxins affected eggs and larvae of ascidians (*Ciona intestinalis*), blue mussels (Granmo *et al.*, 1988), and copepods (Nielsen *et al.*, 1990). The fertilization of gametes and successful development of ascidians and mussels was completely inhibited (Granmo *et al.*, 1988). During a natural bloom of *Chrysochromulina* spp. in Denmark, an almost complete absence of ciliates was noted (Hansen *et al.*, 1995). In bialgal cultures of 1 $\times$ 10^3 *C. polylepis* cells/ml and the diatom *Skeletonema costatum*, *C. polylepis* in many cases caused a 96% decrease in the abundance of diatoms when compared with the control (Myklestad *et al.*, 1995). Atlantic salmon, *Salmo salar*, and rainbow trout, *Oncorhynchus mykiss*, that were exposed to *C. polylepis* showed an increase in plasma osmolality (Leivestad and Serigstad, 1988, cited in Nielsen, 1993).

In May-June 1991, *C. leadbeateri* was responsible for the death of almost 750 metric tons of salmon and trout in Norwegian fish farms (Aune *et al.*, 1992; Eikrem and Throndsen, 1993; Heidal and Mohus, 1995), resulting in an economic loss that exceeded $5 million (Aune *et al.*, 1992). The bottom fauna was generally unaffected by the bloom, but in a few localities a high level of mortality of sea urchins was observed (Johannesen *et al.*, 1991, cited in Hansen *et al.*, 1995). Highest cell counts did not exceed 1 $\times$ 10^4 cells/ml (Heidal and Mohus, 1995). Mice injected with fish muscle extracts from moribund fish exposed to the bloom did not demonstrate any adverse effects. Mice injected with extracts from blue mussels that had been exposed to the bloom showed deviating behavioral patterns such as scratching, narrowing of eyes, and progressive limpness after 30 to 60 min, but they recovered subsequently (Aune *et al.*, 1992).

Subsequent reports of toxic *Chrysochromulina* events have been from Scandinavia or North America (Table 4). *Chrysochromulina leadbeateri* has also been documented in Australia (Hallegraeff, 1993) and in other areas of the North Atlantic (Estep *et al.*, 1984), and *C.* cf. *polylepis* has been reported from New Zealand (Chang, 1995), but thus far none of these species have been associated with aquatic animal mortalities in these areas. A freshwater fish mortality event in Denmark coincided with a bloom of *C. parva* (up to 6.14 $\times$ 10^5 cells/ml), and there was no evidence for low dissolved oxygen or other potential environmental stressors. Although

toxicity tests were not conducted, this species is highly suspect and, if proven to be toxic, would represent the first report of toxicity in a freshwater *Chrysochromulina* species (Hansen *et al.*, 1994). In April-May 1992, a mortality of caged rainbow trout, *Oncorhynchus mykiss*, was associated with a mixed bloom of *Chrysochromulina* spp. in the Lillebaelt, Denmark. Dominant species included *C. birta*, *C. spinifera*, *C. ericina*, and *C. brevifilum*, and maximum total cell concentrations were 5×10^4 cells/ml. Fish swam apathetically near the water's surface prior to death. The total loss of fish was about 50 tons. Fish died principally during the early phase of the bloom, when cell concentrations ranged between 1 to 3×10^4 cells/ml. Although the bloom was not toxic to the plankton community, the effect on the fish suggested that one or several of these *Chrysochromulina* species may be toxic. Further studies on these four species are required (Hansen *et al.*, 1995).

Intraperitoneal injections of hepatopancreas extracts of blue mussels and oysters, *Ostrea edulis*, naturally exposed to the 1988 *C. polylepis* bloom in Norway, were lethal to mice. Toxicity of the bivalves to mice decreased within 20 days after the bloom had disappeared (Underdal *et al.*, 1989; Stabell *et al.*, 1993). Yasumoto *et al.* (1990) extracted hemolytic compounds from water containing *C. polylepis* cells and from blue mussels exposed to the 1988 bloom. As with *Gyrodinium aureolum* (see page 229), the hemolytic compounds were identified as MGDG and a PUFA, octadecapentaenoic acid (C18:5n3). Extracts from mussels exposed to a *C. polylepis* bloom had a higher hemolytic activity (80 HU/g) than did those from uncontaminated mussels (16 HU/g). (A 0.1% saline solution of commerical saponin was used as the standard against a 0.4% mouse red blood cell suspension. If complete hemolysis took place with a 10-µl saponin solution, then the hemolytic potency of 10 µg saponin was used to define one hemolytic unit [HU]). The results indicated that the mussels had accumulated a hemolytic substance, later characterized as H2LC (digalactosylglycerol) (Yasumoto *et al.*, 1990). In addition to hemolysins, other uncharacterized toxins are also suspected to be present in *C. polylepis* (Stabell *et al.*,1993).

The *Chrysochromulina polylepis* toxin acts at the cellular level, interfering with cell membrane functions and ionic balance (Underdal *et al.*, 1989; Meldahl *et al.*, 1993). Because of this nonspecific activity, *C. polylepis* affects a wide range of aquatic organisms from protists to fish (Edvardsen and Paasche, 1998). The toxic compounds in *C. leadbeateri* have not yet been characterized (Meldahl *et al.*, 1994). As well as demonstrating hemolytic activity, crude extracts of toxins from *C. polylepis* and *C. leadbeateri* lysed rat hepatocytes (Aune, 1989; Underdal *et al.*, 1989; Aune *et al.*, 1992). At concentrations of 1 to 2×10^4 *C. polylepis* cells/ml, most of the rat hepatocytes were totally destroyed. Cell size almost doubled and the cell membranes lysed completely. The effects of prymnesin at concentrations of 500 HU/ml on rat hepatocytes were similar to the effects of extracts from *C. polylepis* (Underdal *et al.*, 1989). Mussel extracts exposed to *C. leadbeateri* displayed a dose-dependent toxicity to rat hepatocytes. Enzyme leakage resulted from complete destruction of cell membranes and lysis of cells. Extracts from salmon livers and stomach contents also affected rat hepatocytes (Aune *et al.*, 1992). *Chrysochromulina polylepis* has also been shown to inhibit the *in vitro* uptake of neurotransmitters into synaptosomes and synaptic vesicles (Meldahl *et al.*, 1993).

b. Prymnesium spp.

At least four species of *Prymnesium* are currently recognized as being toxic to aquatic organisms (Table 1). Ichthyotoxic *Prymnesium* spp. blooms have been documented since the late 1800s, mostly from brackish-water systems in Israel, Europe, Ukraine, North America, China, and Australia (Table 4). Some of these reports may have wrongly identified particular species. Although many of the earlier blooms were attributed to *P. parvum* (Table 4), it is possible that some of these harmful events were due to *P. patelliferum*, now commonly reported in Scandinavia (see Larsen *et al.*, 1993) but not recognized as a separate taxon until 1982 (Edvardsen and Paasche, 1998). However, the possibility that *P. parvum* and *P. patelliferum* are actually one species is still being discussed. Apart from slight morphological differences at the light microscopic level, it appears that genetically *P. parvum* and *P. patelliferum* are identical (Larsen, 1999). For the time being mortality reports will be provided as described in the original reports, but readers should be aware that the taxonomy of this genus is still in flux.

Although *P. saltans* was implicated as the causative organism of fish kills in Germany (Kell and Noack, 1991), Moestrup (1994) noted that the kills were more likely due to *P. parvum*. *Prymnesium saltans* has been implicated in fish kills in China (Wang and Wang, 1992). Recently, a new species, *P. calathiferum*, was associated with fish mortalities in New Zealand and is the first report of this genus from marine waters (Chang, 1985; Chang and Ryan, 1985).

Prymnesium spp. have been responsible for significant economic losses caused by fish kills in aquaculture facilities and fish farms around the world (Sarig, 1971; Moestrup, 1994). Except for *P. calathiferum*, *Prymnesium* blooms occur in low-salinity (usually between 1 to 12 ppt), brackish waters in ponds, shallow lakes, or lagoons (Edvardsen and Paasche, 1998). Under suitable conditions in fish ponds, blooms of *P. parvum* can become dominant within 3 to 5 days (Sarig, 1971). Recurrent kills in brackish fish ponds in Israel have been a significant problem since the early 1940s. Routine fish bioassays using suspect pond water and mosquitofish, *Gambusia affinis*, have helped fish farmers take preventative measures and avoid unnecessary economic losses. Ponds are chemically treated with copper sulfate when low concentrations of *P. parvum* are confirmed toxic by the fish bioassay (Sarig, 1971). Fish kills usually occur when *Prymnesium* cell densities exceed 5 to 10×10^5 cells/ml. Since 1989, in the Ryfylke fjords, Norway, mixed blooms of *P. parvum* and *P. patelliferum* have taken place yearly during July-August, and have caused extensive damage to farmed fish (Edvardsen and Paasche, 1998). In the summer of 1983, an unusual fish and shellfish mortality event in New Zealand coincided with the presence of a newly reported *Prymnesium*, *P. calathiferum* (Chang, 1985; Chang and Ryan, 1985). At the height of the bloom, minimum dissolved oxygen levels in the area of the fish kill were 3.8 to 6.3 ppm, and *P. calathiferum* was highly suspected to be a toxic species. In an experimental bioassay, a cell-free supernatant of *P. calathiferum* (approximately 10^8 cells/ml centrifuged at 3000 rpm) was lethal to mosquitofish, *Gambusia* sp. after 170 min exposure (Chang, 1985).

The biological spectrum of activity of prymnesins is extremely broad (Table 1) (Shilo, 1981), but because of the difficulties of purifying the toxin, it was unclear whether this is due to a single molecular entity (Igarashi *et al.*, 1995). Ichthyotoxicity

is enhanced in the presence of cations (Ulitzer and Shilo, 1964). Killifish immersed in a 2-ppm prymnesin solution died at a lower concentration (0.5 to 1.0 ppm) when calcium ions (0.2 to 0.5%) were added to the solution (Igarashi *et al.*, 1995). Prymnesins act on the cytoplasmic membranes of cells and have been demonstrated to affect fish, bird, and mammalian erythrocytes; human liver and amnion cells; tumor cells (Ehrlich ascites and HeLa); bacterial protoplasts and spheroplasts; and *Mycoplasma* (see references in Shilo, 1981). Gill-breathing animals, such as fish, tadpoles, and molluscs, are sensitive to toxins because of the increased permeability of the gill membranes of these animals, especially in conditions that are cation-activated, pH-dependent, and sodium chloride-inhibited (Shilo, 1981). *Rana* and *Bufo* tadpoles are highly sensitive to *P. parvum* toxins; their tails curve, they become paralyzed, and they eventually die when immersed in toxin. After metamorphosis, these amphibians are totally refractory to toxins (Shilo and Aschner, 1953). When exposed to prymnesin-2, chloride cells in the epithelium of the gill filaments of the freshwater white cloud mountain minnow, *Tanichthys albonubes*, were affected noticeably. Vacuolations appeared in the cytoplasm of the chloride cells. The severity of cellular damage was proportional to increasing calcium concentrations and higher pH (Terao *et al.*, 1996).

Purified toxin from *P. parvum* contained fatty acids, amino acids, phosphate, and hexose sugars (Ulitzer and Shilo, 1970). Six hemolytic components were identified (Shilo, 1981; Kozakai *et al.*, 1982) either as a mixture of two galactoglycolipids (Kozakai *et al.*, 1982), or as proteolipids (Shilo, 1981). Hemolysin-1, identified as a mixture of galactolipids, with the major fatty acid component being C18:4 and the minor component C18:5, was present in high amounts (Kozakai *et al.*, 1982). Recently, Igarashi *et al.* (1995) purified two toxins, prymnesin-1 and prymnesin-2, that have hemolytic and ichthyotoxic properties (Shilo, 1981; Igarashi *et al.*, 1995, 1996). Cultures of both *P. parvum* and *P. patelliferum* were toxic to *Artemia*, and crude lipid extracts had toxic effects on human erythrocytes and synaptic vesicles of rat brains (Meldahl *et al.*, 1994). An extract of *P. patelliferum* has been shown to have two different effects on the transport of neurotransmitters across nerve membranes: (1) it inhibits the sodium-dependent uptake of L-glutamate and GABA (γ-aminobutyric acid), and (2) it enhances the calcium-dependent release of acetylcholine (Meldahl and Fonnum, 1995). An extract of *P. patelliferum* at a concentration of 5×10^4 cells/ml caused a rapid inhibition of glutamate accumulation in the synaptosomes. The effect on this transport system is probably due to impairment of one or more gradients (sodium, potassium, and calcium) and depolarization of the plasma membrane (Meldahl *et al.*, 1994, 1995). The toxic extract of *P. patelliferum* increases the permeability of synaptosomes to Ca^{2+}, Na^+, and K^+, and this effect may be responsible for the plasma membrane depolarization and the disturbance of neurotransmitter processes (Meldahl and Fonnum, 1995).

There have been relatively few reports or studies on the potential impact of *Prymnesium* on other animal groups. When the copepod *Acartia clausi* was kept in dense cultures of a toxic strain of *P. patelliferum*, there was no mortality of late copepodids or adults. Strong negative effects on egestion and reproduction were documented, both when *Prymnesium* was offered singly as food and when it was fed in conjunction with the flagellates *Rhodomonas baltica*. However, it was suggested that laboratory studies may significantly underestimate the adverse effects of potentially toxic prymnesiophytes *in situ*. It was concluded that toxic

prymnesiophytes, such as *P. patelliferum*, may not only cause occasional conspicuous bloom effects such as fish kills, but they may also have a substantial impact on the plankton food chain in coastal waters by constraining the zooplankton's feeding and reproduction even at commonly occurring sub-bloom concentrations (Nejstgaard and Solberg, 1996).

L. DOMOIC ACID

Although originally isolated from the red macroalga *Chondria armata* (Takemato and Daigo, 1958), domoic acid (DA) was not known to be produced by microalgae prior to a recent human shellfish poisoning event. In 1987, in Prince Edward Island (PEI), Canada, DA was implicated for the first time in Amnesic Shellfish Poisoning (ASP). After the consumption of toxic blue mussels, *Mytilus edulis*, 3 people died, 19 were hospitalized (12 of whom were in intensive care for a time), and more than 100 suffered from varying degrees of gastrointestinal and neurologic illnesses. Clinical symptoms of DA intoxication are nausea, vomiting, abdominal cramps, diarrhea, memory loss, decreased level of consciousness, seizures, confusion, and disorientation (Debonnel *et al.*, 1989; Wright *et al.*, 1989; Perl *et al.*, 1990; Teitelbaum *et al.*, 1990; Todd 1990, 1993; Nijjar and Nijjar, 2000). Prior to the PEI event, DA was not suspected as a hazard to public health. DA toxicity in mussels was eventually linked to the diatom *Pseudo-nitzschia multiseries* (Subba Rao *et al.*, 1988; Bates *et al.*, 1989). Edible tissue of blue mussels contained up to 900 μg/g DA (Addison and Stewart, 1989), which exposed consumers to an extremely high dose of the toxin.

The production of DA has now been identifed in nine species of *Pseudo-nitzschia* and one species of *Nitzschia* (Table 1) (Bates *et al.*, 1998; Bates, 2000), and DA has also been confirmed in shellfish in North America (Bates *et al.*, 1989; Wright *et al.*, 1989; Martin *et al.*, 1990; Gilgan *et al.*, 1990; Haya *et al.*, 1991; Dickey *et al.*, 1992; Garrison *et al.*, 1992; Adams *et al.*, 2000), New Zealand (Mackenzie *et al.*, 1993; Chang *et al.*, 1995; Rhodes *et al.*, 1996), Japan (Kotaki *et al.*, 1999), Denmark (Lundholm *et al.*, 1994), Scotland (Gallacher *et al.*, 2000; Campbell *et al.*, 2001), France (Amzil *et al.*, 2001); Spain (Miguez *et al.*, 1996; Arévalo *et al.*, 1998), and Portugal (Vale and Sampayo, 2001).

DA is an analog of glutamate, an excitatory neurotransmitter that binds to the kainate type of glutamate receptors. DA is a water-soluble, heat-stable amino acid excitotoxin that binds to receptors in the brain, in particular in the hippocampus (Debonnel *et al.*, 1989; Sutherland *et al.*, 1990). DA causes massive depolarization of the neurons, with a subsequent increase in cellular Ca^{2+}, neuronal swelling, and cell death (Novelli *et al.*, 1990; Bates *et al.*, 1998). Nerve cells located in the hippocampus are associated with memory retention, hence the loss of memory associated with ASP cases (Bates *et al.*, 1998). Neurotoxicity of DA to rats and monkeys has been demonstrated (Tryphonas *et al.*, 1990a, 1990b, 1990c; Xi *et al.*, 1997). In rodents, DA causes inactivity, seizures, and a characteristic scratching response (Work *et al.*, 1993). Domoic acid causes extreme neurodegenerative disorders in mammals and birds. As discussed by Shaw *et al.* (1997), in mammalian systems, DA acts as a glutamate agonist, causing damage to neurons by binding to the glutamate receptor and overexciting the neurons. Thus, the toxicity is caused by an indirect, receptor-mediated mechanism. Because this mechanism involves ampli-

fication of the initial response to receptor binding, DA has a low threshold concentration for toxicity.

A few studies have investigated the effects of DA on zooplankton. Domoic acid is toxic to the small estuarine copepods *Temora longicornis* and *Pseudocalanus acuspes*, but only at relatively high concentrations (LC_{50} at 72 h was 135 and 38 μg/ml, respectively) in seawater. When fed toxic *Pseudo-nitzschia multiseries*, there was less than 90% mortality of the copepods *T. longicornis* and *Calanus glacialis* over a 9-day period. About 50% of the ingested DA was retained, suggesting that copepods can act as toxin vectors (Windust, 1992, cited in Bates, 1998). When fed toxic *P. multiseries* in 24-h experiments, the copepods *T. longicornis* and *C. glacialis* showed no adverse effects, such as decrease in feeding rate, egg-hatching success, unusual feeding behavior, or mortality. As pointed out by Bates (1998), the lack of toxicity to copepods is surprising, given that DA can depolarize neuromuscular junctions in crayfish and insects (Maeda *et al.*, 1984). Feeding rates, egg production rates, egg hatching success, and mortality of the calanoid copepods *T. longicornis* and *Acartia tonsa* were not significantly different when copepods were fed toxic *P. multiseries* or a nontoxic strain of *P. pungens* (Lincoln *et al.*, 2001). This apparent lack of effect on copepods suggests that copepods could act as vectors for DA transfer to higher-level zooplankton consumers (Turner and Tester, 1997). Recently, however, another study demonstrated that DA was toxic to the copepods *Tigriopus californicus* at very low concentrations. The experimental results for the effects of DA on *T. californicus* suggest that the mechanism for action is the same in this copepod as it is in mammalian systems (Shaw *et al.*, 1997). Because compounds such as PST and microcystin-LR (MC-LR) can be detected by chemoreceptors, the copepod can cease feeding and thus avoid the potential toxicity of these compounds. DA, however, does not appear to be detected and avoided and therefore probably acts as a neurotoxin (Shaw *et al.*, 1997). Presumably, there are species-specific differences in susceptibility to DA. When fed *P. multiseries*, the rotifer *Brachionus plicatilis* assimilated DA rapidly for 27 h. Toxin levels then declined rapidly to a minimum after 75 h of exposure. The mean fecundity of the rotifers was reduced considerably, from 0.70 to 0.39 eggs per female, and this change in fecundity was attributed to the feeding inhibition caused by DA rather than to nutritional insufficiency (Whyte *et al.*, 1996).

In addition to blue mussels, DA has been found naturally in numerous species of invertebrates, including Mediterranean mussels, *Mytilus galloprovincialis* (Miguez *et al.*, 1996); northern horsemussels (*Modiolus modiolus*), softshell clams (*Mya arenaria*) (Gilgan *et al.*, 1990); Pacific razor clams, *Siliqua patula* (Drum *et al.*, 1993; Wekell *et al.*, 1994a); razor clams (*Ensis siliqua*), peppery furrow shells (*Scrobicularia plana*) (Vale and Sampayo, 2001); tuatua clams, *Paphies subtriangulata* (Rhodes *et al.*, 1996); Pacific oysters (*Crassostrea gigas*), dredge oysters (*Tiostrea chilensis*), greenshell mussels (*Perna canaliculus*) (Rhodes *et al.*, 1996); the sea scallops, *Placopecten magellanicus* (Gilgan 1996 in Stewart *et al.*, 1998); *Pecten maximus* (Arévalo *et al.*, 1998; Campbell *et al.*, 2001) and *P. novaezealandiae* (Rhodes *et al.*, 1996); Japanese scallops, *Patinopecten yessoensis* (Kotaki *et al.*, 1996); Dungeness crab, *Cancer magister* (Wekell *et al.*, 1994a); blue crab (*Callinectes sapidus*), rock crab (*Cancer pagurus*), stone crab (*Menippe adina*), and spiny lobster (*Palinurus elephas*) (Altwein *et al.*, 1995). As with other bivalves and certain phycotoxins, there are species-specific differences in the response of some species to *Pseudo-nitzschia*

spp. and to DA. Jones *et al.* (1995b) discussed the possibility that because DA causes observed excitoxic effects on mammalian systems, physiological aberrations in shellfish might be expected because they concentrate high levels of toxin. Although there appear to be no obvious adverse effects of DA on sea scallops (Douglas *et al.*, 1997), blue mussels (*Mytilus* spp.), or California mussels (*Mytilus californianus*) (Jones *et al.*, 1995a; Whyte *et al.*, 1995), there is some indication that Pacific oysters (Jones *et al.*, 1995a), spiny scallops (*Chlamys hastata*) (J. Whyte, personal communiction, in Douglas *et al.*, 1997), and pink scallops (*C. rubida*) are physiologically stressed (Bates, 1998). Within 4 h of exposure to *Pseudo-nitzschia pungens,* the shells of Pacific oysters closed tightly, which is a typical initial stress response by bivalves to some microalgae (see PST). Before the shells closed, levels of DA increased in all the tissues examined: mantle, gill, muscle, and remaining soft tissue (Jones *et al.*, 1995a). When Pacific oysters were exposed to *P. pungens* f. *multiseries*, another initial stress response was a marked increase in the number and activity of hemocytes after a 4-h exposure to the algae. Toxin levels in the oysters increased during the 48 h of exposure, and the number and activity of hemocytes declined from the 4-h peak values to values significantly lower than those of controls after a 24-h clearance period. The suppression in number and activity of circulating hemocytes following initial toxin response was rectified only after a 48-h clearance period, when DA levels in the oyster tissue had declined to trace levels, allowing blood cells to regain their normal characteristics (Jones *et al.*, 1995b).

In blue mussels, DA is found only in the viscera (Wekell *et al.*, 1994b). In animals from a naturally contaminated area in PEI, the hepatopancreas, which composed 30% of the mussel weight, contained 93.4±1.9% of the toxin (Grimmelt *et al.*, 1990). When DA was presented to live mussels in dissolved form or as a food encapsulated in liposomes, less than 1% of the dissolved DA and up to 6% of the foodborne DA was incorporated into mussel tissues. Domoic acid ingested as food was mostly concentrated in the digestive gland and kidney. For their relative proportion of body weight, the kidneys, digestive gland, and gills retained larger than expected proportions of the total toxin burden. The concentration of toxin in mussel tissues did not decrease consistently over a depuration period of 48 h, or did DA appear to be translocated to any tissue for storage (Novaczek *et al.*, 1991). After a 72-h period, the majority of the DA was present in the gut lumen of mussels, more than 50% was eliminated within the first 24 h (Novaczek *et al.*, 1992). Because DA is essentially hydrophilic (Wright *et al.*, 1989), it is more likely that toxin will be excreted than that it will be bioaccumulated (Novaczek *et al.*, 1992). In the digestive system of mussels domoic acid can be converted to isodomoic acid isomers (Wright *et al.*, 1990).

Maximum DA concentrations of up to 3100 μg/g tissue were observed in sea scallops, *Placopecten magellanicus*, with the majority of toxin being found in the digestive gland. Levels remained high up to 15 days after exposure (Douglas *et al.*, 1997). In razor clams, DA can also occur in the foot and the siphon as well as in the viscera, and DA can be retained for up to six months (Drum *et al.*, 1993; Wekell *et al.*, 1994b). In king scallops, *Pecten maximus*, DA concentrations in all tissues except gonad and adductor muscle accounted for 99% of the total individual burden (580 to 760 μg/g tissue), with less than the regulatory limit (20 μg DA) in the gonad (8.2 to 11.0 μg/g tissue) and adductor muscle (0.38 to 0.82 μg/g tissue) (Campbell *et al.*, 2001).

Domoic acid has been detected in the flesh and viscera of bay anchovies, *Anchoa mitchilli*, and Californian anchovies, *Engraulis mordax* (Work *et al.*, 1992; Altwein *et al.*, 1995; McGinness *et al.*, 1995), and gut content of sardines (Vale and Sampayo, 2001), but fish mortalities or neurotoxic effects in the field have not been reported. In experiments, intracoelomic injection of anchovies with DA concentrations ranging 1 to 14 μg/g total fish weight resulted in severe neurotoxic symptoms, including spinning, spiraling, and swimming upside down; circling at the surface, mouths gaping; inability to school; with eventual mortality. DA levels as high as 1175 μg/g were measured in anchovy viscera, with brain and muscle levels 3 orders of magnitude lower, indicating low but measurable DA uptake (Lefebvre *et al.*, 2001).

Planktivores are able to vector DA, and toxin transfer via Californian anchovy (Wekell *et al.*, 1994a) has been responsible for significant bird mortalities. Although DA was implicated in the 1987 human ASP event in Canada, it was not until September 1991 that the first aquatic animal mortality was attributed to this toxin. In Santa Cruz, California, at least 43 brown pelicans, *Pelecanus occidentalis*, and 95 Brandt's cormorants, *Phalacrocorax penicillatus*, died from ingesting anchovies contaminated with DA. The birds displayed a characteristic slow, side-to-side head motion, held their wings partially extended, and were unable to fly for more than 10 m without having to land. Vomiting was common, and the birds would lose awareness of their surroundings, display torticollis, lose righting reflex, and lie either on their back or side with their feet paddling slowly prior to death. The only consistent gross and histopathologic lesions observed were hemorrhages and necrosis of the skeletal muscle. Serum blood urea nitrogen and creatinine phosphokinase were higher in affected birds than they were in controls. Domoic acid was detected in the stomach contents of the sick and dead birds, in the flesh and viscera of Californian anchovies, and in plankton samples dominated by *Pseudo-nitzschia* (Work *et al.*, 1992, 1993). In this case, *P. australis* was demonstrated to produce DA (Buck *et al.*, 1992; Fritz *et al.*, 1992; Garrison *et al.*, 1992).

Recently, Sierra Beltran *et al.* (1997) reported another DA event in Cabo San Lucas, Mexico, where brown pelicans were killed after feeding on DA-contaminated chub mackerel, *Scomber japonicus*. At least 150 birds were found during a period of 5 days in January 1996. Live pelicans showed symptoms of intoxication, such as disorientation and agitation, difficulty in swimming, and not being able to right themselves if they had turned upside down during swimming causing them to drown. At least 50% of the pelican colony died as a result of DA intoxication, and surviving birds still showed symptoms of weakness and disorientation 2 months after the event. *Pseudo-nitzschia* sp. frustules were found in the stomach contents of pelicans and mackerel; mouse bioassay of bird stomach contents and HPLC confirmed the presence of DA. In the mouse bioassay using pelican stomach extracts, mice showed symptoms corresponding to DA toxicity, including akinesis, prostration and scratching, diarrhea, convulsions, and loss of lateral movement and motor coordination.

In May 1998, near Monterey Bay, California, more than 400 California sea lions, *Zalophus californianus*, died, and others suffered severe neurological dysfunction. Characteristic clinical signs were scratching, dullness, ataxia, seizures, and convulsions. Predominant histological lesions were neuronal necrosis of the hippocampus. Domoic acid was detected in urine, feces, and serum from examined animals. A concurrent bloom of *Pseudo-nitzschia australis* was detected, and DA was

confirmed in Californian anchovies from the same area (Scholin *et al.*, 2000). The primary route of sea lion exposure to DA was considered to be through consumption of toxic fish. The highest DA concentrations in anchovies occurred in the viscera (223 ± 5 μg DA/g), exceeding values in the body tissues by sevenfold and suggesting minimal bioaccumulation of DA in muscle tissue (Lefebvre *et al.*, 1999). In contrast, blue mussels contained no or only trace amounts of DA. Histopathological analyses of sea lions that suffered acute exposure to DA revealed brain lesions in the anterior ventral hippocampus. This was the first proven case of fatal DA toxicity in marine mammals (Gulland *et al.*, 1998; Lefebvre *et al.*, 1999; Scholin *et al.*, 2000).

The presence of DA in shellfish and fish certainly provides an opportunity for toxin transfer through the food chain, and even if DA is not accumulated at the high lethal doses recorded during mortalities of birds and mammals, there could still be a potential for chronic health effects. However, as with the selective neurological or gastrointestinal impacts of other toxins on vertebrates, it is unclear what chronic effects could be anticipated.

M. ANATOXINS

There are three main anatoxins that have been isolated from cyanobacteria: anatoxin-a, anatoxin-a(s), and homoanatoxin-a (Table 1). In addition to the terrestrial animal mortalities associated with drinking anatoxins (Table 7), there are a few documented reports of the effects of anatoxins on aquatic life. Because several of the known anatoxin-producing species also produce microcystins or PST (Table 1), it appears that most mortalities in water are associated with these toxins rather than the anatoxins, but a recent mortality of birds was associated with anatoxin-a(s) (see below).

1. Anatoxin-a

Anatoxin-a was originally isolated from *Anabaena flos-aquae* (Devlin *et al.*, 1977) and has also been reported from strains of *A. circinalis*, *A. planctonica*, *Aphanizomenon* sp., *Cylindrospermum* sp., *Planktothrix* (= *Oscillatoria*) (Sivonen *et al.*, 1989), and in benthic mats of *Planktothrix* (= *Oscillatoria*) (Edwards *et al.*, 1992) (Table 1). Most recently (and uncommonly) anatoxin-a was also reported from microcystin-producing strains of *Microcystis aeruginosa* in Japan (Park *et al.*, 1993); this report remains to be confirmed (Codd, 1998). Anatoxin-a is a low-molecular-weight secondary amine (Devlin *et al.*, 1977) that is highly neurotoxic. It is a postsynaptic cholinergic nictotine agonist that causes death via a depolarizing blockage of neuromuscular transmission and subsequent respiratory paralysis. The LD_{50} intraperitoneal mouse dose for purified toxin is about 200 μg/kg body weight, with a survival time of 4 to 7 min (Carmichael, 1988, 1992). Symptoms of anatoxin-a toxicity in mouse bioassays include muscle fasciculation, loss of coordination, gasping, convulsions, and death by respiratory arrest (Carmichael *et al.*, 1990). In field reports, the signs of poisoning in wild and domestic animals include staggering, muscle fasciculations, gasping, convulsions, and opisthotonus (in birds). Death by respiratory arrest occurs within minutes to a few hours, depending on species, dosage, and prior food consumption. Animals need to ingest only a few milliliters to a few liters of the toxic surface bloom to receive a lethal bolus (Carmichael, 1988).

Clinical signs of anatoxin-a in vertebrates are often difficult to distinguish from those of PSP. Both result in all or some of the following symptoms: trembling, loss of coordination, staggering, and collapse and death by respiratory failure. Anatoxin-a additionally causes salivation (Negri *et al.*, 1995).

Recently, several dog mortalities have been associated with the production of anatoxin-a from benthic mats of *Planktothrix* (= *Oscillatoria*) (Edwards *et al.*, 1992; Gunn *et al.*, 1992; James *et al.*, 1997a). After drinking surface water, dogs displayed severe respiratory discomfort, coma, rigors, cyanosis, limb twitching, hypersalivation, and convulsions before dying (Gunn *et al.*, 1992; James *et al.*, 1997a). Although no surface blooms were detected, benthic mats of *Planktothrix* appeared to be linked to the presence of high levels of anatoxin-a (up to 444 μg/l) in the water (James *et al.*, 1997a).

Few studies have determined or investigated effects by anatoxin-a on aquatic organisms. Reproduction in the planktonic rotifers *Asplancha girodi*, *Brachionus calyciflorus*, *Keratella cochlearis*, and *Synchaeta pectinata* fed *Cryptomonas* was inhibited by a strain of *Anabaena flos-aquae* (IC-1) that produces anatoxin-a. In the most susceptible species, *B. calyciflorus*, reproduction was suppressed at an *Anabaena* dry-mass concentration of 0.5 μg/ml; the other species' reproduction was suppressed at a concentration of 4.0 μg/ml. *Asplancha girodi* and two clones of *B. calyciflorus* were not inhibited reproductively by filtrates of very dense *Anabaena* suspensions, which showed that *Anabaena* did not release extracellular toxin and thus could inhibit only rotifers that ingested it (Gilbert, 1994).

2. Anatoxin-a(s)

Anatoxin-a(s) is produced by *Anabaena flos-aquae* (Carmichael and Gorham, 1978) and *A. lemmermannii* (Henriksen *et al.*, 1997). The strain *A. flos-aquae* NRC 525-17 can simultaneously produce anatoxin-a(s) and microcystins (Harada *et al.*, 1991). Anatoxin-a(s) is a potent acetylcholinesterase inhibitor (Mahmood and Carmichael, 1986b, 1987) with an LD_{50} (i.p. mouse) of 20 μg/kg, about 10 times more lethal than anatoxin-a (Carmichael *et al.*, 1990). Anatoxin-a(s) was first reported from a culture of *Anabaena flos-aquae* isolated from Buffalo Pound Lake, Saskatchewan, Canada (Carmichael and Gorham, 1978). In mouse or rat bioassays, symptoms include marked viscous salivation (which gives the terminology for the toxin — the [s] label), lachrymation in mice, chromodacryorrhea (red-pigmented tears) in rats, urinary incontinence, muscular weakness, fasciculation, convulsion, defecation, and death from respiratory failure (Carmichael *et al.*, 1990).

There is little information on the effect of anatoxin-a(s) on aquatic animals. Anatoxin-a(s) from *A. flos-aquae* strain NRC 525-17 was recently shown to inhibit *in vitro* acetylcholinesterase activity in *Daphnia pulicaria* (Barros *et al.*, 1998). In July 1993 and June-July 1994 at lakes in Denmark, deaths of wild birds coincided with massive cyanobacterial blooms dominated by *A. lemmermannii* var. *minor* (Onodera *et al.*, 1997). Extracts of field samples were neurotoxic to mice and subsequently showed an anticholinesterase activity similar to anatoxin-a(s). Neither anatoxin-a nor saxitoxin or its derivatives were detected by HPLC, which together with the pharmacological evidence (Henriksen *et al.*, 1997) confirmed for the first time that anatoxin-a(s) was the cause of deaths of wild animals (Onodera *et al.*, 1997). Although the previous involvement of the toxin in the poisonings of dogs

(Mahmood *et al.*, 1988) and of birds and swine (Cook *et al.*, 1989) was suspected to be related to *A. flos-aquae* blooms on the basis of toxicological properties and chromatographic results, the causative agent was not characterized chemically (Onodera *et al.*, 1997).

3. Homoanatoxin-a

Recently, a new neurotoxin, homoanatoxin-a, was isolated from *Planktothrix formosum* (= *Oscillatoria formosum*) strain NIVA-CYA-92 (Skulberg *et al.*, 1992). In preliminary experiments, homoanatoxin-a was shown to be toxic to mice when i.p. injected — it blocked muscular contractions induced by neurostimulation in the isolated phrenic nerve-hemidiaphragm preparation of the rat (Lilleheil *et al.*, 1997). The toxin is readily absorbed from the gastrointestinal tract in mice after oral exposure to algal suspensions, but the toxicity resulting from such exposure was less than that induced by parenteral admininstration. Homoanatoxin-a acted very quickly and caused death by respiratory arrest within a few minutes, an action similar to that of anatoxin-a produced by *A. flos-aquae* NRC-44-1 (Carmichael *et al.*, 1975; Skulberg *et al.*, 1992; Lilleheil *et al.*, 1997). Field reports of toxicity are currently unknown.

N. MUEGGELONE

A newly identified C18 lipid, mueggelone, and the previously known lupenyl acetate were isolated from a field-collected freshwater sample of *Aphanizomenon flos-aquae* (Papendorf *et al.*, 1997). When zebrafish larvae (*Danio rerio*) were exposed to a concentration of 10 μg/ml mueggelone for up to 32 hours, there was a 45% mortality. In larvae surviving from 24 to 32 h, no blood circulatory system had developed, whereas after 3 days there was edema and thrombosis in the heart region. At a concentration of 1 μg/ml mueggelone, there was no effect on larval development. At a concentration of 100 μg/ml lupenyl acetate, larvae had edema in the heart region and showed tail bending (30%) after 3 days. After 5 days, all larvae had edema in the heart region and bent tails. At a concentration of 10 μg/ml lupenyl acetate, there were no obvious effects on development. Lupenyl acetate did not cause any larval mortality.

Another experiment in which fish and green frog mortalities were associated with exposure to *A. flos-aquae* was described by Sawyer *et al.* (1968). Young-of-the-year pumpkinseeds (*Lepomis gibbosus*), white suckers (*Catostomus commersoni*), and guppies (*Lebistes reticulatus*) were exposed to lyophilized cells of *A. flos-aquae* obtained from lake water containing approximately 4×10^2 cells/ml. Survival times varied from 30 to 240 min for *Lepomis gibbosus*, from 15 to 60 min for *C commersoni*, and from 60 to 240 min for *Lebistes reticulatus*. When injected intraperitoneally with a dosage of 60 mg/kg, the survival time for the green frog, *Rana clamitans*, was 32 min at 12°C (Sawyer *et al.*, 1968). Whether these mortalities were due to the potent effects of mueggelone, PST, or other undescribed toxins is unknown. In the case of PST and dinoflagellate blooms, it appears that fish can be affected by toxin exudates (see section on uncharacterized toxins and *Alexandrium tamarense*) rather than from just PST, which are normally ingested (see PST), but in the case of *Aphanizomenon flos-aquae*, it is unclear if other mechanisms are operating.

O. CYLINDROSPERMOPSIN

Cylindrospermopsin (CY) is a hepatotoxin that was isolated recently from *Cylindrospermopsis raciborskii* (Ohtani *et al.*, 1992), *Umezakia natans* (Harada *et al.*, 1994), and *Aphanizomenon ovalisporum* (Banker *et al.*, 1997) (Table 1). An outbreak of human hepatoenteritis was associated with a bloom of *C. racbiorskii* after a domestic drinking water reservoir became contaminated on Palm Island, northeastern Australia (Bourke *et al.*, 1983; Hawkins *et al.*, 1985). The majority (139) of cases (148) were in children. The liver was enlarged in all cases, and the initial symptoms resembled hepatitis accompanied by abdominal pain. Kidney malfunction and profuse bloody diarrhea followed. Symptoms occurred after the application of copper sulfate to a dense algal bloom in the water supply (Blyth, 1980; Bourke *et al.*, 1983; Hawkins *et al.*, 1985, 1997). Extracts of *C. raciborksii* cultures proved to be lethal to mice; the LD_{50} was 64 mg of freeze-dried culture per kg mouse. Affected mice were huddled, anorexic, and had mild diarrhea; those dying in the shortest times (6 to 9 h) had slow, gasping respiration and exhibited occasional limb paddling. The principal lesion produced was centrilobular to massive hepatocyte necrosis in the liver, but various degrees of injury were also seen in the kidneys, adrenal glands, lungs, and intestine (Hawkins *et al.*, 1985).

Recently, *Cylindrospermopsis raciborskii* was implicated in mortalities of cattle in Australia (Thomas *et al.*, 1998). After drinking from a contaminated area, a calf became weak and was seen staggering before it died. Gross pathology indicated severe abdominal and thoracic hemorrhagic effusion, hyperemic mesentery, pale and swollen liver, and an extremely distended gall bladder containing dark yellow bile. Histopathology of the liver revealed extensive fibrosis and bile duct proliferation. Two mice that received a 1.0-ml-i.p. dose of freeze-dried pure culture of *C. raciborksii* died within 7 to 8 h of inoculation. Livers were reddened, swollen, and represented 12.6 to 13.0% of the total body weight. Control mice had livers that were 5.7 to 7.7% of total body weight (Thomas *et al.*, 1998). At the ultrastructural level, the livers of mice experimentally exposed to CY showed inhibition of protein synthesis, membrane proliferation, fat-droplet accumulation, and finally cell death (Terao *et al.*, 1994).

Reports of the effects of CY on aquatic organisms are few, but it is likely that effects do occur. Recent mortalities of alligators and concurrent blooms of *C. raciborskii* in Lake Griffin, Florida, suggest a possible connection, but this has not yet been confirmed (J. Burns, personal communication). Cylindrospermopsin was shown to accumulate in redclaw crayfish, *Cherax quadricarinatus*, and rainbow fish, *Melanotaenia eachamensis*, exposed to a natural bloom of *Cylindrospermopsis raciborskii* in aquaculture ponds in Australia. Toxin accumulated in the hepatopancreas of the crayfish and viscera of the fish. Trichomes of *C. raciborskii* were found in the gut contents, indicating that ingestion of cells was one mechanism of toxin accumulation (Saker and Eaglesham, 1999). In experimental exposures, CY accumulated in the hepatopancreas (4.3 μg/g) at a concentration five times that of the muscle (0.9 μg/g) in crayfish, but no mortalities occurred. No histopathological abnormalities were observed in crayfish exposed either to extracellular or pure cultures of *C. raciborskii*. The accumulation of CY in the flesh of crayfish raised some concern about possible long-term effects (Saker and Eaglesham, 1999). As in the case

of PST produced by dinoflagellates (see PST), there is a high likelihood of toxin transfer up the food chain.

Cylindrospermopsin was demonstrated recently to have carcinogenic activity. Cylindrospermopsin induces cytogenetic damage via two mechanisms: one at the DNA level inducing strand breaks, and the other at the level of the kinetochore/spindle function, inducing loss of whole chromosomes (aneuploidy). These findings substantiate the concern that potential public health risks associated with drinking water sources and *Cylindrospermopsis* blooms are real (Humpage *et al.*, 2000). Preliminary evidence for *in vivo* tumor initiation was demonstrated when Swiss Albino mice were orally exposed with a crude saline extract of freeze-dried *C. raciborskii* followed by either dimethyl sulfoxide or tetradecanoyl phorbol acetate (known tumor promoters). After 30 weeks, 5 out of 53 *Cylindrospermopsis*-treated animals showed histological evidence of neoplastic processes; three of which showed frank tumors, including one fibroblastic osteosarcoma, one hepatocellular carcinoma, and one lymphoma. Although these results represent a statistically small sample, Falconer and Humpage (2001) recognized the potential biological and public health significance of such findings and recommended further investigation.

P. MICROCYSTINS

Excellent reviews on the biology, toxicity, and pathology of microcystins have been published recently (Rinehart *et al.*, 1994; Kaya 1996; Carmichael, 1996, 1997; Dawson, 1998). As with other cyanobacteria, most documented reports concern microcystin toxicity in terrestrial animals, including livestock and wildlife, after they ingest contaminated pond water (Table 7). This section briefly reviews known effects of microcystins in aquatic organisms.

Until recently, it was known that other cyanobacteria can produce both microcystins and anatoxins (e.g., *Anabaena* and *Oscillatoria*), but it is thought that *Microcystis* produces only microcystins (Carmichael, 1992, 1997). Unlike other toxic planktonic cyanobacteria, which may have nontoxic strains, *Microcystis* is almost always toxic. Microcystins are the most common cause of water-based toxicosis caused by cyanobacteria (Carmichael, 1996). About 60 structural variants of microcystins are currently known (Sivonen and Jones, 1999), more than half of which have been isolated from species and strains of *Microcystis aeruginosa* and *M. viridis*. Other microcystins are produced by *Anabaena flos-aquae*, *Anabaena* spp., *Anabaenopsis milleri*, *Nostoc* spp., and *Planktothrix* (= *Oscillatoria*) *agardhii* (Lanaras and Cook, 1994; Rinehart *et al.*, 1994; Sivonen, 1996; Carmichael, 1997; Namikoshi *et al.*, 1998; Sano *et al.*, 1998; Sano and Kaya, 1998; Sivonen and Jones, 1999) (Table 1). The microcystins differ principally in the two L-amino acids at positions 2 and 4. The most common microcystin is microcystin-LR (MC-LR), where the variable amino acids are leucine (L) and arginine (R) (Dawson, 1998).

As with other microalgal toxins, most information regarding the mechanism of action has been obtained from rodent bioassay models. The LD_{50} of MC-LR i.p. or i.v. in mice and rats is in the range of 36 to 122 μg/kg, and the inhalation toxicity in mice is similar: LCT_{50} 180 mg/min/mm, LD_{50} = 43 μg/kg (Dawson, 1998, and references therein). Symptoms of microcystin intoxication are diarrhea, vomiting, piloerection, weakness, and pallor (Bell and Codd, 1994). Microcystin targets the

liver, causing cytoskeletal damage, necrosis, and pooling of blood in the liver, which consequently increases liver weight (Hooser *et al.*, 1989) (up to 100% increase) (Dawson, 1998). Microcystins mediate their toxicity by uptake into liver hepatocytes via multispecific bile acid transport systems; by inhibition of serine/threonine protein phosphatases 1 and 2A (Eriksson *et al.*, 1990; Honkanen *et al.*, 1990, 1994; MacKintosh *et al.*, 1990; Yoshizawa *et al.*, 1990); by depolymerization of intermediate filaments and microfilaments; and by disruption of the liver cytoskeleton, which leads to loss of cell morphology, loss of cell-to-cell adhesion, and cellular necrosis (Hooser *et al.*, 1991; Falconer and Yeung, 1992; Eriksson and Goldman, 1993; Runnegar *et al.*, 1993; Sivonen, 1996). At acutely toxic doses, microcystins cause rounding or shrinkage of the hepatocytes and loss of normal hepatocyte structure. This disorganization of the tissue leads to massive hepatic hemorrhage, often followed by the death of animals from hypovolemic shock or hepatic insufficiency (Falconer *et al.*, 1981; Eriksson *et al.*, 1990; Honkanen *et al.*, 1990; Hooser *et al.*, 1991; Carmichael, 1992; Dawson, 1998). Death can occur within a few hours after a high dose (Falconer *et al.*, 1981; Bell and Codd, 1994; Dawson, 1998). More recently, a disastrous case of acute poisoning was caused by the unusual exposure of humans to microcystins via hemodialysis: about 50 people died in Brazil when patients at a dialysis center received untreated water contaminated with microcystins from a nearby water reservoir (Jochimsen *et al.*, 1998; Carmichael *et al.*, 2001).

Microcystins are also potent tumor promoters that are mediated through the inhibition of protein phosphatase type 1 and 2A activities. Their mode of action appears to be different from modes of other protein phosphatase inhibitors, such as okadaic acid (Falconer, 1993), and their effects are organ specific (liver) (Falconer and Buckley, 1989; Honkanen *et al.*, 1990; Matushima *et al.*, 1990; Falconer, 1991; Nishiwaki-Matsushima *et al.*, 1991, 1992; Ito *et al.*, 1997). Microcystins do not easily penetrate epithelial cells and they do not promote tumors on mouse skin (Matushima *et al.*, 1990; Fujiki and Suganuma, 1993). In countries where water supplies contain cyanobacteria, the potential threat of primary liver cancer by human exposure to microcystins has been recognized (Yu, 1991; Ueno *et al.*, 1996). The incidence of primary liver cancer in the populations of Qidong County, Shanghai, China, where people drink pond and ditch water, is about eight times higher than in populations drinking well water (Yu, 1991), and microcystins were found in the areas where cancer incidence was high (Yu and Chen, 1994).

When quail were exposed to microcystins, the toxic effects observed were quite different from those observed in rodents. Quails usually died 14 to 18 h after injection, whereas rats and mice died in 1 to 3 h. After the administration of the variant microcystin-RR, quail spleens were enlarged to double the size of those of the controls, but there was no change in the liver. Slight hemorrhagic necroses were also observed in the gizzard, liver, intestine, and subcutaneous tissue. Such necroses, except for those in the liver, were not seen in mice and rats (Takahashi and Kaya, 1993; Kaya, 1996). Although the experimental effects in birds such as the quail appear to be different from those in mammalian models, a recent mortality of birds in Japan also indicated hepatotoxicity (see below, Matsunaga *et al.*, 1999).

In aquatic systems, most documented cyanobacterial effects are those on zooplankton. There have been a large number of studies of individual species and of specific trophic levels in which the fate of microcystins and their effects on zooplankton in freshwater habitats were investigated (e.g., see Lampert, 1982, 1987;

Infante and Abella, 1985; Fulton and Paerl, 1987; De Bernardi and Guissani, 1990; De Mott *et al.*, 1991; Watanabe *et al.*, 1992; Reinikainen *et al.*, 1994, 1995a, 1995b, 1999; Christoffersen, 1996; Hanazato, 1996; Sbiyya *et al.*, 1998). The lethality of microcystins to zooplankton has been well documented (e.g., Lampert, 1981a, 1981b; Fulton and Paerl, 1987), but the actual dose of ingested toxin depends on feeding behavior as well as cell concentration in the water (De Mott *et al.*, 1991). For example, reactions of daphnids exposed to *Microcystis aeruginosa* have ranged from using cells as a food source, to completely avoiding the cells, to dying; in some cases, responses depend upon the toxicity of individual microalgal strains (De Bernardi *et al.*, 1980; Lampert, 1981a; Jungmann *et al.*, 1991; Peñaloza *et al.*, 1990). Acute toxicity experiments with purified toxins, toxic cyanobacteria, and cell extracts showed that four species of zooplankton differed markedly in their physiological sensitivity to microcystin. The copepod *Diaptomus birgei* was the most sensitive (48-h LC_{50}, 0.45 to 1.0 μg/ml), *Daphnia hyalina* (48-h LC_{50}, 11.6 μg/ml) and *D. pulex* (48-h LC_{50}, 9.6 μg/ml) were intermediate in sensitivity, and *D. pulicaria* was the least sensitive (48-h LC_{50}, 21.4 μg/ml). Survival in the presence of toxic *Microcystis* was strongly influenced by both physiological sensitivity and feeding behavior. Relatively good survival by *D. pulicaria* was associated with low sensitivity to purified toxin and a rapid inhibition of feeding in the presence of toxic cells. In contrast, the very poor survival of *D. pulex* was associated with greater physiological sensitivity and nearly uninhibited feeding on toxic *Microcystis*. Intermediate survival by *Diaptomus birgei* was positively associated with food selection capabilities and negatively associated with high physiological sensitivity and uninhibited feeding (De Mott *et al.*, 1991). When the copepod *Tigriopus californicus* was exposed to microcystin-LR, no toxicity was demonstrable even at high concentrations (Shaw *et al.*, 1997). As previously noted, it is important to recognize that the interpretation of effects on organisms may be different when exposure is to whole organisms (and therefore potentially to multiple toxins) rather than purified toxins.

Until recently, little information regarding the toxicity of *Microcystis* to aquatic animals was available, yet their impacts in aquatic systems are probably more ecologically significant than to terrestrial systems. Studies have largely concentrated on the effects of microcystin-producing cyanobacteria on terrestrial mammals, and it has sometimes been assumed that toxicity to zooplankton was caused by the same compound (Lampert, 1987). As Jungmann (1992) recently stated, "toxicity to higher animals cannot be of evolutionary adaptive value to *Microcystis*; nevertheless only a few publications deal with the response of MC-LR in lake ecosystems" (Peñaloza *et al.*, 1990; DeMott *et al.*, 1991). In some cases, in addition to microcystins, other bioactive compounds produced by *Microcystis* or *Planktothrix* (= *Oscillatoria*) *agardhii* may affect aquatic organisms even though they have no known effect on mammals. Bioassays have shown that *Microcystis* and *P.* (= *O.*) *agardhii* strains that were nontoxic to mice were highly toxic to brine shrimp (*Artemia salina*), daphnia (*Daphnia pulex*), and aquatic larval stages of the yellow fever mosquito (*Aedes aegypti*) (Nizan *et al.*, 1986; Kiviranta and Abdel-Hameed, 1994; Reinikainen *et al.*, 1995b). Evidence for toxic compounds in addition to microcystins has recently been found for several species (Peñaloza *et al.*, 1990; Jungmann *et al.*, 1991; Jungmann, 1992, 1995; Jungmann and Benndorf, 1994; Kiviranta and Abdel-Hameed, 1994; Reinikainen *et al.*, 1995b). Fractions obtained from *Microcystis* sp. were toxic to zooplankton, and although these fractions had a molecular weight similar to that of

MC-LR, toxicity was destroyed by boiling. Because microcystins are heat-stable to 160°C, it was inferred that other bioactive compounds are produced by this species (Peñaloza *et al.*, 1990; Bury *et al.*, 1996b). A new compound that is toxic to *Daphnia* was isolated and purified from water extracts of *Microcystis flos-aquae* PCC7806 (Jungmann and Benndorf, 1994; Jungmann, 1995). The molecular weight of a toxin isolated from *P.* (= *O.*) *agardhii* was less than 10,000, and the molecular weight of the toxin from *Microcystis* PCC7806 is 35,000 (Reinikainen *et al.*, 1995b). Some strains of *P.* (= *O.*) *rubescens* that were toxic to *Artemia* produced microcystin-RR, whereas other strains produced different, uncharacterized compounds (Feuillade *et al.*, 1996).

Among the zooplankton, there is an apparent differential toxicity of *Microcystis* to rotifers, copepods, and cladocerans (Gilbert, 1990), and a range of sublethal effects have been found (Tables 10 and 11). Copepods avoid handling *Microcystis* because of their highly selective chemosensory feeding behavior (Fulton and Paerl, 1987). Because certain species are apparently unaffected by exposure to microcystins, this allows for accumulation of toxins and for their potential transfer up the food chain (Watanabe *et al.*, 1992; Hanazato, 1996). In Lake Kasumigaura, Japan, where natural blooms of *Microcystis* are common, microcystin (75 to 1387 μg/g dry weight) was found to accumulate in the cladoceran *Bosmina fatalis*. Other dominant species, such as the cladoceran *Diaphanosoma brachyurum* and the copepod *Cyclops vicinus*, that co-occurred with the bloom did not accumulate microcystin because of feeding avoidance. Because mortalities of *B. fatalis* were high because of predation by fish and prawns, it was suggested that microcystins would be transferred to higher trophic levels (Watanabe *et al.*, 1992). In a recent field study in several lakes in Alberta, Canada, Kotak *et al.* (1996b) confirmed the presence of MC-LR in phytoplankton, zooplankton, and in the gastropods swamp lymnaea (*Lymnaea stagnalis*), marsh rams-horn (*Planorbella trivolvis* [as *Helisoma trivolvis*]), and tadpole physa (*Physella gyrina* [as *Physa gyrina*]) in amounts of up to 120 μg/g. The absence of detectable MC-LR in numerous other macroinvertebrates (e.g., damselfly and dragonfly larvae and chironomids) suggested that the toxin is not taken up from the water or that, given its high water solubility, it is rapidly eliminated. The MC-LR present in gastropods was thought to have been ingested. In the same lake system, MC-LR was not detected in the livers of northern pike (*Esox lucius*) or white sucker (*Catostomus commersonii*), although the HPLC method used would not have detected covalently bound microcystin (Kotak *et al.*, 1996a; Williams *et al.*, 1997b).

Crayfish (*Procambarus clarkii*) larvae survived acute exposures to toxic *Microcystis aeruginosa*, while juvenile crayfish tolerated toxic strains better than nontoxic ones. Because crayfish accumulate microcystins primarily in the intestine and hepatopancreas, this is not considered to pose a risk to human health if these organs are removed from the animals prior to consumption (Vasconcelos *et al.*, 2001).

There have been a few reports of microcystin accumulation in bivalves (Eriksson *et al.*, 1989; Vasconcelos, 1995; Prepas *et al.*, 1997; Watanabe *et al.*, 1997; Williams *et al.*, 1997a; Amorim and Vasconcelos, 1999), and although there do not appear to be any short-term lethal effects it is unclear whether these animals experience chronic health effects. When swan mussels (*Anodonta cygnea*) were exposed in laboratory aquaria to a strain of *Oscillatoria agardhii* in which the toxin was present at low concentrations (up to 40 to 60 μg *Oscillatoria* toxin/l), swan mussels accumulated up to 280 μg toxin per mussel. The highest concentrations were present in the hepatopancreas, and low levels were present in the intestine, gonad, muscle,

kidneys, and connective tissue. Because high concentrations of the toxin were present in the swan mussel tissues and because the toxins were lethal to mice, it was concluded that microcystins were not metabolized in the swan mussels. After 2 months in clean water, toxins were still detectable in the swan mussels (Eriksson *et al.*, 1989). However, recently it has been determined that microcystins can occur either as a covalent complex or as free toxin. Enzyme and HPLC assays for microcystin will detect only low levels of free toxin, whereas levels of covalently bound toxin can be thousands of times higher and can be detected only by other methods. Therefore, earlier studies in which only free toxins were measured may have significantly underestimated the concentrations of microcystins present in tissues (Williams *et al.*, 1997a).

When the freshwater clams *A. grandis simpsoniana* (= *Pyganodon grandis*) were exposed either to dissolved microcystin (MC-LR) or to natural blooms of *M. aeruginosa*, it was determined that the freshwater clams accumulate microcystins principally by ingesting toxic phytoplankton and minimally via uptake of the dissolved toxin. Freshwater clams exposed to relatively high (55 μg/l) concentrations of dissolved MC-LR for 3 days did not accumulate significant levels of toxin, whereas those exposed to the far lower toxin concentrations present in intact phytoplankton (< 4 μg/l) accumulated measurable levels (between 13 to 21 μg/l) after 4 days of exposure. The persistence of microcystins in freshwater clams for more than 21 days was considered to be important because of the potential transfer of toxins to mammals such as the muskrat, *Ondatra zibethicus* (Prepas *et al.*, 1997). When marine Mediterranean mussels, *Mytilus galloprovincialis*, were experimentally exposed daily to 10^5 cells/ml *Microcystis aeruginosa* over a 4-day period, they accumulated up to 16.0 μg MC-LR without any detectable ill effects. After 2 weeks without further exposure, low levels of microcystin were still present in the feces (Amorim and Vasconcelos, 1999).

The recent detection of microcystins in marine mussels (species not identified) from Vancouver Island and Prince Edward Island, Canada, and from the Netherlands, has identified the potential for a new type of shellfish intoxication (proposed as hepatotoxic shellfish poisoning [HSP]) that could represent a serious hazard to human health (Chen *et al.*, 1993; Luu *et al.*, 1993; Williams *et al.*, 1997a). The detection of microcystins in bivalves, the reports of venerupin shellfish poisoning (VSP), and the associated human hepatoxicity in Japan after people consumed toxic oysters and clams, and the fact that venerupin has not been chemically characterized (see section under *Prorocentrum*) has led to the suggestion that "VSP" may in fact have been associated with microcystins and not with the dinoflagellate *P. minimum* (Williams *et al.*, 1997a). From cultivated mussels collected from Prince Edward Island, Canada, Chen *et al.* (1993) detected 15 μg OA, 30 μg DTX-1, 0.2 μg microcystin-LR, and 0.02 μg nodularin per 100 g of shellfish. Williams *et al.* (1997) raised concerns that chronic exposure of humans to low concentrations of microcystins through shellfish consumption could increase the risk of cancer. The likelihood that many marine cyanobacteria produce protein phosphatase inhibtors has been raised; for example, 60% of 15 species produced such inhibitors (Holmes and Taylor, unpublished results in Chen *et al.*, 1993). The need to identify the bioorigin of such marine microcystins in the apparent absence of known microcystin producers is an important priority.

Approximately 1000 brown trout, *Salmo trutta*, died when *Anabaena flos-aquae* bloomed in Loch Leven, Scotland (Rodger *et al.*, 1994). Analyses of the water and fish determined that the most likely cause of mortality was exposure to microcystins and the consequent hepatotoxicity. The *A. flos-aquae* scum was highly hepatotoxic to mice in intraperitoneal assay. In addition to changes in the liver consistent with hepatoxin exposure, some pathological changes to the gills caused acute irritation and mucus production. The cause of the gill pathology was suggested to be (1) irritation due to high pH, (2) physical irritation due to the density of the bloom, (3) a direct toxic effect of the toxins, or (4) a combination of all of these factors. Hepatic pathology was indicative of toxic damage and may have resulted either directly through ingestion or absorption of toxins or secondarily after gill damage and a consequent increase in epithelial permeability that allowed toxin to accumulate in the fish's tissues (Rodger *et al.*, 1994).

Although algal blooms producing microcystins have been linked directly with fish mortalities (Table 7), the exact route of exposure is unclear. The majority of such fish kills have been attributed to hypoxic conditions resulting from the high oxygen demand caused by bloom respiration at night and/or bloom senescence (Bury *et al.*, 1998a). However, dissolved oxygen levels were 90% of normal values in Loch Leven, Scotland, when moribund brown trout were found after lysis of an *A. flos-aquae* bloom (Rodger *et al.*, 1994; Bury *et al.*, 1998a). Histopathological evidence was found for gill and liver damage that was similar to damage observed in fish treated with microcystins (Phillips *et al.*, 1985; Råbergh *et al.*, 1991; Tencalla *et al.*, 1994). Immersion trials using concentrations of aqueous extracts of the hepatotoxic cyanobacterial cells similar to those found in eutrophic environments did not cause deaths (Bury *et al.*, 1995). Consequently, the exact cause of natural death, that is, the biochemical mechanism underlying death following exposure to cyanobacterial blooms, has yet to be established (Bury *et al.*, 1998a).

Recent research has advanced a number of explanations for the fish kills (Bury *et al.*, 1998a): (1) fish may ingest toxins or toxic cyanobacteria, which may then result in liver malfunction (Tencalla *et al.*, 1994), (2) fish exposed to cyanobacterial extracts display a stress response (Bury *et al.*, 1995, 1996a) that may be detrimental to their health, or (3) toxic compounds affect fish-gill ion transport by inhibiting ATPase activities in the plasma membranes of the branchial epithelium (Gaete *et al.*, 1994; Bury *et al.*, 1996b; Zambrano and Canelo, 1996). Fish have been experimentally exposed to microcystins via a number of routes, including intraperitoneal injection, oral ingestion (fed *ad libitum* or by gavage), and bath immersion (Phillips *et al.*, 1985; Sugaya *et al.*, 1990; Råbergh *et al.*, 1991; Andersen *et al.*, 1993; Johnston *et al.*, 1994; Keshavanath *et al.*, 1994; Tencalla *et al.*, 1994; Williams *et al.*, 1995, 1997b; Carbis *et al.*, 1996a, 1996b; Kotak *et al.*, 1996a; Sahin *et al.*, 1996; Bury *et al.*, 1997, 1998a, 1998b). In general, fish are insensitive to short-term immersion in toxic microcystin solutions (Phillips *et al.*, 1985; Sugaya *et al.*, 1990; Johnston *et al.*, 1994; Tencalla *et al.*, 1994; Bury *et al.*, 1995). When exposed to freeze-dried toxic *Microcystis* in water, rainbow trout, *Oncorhynchus mykiss*, did not die and showed no significant clinical or histological changes over a 96-h period (Tencalla *et al.*, 1994). However, Peñaloza *et al.* (1990) demonstrated that a soluble fraction obtained from *Microcystis* sp. was lethal to mosquitofish, *Gambusia affinis*. As recently demonstrated with zooplankton (see above), it is possible that fish are also sensitive to additional bioactive compounds that are produced by *Microcystis*. Intraperitoneal

exposure to microcystin causes tissue damage in the gills, liver, kidneys, and cerebellar and optic neurons (Phillips *et al.*, 1985; Råbergh *et al.*, 1991; Carbis *et al.*, 1996b; Kotak *et al.*, 1996a). In common carp, *Cyprinus carpio*, microcystin damaged the branchial epithelium, so impaired health or death may result from respiratory failure or an imbalance in ionic homeostatis (Carbis *et al.*, 1996a, 1996b). In some treatments, exposure of common carp to microcystin via gavage caused changes, indicating mild liver damage and changes in the cation-anion equilibrium. The results from gavage exposure indicated that acute toxicity is unlikely to occur in wild carp populations, but chronic poisoning may follow repeated sublethal exposures (Carbis *et al.*, 1996a).

Although the skin epithelia of freshwater fish form a barrier to microcystin transport (Tencalla *et al.*, 1994; Bury *et al.*, 1995), there are inconclusive findings regarding the gills as possible routes of exposure (Gaete *et al.*, 1994; Tencalla *et al.*, 1994; Bury *et al.*, 1995, 1998a; Carbis *et al.*, 1997). One suggested mechanism for toxicity is that microcystin inhibits the enzymes of the gill microsomal fraction that are involved in ion pumps and exchanges. Fish may die during a bloom because microcystins affect the ability of the gill to maintain homeostasis of the internal medium. Freshwater fish maintain a large ion concentration gradient between their extracellular fluids and the dilute aquatic environment. Ions lost by osmosis from the branchial circulation into the water are replaced by active ion uptake from the medium through active transport sites on the gill epithelium. Microcystin inhibition of the transport processes exchanging calcium or sodium via the gill chloride cells can lead to osmoregulatory disruption. MC-LR inhibited the Ca^{2+}, Na^{+}, and K^{+} ATPases, which are the major enzymes involved in the transport of ions. Microcystins block the hydrolysis of phosphorylated proteins and inhibit the aspartic dephosphorylation step of the sodium pump enzymes (Gaete *et al.*, 1994; Zambrano and Canelo, 1996). However, Bury *et al.* (1998a) could find no evidence that inhibition of ionic exchange in tilapia gills was due to microcystin activity, but rather found that it was due to the action of fatty acids. Fatty acids produced by *M. aeruginosa* inhibited fish-gill Na^{+}/K^{+} ATPase (Bury *et al.*, 1996b, 1998a), again providing evidence that *Microcystis* produces additional bioactive compounds that can harm aquatic organisms. Bury *et al.* (1998a) suggested that lipids, rather than MC-LR, interfere with gill basolateral membrane ion-extrusion mechanisms and thus may contribute to the fish deaths seen after lysis of a cyanobacterial bloom. Interestingly, the fatty acid profile of *M. aeruginosa* includes MGDG and DGDG (Bury *et al.*, 1998a) (Table 12), both of which are implicated in the hemolytic and ichthyotoxic properties of *Karenia mikimotoi* and *Chrysochromulina polylepis* (see section on hemolysins).

Trout died within 96 h when gavaged with an amount of microcystins equivalent to that which passed through the gills within 18 h in aqueous exposure tests (i.e., 1440 mg freeze-dried algae/kg body weight or 6600 μg microcystin/kg body weight) (Tencalla *et al.*, 1994). Following intraperitoneal injection, the main uptake route of microcystin in salmonids is the gastrointestinal tract (Tencalla *et al.*, 1994; Bury *et al.*, 1998b), and toxicity is manifested as massive hepatic necrosis (Råbergh *et al.*, 1991; Tencalla *et al.*, 1994; Kotak *et al.*, 1996a; Bury *et al.*, 1997). Lethal doses of MC-LR induced a total loss of parenchymal architecture of the liver and necrosis of the hepatocytes (Råbergh *et al.*, 1991). Unlike in mammals, hemorrhage of the liver was rare in fish (Råbergh *et al.*, 1991; Kotak *et al.*, 1996a), and death was

considered to be by general hepatic failure caused by massive hepatocyte necrosis (Kotak *et al*., 1996a) rather than death by hypovolumic shock, as reported for mice (Carmichael, 1992). When common carp were gavaged with a single sublethal bolus dose of microcystin, damage to the renal proximal tubular cells of the kidney and to the hepatocytes of the liver was seen as early as 1 h after treatment, while pathological changes in the intestinal mucosa were reported after 12 hours (Fischer and Dietrich, 2000).

When monthly samples of common carp that had been exposed to a natural bloom of *Microcystis aeruginosa* were examined, hepatic lesions were found in more than 50% of the fish from February to April. This pathology was considered to be consistent with the possibility that microcystins were absorbed through the intestine. However, degenerative changes in the branchial epithelium of carp were also consistent with toxic injury caused by microcystins. The branchial injury was accompanied by a reduction in serum sodium and chloride concentrations (Carbis *et al*., 1997), which confirmed previous experimental findings (Carbis *et al*., 1996a, 1996b). Previous investigations indicated that branchial injury is more likely to occur when microcystins have access to the bloodstream, because carp are not particularly susceptible to branchial injury from microcystins dissolved in water (Carbis *et al*., 1996a). Therefore, it appears that the differences noted in the effects of *Microcystis* on fish via the gills may depend on the species, habitat, route by which microcystin reaches the gills (i.e., internal or external), and the active compounds to which fish are exposed (pure microcystin or other bioactive compounds).

In addition to the association of microcystins with acute mortalities, a number of sublethal effects on poikilotherms have also been demonstrated. In zebrafish (*Danio rerio*) (Oberemm *et al*., 1997) and frogs (Gromov *et al*., 1995), microcystins have been experimentally shown to produce gross malformations and high mortalities during embryonic development, to affect behavior and reproductive success (Baganz *et al*., 1998); and to influence growth rates, stress responses, and ionic regulation. Sublethal effects of immersion in microcystin solutions include increasing plasma cortisol and glucose levels and decreasing plasma Na^+ and Cl^- concentrations during a 4-h exposure (Bury *et al*., 1995, 1996a). Some fish species may be susceptible to toxicity via ingestion of microcystin, but others — such as tilapia, *Oreochromis niloticus*, and silver carp, *Hypophthalmichthys molitrix* — decrease grazing activity as concentrations of toxic *Microcystis* increase (Beveridge *et al*., 1993; Keshavanath *et al*., 1994).

In August 1996, routine monitoring for *M. aeruginosa* was begun in the Jacarepaguá Lagoon, Rio de Janeiro, Brazil, with bimonthly collections of water, sediments, and fish samples. By the first week of November, an atypical surface bloom of *M. aeruginosa* appeared. Microcystin (12 μg/l) was confirmed in the plankton samples (the relative abundance of *M. aeruginosa* was 13% of the total plankton mass). By the end of November, microcystins were detected in the liver and viscera of fish (unspecified species) and in the ovaries by January, 1997. Ranges of 1 to 150 μg/g and 3 to 15 μg/g microcystins were found in the viscera and liver, respectively. More significant findings demonstrated that microcystin concentrations in fish muscle were close to or above the recommended limit (0.04 μg/kg/day) for human consumption. The confirmation of microcystins in fish fillets warrants concern about potential human health implications (Magalhães and Azevedo, 1998;

Magalhães *et al.*, 2001) and suggests that fish for consumption should be tested for toxins in waterbodies known for microcystins.

In several reports, ill health in salmonids from what appears to be chronic exposure to microcystins has been deemed to be a new syndrome, "netpen liver disease" (NLD) (Kent *et al.*, 1988; Kent, 1990; Andersen *et al.*, 1993; Williams *et al.*, 1997b). Although the etiology of NLD has not been definitively proven, field and experimental evidence strongly suggests that NLD is caused by exposure of fish to naturally occurring microcystins. However, the bioorigin of microcystins in this area is not known and cyanobacterial blooms are typically uncommon (Horner *et al.*, 1997). NLD is characterized by severe necrosis and megalocytosis of the liver and has been observed in netpenned Atlantic salmon, *Salmo salar*, chinook salmon, *Oncorhynchus tshawytscha*, and Donaldson steelhead trout (rainbow trout × steelhead trout), *O. mykiss*, along the Pacific Northwest since 1986 (Kent *et al.*, 1988; Kent, 1990). Liquid chromatography-linked protein phosphatase bioassay analysis of liver extracts taken from Atlantic salmon affected by NLD showed the presence of a protein phosphatase inhibitor that was chromatographically indistinguishable from MC-LR. Intraperitoneal injection of MC-LR into healthy Atlantic salmon recreated the pathology of NLD, which included diffuse necrosis and hepatic megalocytosis (Andersen *et al.*, 1993). Latest findings indicate that a zooplankton vector is involved (Andersen *et al.*, 1993; Williams *et al.*, 1995), and MC-LR was detected in copepods and crab larvae collected from NLD-affected salmon farms (McReady *et al.* submitted, cited in Williams *et al.*, 1997a).

During the summer of 1995, about 20 spot-billed ducks died from unnatural causes in a pond (Shin-ike) in Nishinomiya, Hyogo Prefecture, Japan. The suspected cause was the sudden appearance of a cyanobacterial bloom identified as *M. aeruginosa*. Lyophilized algal cell powder from Shin-ike contained large amounts of microcystins that showed acute toxicity in mice, whereas algal samples from a neighboring pond (with no bird mortalities) were not acutely toxic. Bird necropsies showed necrotic livers that were severely jaundiced (dark-green), suggestive of microcystin toxicity. The results suggested that the cause of the deaths was the sudden appearance of toxic *Microcystis*. Apparently, there was a significant influx of untreated sewage into the pond following the Hanshinn earthquake of January 1995. Eutrophic conditions likely contributed to the development of the bloom (Matsunaga *et al.*, 1999). Also in the summer of 1995 in Jehay, Belgium, mortalities of about 30 ducks and herons coincided with a massive bloom of *M. aeruginosa*. HPLC and rat hepatocyte assays confirmed the presence of microcystins from bloom material, but animal tissues were apparently not examined (Wirsing *et al.*, 1998).

Q. NODULARIN

A bloom of *Nodularia spumigena* in Lake Alexandrina, Australia, was the first documented report of an animal mortality event associated with cyanobacteria (Francis, 1878). Since that time, *N. spumigena* has been associated with several livestock, canine, and wildlife mortality events (Table 7), principally occurring in brackish waters in Australia, New Zealand, and the Baltic Sea (Carmichael *et al.*, 1988; Sivonen *et al.*, 1989; Baker and Humpage, 1994; Jones *et al.*, 1994). As with

other cyanobacteria, most of these events are caused by the consumption of nodularin by terrestrial animals (Table 7).

Thus far, only *N. spumigena* has been determined to produce nodularin (Bolch *et al.*, 1999), which is a cyclic pentapeptide hepatotoxin that is, like microcystin, a protein phosphatase 1 and 2A inhibitor and tumor-promoter (Yoshizawa *et al.*, 1990; Honkanen *et al.*, 1991; Carmichael 1992; Rinehart *et al.*, 1994). Several nodularins have now been characterized (Rinehart *et al.*, 1994). In rodents, nodularin induces enlarged hemorrhagic livers, centrilobular necrosis, lysis of hepatocytes, and death within 1 to 2 h (Runnegar *et al.*, 1988). Nodularin promotes liver tumors (Yoshizawa *et al.*, 1990) and is also considered to be a direct liver carcinogen (Ohta *et al.*, 1994). Not all strains of *Nodularia* are toxic (Bolch *et al.*, 1999). Both in experimental animals and based on observations in field reports, the toxicity and pathogenicity of nodularin is very similar to that of microcystin (Runnegar *et al.*, 1988; Sivonen, 1996). Along with microcystin, nodularin has also been found in marine mussels (Chen *et al.*, 1993), but the biogenic origin of these toxins is currently unknown.

A few studies have demonstrated effects of nodularin on zooplankton. Acute toxicity experiments with purified toxins showed that four species of zooplankton differed markedly in their physiological sensitivity to nodularin. The copepod *Diaptomus birgei* (48-h LC_{50}, 0.52 to 1.25 μg/ml) and the cladoceran *Daphnia hyalina* (48-h LC_{50}, 3.9 μg/ml) were the most sensitive; *Daphnia pulicaria* was the least sensitive (48-h LC_{50}, 14.1 μg/ml) (De Mott *et al.*, 1991). Sublethal effects such as reduced feeding and fecundity have also been noted (Table 10). The copepod *Eurytemora affinis* fed less actively on the toxic strains of *Nodularia* sp. than on the nontoxic strains (Engström *et al.*, 2000), but when the copepod had been fed toxic *Nodularia* sp. for 3 to 5 days, their rates of mortality increased (Koski *et al.*, 1999). Similarly, there was reduced grazing on toxic *N. spumigena* by mysid shrimp *Mysis mixta*, when compared with grazing on nontoxic strains of *N. sphaerocarpa* and *Aphanizomenon flos-aquae* (Engström *et al.*, 2001).

Few reports have associated nodularin with aquatic animal mortalities, although recently, fish mortalities in the Black Sea, Georgia, coincided with *N. spumigena* blooms (Table 7). However, it was noted that other plankton, such as *Anabaenopsis* or *Rhizosolenia*, were also present in the bloom, so it is unclear to what extent *Nodularia* alone was responsible for the fish kills (Devidze, 1998). Fish and crabs have been reported to avoid the waters of the estuaries during *Nodularia* blooms (Potter *et al.*, 1983).

There are potential human health risks associated with shellfish that have consumed *Nodularia*. Some tissues from edible blue mussels, *Mytilus edulis*, tested during an *N. spumigena* bloom in Peel-Harvey Inlet, western Australia, were shown to be toxic to mice. Mice showed characteristic hepatic hemorrhage and hepatocyte degeneration. Administration of extracts of nonintestinal tissues did not result in any mouse toxicity. Only the gastrointestinal tracts in the mussels retained toxicity; this toxicity declined after the *Nodularia* bloom ended. It was recommended that edible mussels should not be collected for human consumption during a *Nodularia* bloom (Falconer *et al.*, 1992). Mussels that were found to be ingesting *Nodularia* initially showed little sign of ill health or pathology. However, after several months of exposure, slight hepatopancreatic tubular lesions developed, and extensive secretion of algal pigment by diapedesis of engorged hematocytes was evident. It was suggested that long-term effects on the health of mussels should be investigated

(Langdon, 1990). Extracts from *N. spumigena* from Orielton Lagoon, Tasmania, elicited histological alterations in the livers and pyloric ceca of Atlantic salmon, *Salmo salar*, but additional information was not provided (A. Goodsell, personal communication, in Jones *et al.*, 1994). Low concentrations of nodularin were also detected recently in livers of flounder and cod caught in the Baltic Sea (Sipia *et al.*, 2001). The potential chronic effects of nodularin exposure in aquatic animals merits further investigation.

R. REACTIVE OXYGEN SPECIES

The raphidophytes *Chattonella marina, C. antiqua, Fibrocapsa japonica*, *Heterosigma akashiwo*, and *Olisthodiscus luteus* and the dinoflagellate *Cochlodinium polykrikoides* generate reactive oxygen species (ROS) (e.g., superoxide anions, hydroxyl radicals, singlet oxygen, and hydrogen peroxide) (Shimada *et al.*, 1989, 1991; Tanaka *et al.*, 1992, 1994; Oda *et al.*, 1992a, 1992b, 1994, 1995, 1997; Kim *et al.*, 1999a, 1999b, 2000b; Twiner and Trick, 2000), which can have adverse effects on aquatic organisms. During photosynthesis, superoxide and hydrogen peroxide are generated as a result of the photoreduction of dioxygen that occurs in illuminated chloroplasts (Mehler, 1951). Environmental stress can trigger ROS production, which disturbs the steady-state balance of prooxidants and antioxidants (Okamoto and Colepicolo, 1998). The toxicity of oxygen radicals to biological systems has been well documented (Fridovich, 1978; Cunningham and Capone, 1992). At the cellular level, the damaging effects of ROS include denaturation of enzymes, depolymerization of polysaccharides, DNA damage that results in genetic mutation (Cunningham and Capone, 1992), and severe cellular injury or death (Okamoto and Colepicolo, 1998). Lipid molecules are susceptible to oxygen-radical-induced peroxidation via the removal of hydrogen radicals, and such damage can lead to destruction of membrane integrity (Cunningham and Capone, 1992). The production of ROS by microalgae appears to principally affect fish (Tanaka *et al.*, 1992; Yang *et al.*, 1995; Ishimatsu *et al.*, 1996a, 1996b), although other organisms may also be affected (Tables 10 and 11).

Thus far in the wild or in aquaculture, raphidophytes have, with the exception of one case (Table 5) (and one unconfirmed case, see Section T.3) been documented to be only ichthyotoxic. Some fish mortalities (Table 5) may be attributable to the production of brevetoxin-like compounds (see brevetoxins), to ROS, or to a combination of both. ROS contribute to pathological changes in the gills of fish (see below), and the brevetoxin-like neurotoxins impair cardiac function (Endo *et al.*, 1992). The hydroxyl radical generated by *C. marina* is the most toxic ROS known (Kim *et al.*, 1999b). *Chattonella marina* has many small and large verruciform protrusions on the cell surface, and these are probably involved in the production of superoxide anions (Shimada *et al.*, 1993). All raphidophytes tested that produced ROS inhibited the growth of the marine bacterium *Vibrio alginolyticus* (Oda *et al.*, 1992b, 1997; Kim *et al.*, 1999b). The production of small quantities of hydrogen peroxide has also been detected in *Prorocentrum micans*, *Akashiwo sanguinea* (= *Gymnodinium sanguineum*) Hansen and Moestrup (Daugjberg *et al.*, 2000), and *Alexandrium tamarense* (Kim *et al.*, 1999a), but to what extent these concentrations may be significant is currently unclear. An ROS has also been

identified presumptively in *Karenia mikimotoi* (as *Gymnodinium aureolum*, Gentien, 1998).

1. *Chattonella* spp.

Chattonella spp. have caused significant fish mortalities in the Far East, particularly in Japan (Table 5). In the summer of 1972, in Harima-Nada, eastern Seto Inland Sea, a *C. antiqua* red tide caused a mass mortality of about 14 million cultured yellowtail, *Seriola quinqueradiata*, worth more than 7 billion yen (Okaichi, 1989; Imai *et al.*, 1998). When fish are exposed to *Chattonella* spp., a series of histopathological and physiological changes occur in the gills. The stripping of the mucus goblet cells and the mucus coat, along with the structural alteration in the chloride cells, leads to impaired osmoregulation, the development of edema in the gill lamellae, and reduced oxygen transfer, which results in asphyxiation (Matsusato and Kobayashi, 1974; Shimada *et al.*, 1983, 1991; Endo *et al.*, 1985; Toyoshima *et al.*, 1985, 1989; Sakai *et al.*, 1986; Kobayashi, 1989; Kobayashi *et al.*, 1989; Oda *et al.*, 1992b; Ishimatsu *et al.*, 1996a; Hishida *et al.*, 1997). A decrease in the oxygen partial pressure of arterial blood and an increase in plasma catecholamines are early physiological changes observed in fish after exposure to *Chattonella* spp. (Ishimatsu *et al.*, 1990, 1991; Tsuchiyama *et al.*, 1992). Yellowtail were exposed to two strains of *C. marina* that had been subjected to differing light-dark regimes, filtering, mechanical disruption, freezing, or disturbance by mechanical agitation; the highest fish mortality (19 out of of 20) occurred in the presence of intact cells. The production of oxygen radicals was significantly affected by the various experimental treatments, and there was a clear correlation between oxygen radical production and toxicity. Dead cells or cell-free filtrate were not toxic to fish (Ishimatsu *et al.*, 1996a). The generation of oxygen radicals by *C. marina* depends on the growth phase; the rate of superoxide and hydrogen peroxide generation was highest during the exponential-growing phase and subsequently decreased to one-fifth of its maximal level in the stationary-growth phase (Oda *et al.*, 1995).

In April-May 1996 a mortality of an estimated 1700 tonnes of cultured southern bluefin tuna, *Thunnus maccoyi*, in Boston Bay, Australia, coincided with a bloom of *Chattonella marina*. Counts of up to 6.6×10^2 cells/ml were recorded. *Chattonella* cultures tested positive for brevetoxin-like compounds (0.03pg PbTx-3 equivalent/cell in log phase). Fish were observed to be distressed, swimming in a haphazard manner on the surface, and in some cases, gasping. No other finfish or shellfish in the area were reported dead. Excess mucus was present on the gills of the fish. Gill pathology showed marked epithelial swelling and separation of the epithelium. Breve-like toxins were detected in the livers of the tuna by using a sodium-channel receptor binding assay with up to 142 μg per 100 g of tissue. A likely scenario for mortality caused by *Chattonella* spp. is that fish die because of the direct toxic effect of oxygen radicals on the gills in combination with the cardiotoxic effects of brevetoxins (Ishimatsu *et al.*, 1990; Hallegraeff *et al.*, 1998; Munday and Hallegraeff, 1998).

2. *Heterosigma akashiwo*

In the Seto Inland Sea, Japan, the economic damage caused by *Heterosigma akashiwo* red tides totaled 2 billion yen from 1972 to 1987 (Honjo, 1993). Blooms

of *H. akashiwo* (or as *Olisthodiscus luteus*) have also been associated with fish kills in British Columbia since 1976 (Table 5). In 1986, a bloom of more than 2×10^5 cells/ml led to losses to the salmonid industry of at least $2.5 million, which at the time represented a third of the value normally produced (Taylor, 1993). Penned salmonids die when concentrations of *H. akashiwo* reach several million per l, and some species — such as rainbow trout, *Oncorhynchus mykiss*, and Atlantic salmon, *Salmo salar* — are more sensitive to *Heterosigma* than others, such as the chinook salmon, *O. tschawytscha* (Taylor and Haigh, 1993). In early January 1989, a dense phytoplankton bloom of *H. akashiwo* (originally as *H.* cf. *akashiwo*) was associated with chinook salmon kills in New Zealand (Table 5). During the mortality, cell concentrations of up to 2×10^3 cells/ml were recorded. Histopathology of affected salmon showed degenerative changes of the branchial epithelium and vasculature, including swelling of the respiratory epithelium, mucus discharge, and separation of the secondary epithelium from the pillar cells by edema. Impairment of respiratory and osmoregulatory function of the gills was concluded to be the cause of death (Chang *et al.*, 1990).

When juvenile red seabream, *Pagrus major*, were exposed to cultures of *H. akashiwo*, no abnormal behavior was noted at a cell density of 3.4×10^5 cells/ml, but fish were paralyzed and eventually died when the cell density exceeded 1.2×10^6 cells/ml. When fish were experimentally exposed to a density of 3.0×10^4 cells/ml of *H. akashiwo* obtained from an ongoing 1995 red tide that was responsible for wide-scale fish kills, these fish showed a transient but not fatal paralysis. Fish were dying in the wild at concentrations of 1.0×10^5 cells/ml (Khan *et al.*, 1996c). *Heterosigma akashiwo* generates reactive oxygen intermediates that probably first attack the membranes of the epithelial cells of the secondary gill lamellae. When *H. akashiwo* cultures were disturbed, the release of superoxide increased, thus mimicking the situation that occurs when water containing *H. akashiwo* passes over the secondary lamellae of finfish. The reactive oxygen intermediates generated by *H. akashiwo* probably first attack the membranes of the epithelial cells of the secondary lamellae, causing lipid peroxidation damage, inactivation of ATPase of the epithelial cell plasma membrane, and edema in the gill lamellae (Yang *et al.*, 1995).

Heterosigma akashiwo (as *O. luteus*) has been reported to affect numerous species of zooplankton and ichthyoplankton both lethally and sublethally (Tables 10 and 11) (Verity and Stoecker, 1982; Egloff, 1986 and references therein). Undefined cell concentrations or cell-free filtrate from *H. akashiwo* (as *O. luteus*) cultures produced teratologies or mortality in echinoderm eggs and larvae (Wilson, 1981).

3. Olisthodiscus luteus

The copepod *Pseudodiaptomus marinus* was fed different plankton species, and extremely high mortalities were observed (32% by the second day) when this copepod was exposed to *Olisthodiscus luteus* (Uye and Takamatsu, 1990). That ROS were involved in the mortality still needs to be verified.

S. SPECIES WITH MULTIPLE TOXINS

There are numerous species or strains of microalgae that have been shown to produce multiple toxins or bioactive compounds (Table 1). In some cases, the

coincidental occurrence of a particular species for which toxins have already been described at the site of an aquatic mortality event may have led researchers to make assumptions about the cause of the mortality. However, more and more examples are being found in which other minor (or less well studied) toxins are now being implicated. In some cases, it is often unclear which compounds are involved. Many of the species producing multiple toxins and bioactive compounds have been discussed in other sections; the reader should refer to Table 1 and its text reference column to determine where in this article particular species or toxins are discussed.

1. Dinoflagellates

a. Cochlodinium spp.

Occasionally, blooms of *Cochlodinium* spp. have been noted to coincide with mortalities of aquatic organisms (Table 2). In 1985, coral reefs at Cañon Island, Costa Rica, and Uva Island, Panama, were affected during a dinoflagellate bloom dominated by *C. catenatum* (97% by relative abundance); *Alexandrium monilatum* (1.4%) was also present. At Cañon Island, surface waters to depths of 2 to 3 m were colored red-yellow by viscous foam, which was presumably produced by the bloom. Numerous fish were affected, with hundreds of scarids, balistids, acanthurids, pomacentrids, and tetraodontids, as well as hermit crabs, brachyuran crabs, and gastropods found dead on the beach. Some shallow-water corals were also affected, especially *Pocillopora elegans*, *P. damicornis*, and the azooxanthellate coral *Tubastrea coccinea*. At Uva Island, numerous pocilloporid corals had bleached and were sloughing tissues. It was suggested that the mortality was possibly caused by a combination of toxicity, oxygen depletion, and smothering by mucus produced during the blooms. Adhesion of mucus to the polyps, which interfered with polyp expansion, was deemed the most likely cause of coral mortality (Guzmán *et al.*, 1990).

In late August 1985, a small-scale *Cochlodinium* sp. red tide (4 to 5×10^2 cells/ml) occurred in Harima-Nada, Japan, where cultured yellowtails, *Seriola quinqueradiata*, showed unusual behavior, possibly because of toxin exposure (Yuki and Yoshimatsu, 1989). During mid-June 1990, an unusual red tide event, a toxic bloom of *Cochlodinium* sp., occurred from Weitou Bay to Quanzhou Bay, China. A large variety of fish, shellfish, and jellyfish species were killed (Table 2). Interestingly, crustaceans such as crabs, lobsters, and shrimp were not affected (Qi *et al.*, 1993a).

Cultured straight-hinge larvae of eastern oysters, *Crassostrea virginica*, were initially deformed when cultured in water containing *Cochlodinium polykrikoides*, but after the water was filtered they were able to reach apparently normal umbo stage. In experimental exposures, when densities of the dinoflagellates were approximately 5×10^2 cells/ml, calcium uptake rate in the oyster larvae was depressed to approximately 10% of that of the control, and high mortality occurred. At densities greater than 1.0×10^4 cells/ml, calcium uptake was negligible, and the larvae died promptly (Ho and Zubkoff, 1979).

Although recognized to be a potential risk to aquaculture facilities in Japan, two *Cochlodinium* species, *C. polykrikoides* (= *C. heterolobatum*, *Cochlodinium* type '78) and *Cochlodinium* sp., were demonstrated to be ichthyotoxic in experimental

assays. Juvenile slipmouths, *Leiognathus nuchalis*, were exposed to 1.74 to 6.51 × 10^3 *C. polykrikoides* cells/ml and 1.0 × 10^1 to 1.79 × 10^3 *Cochlodinium* sp. cells/ml; after 48 h, mortalities were 20 to 40% and 80%, respectively. Seawater filtered from the cultures had no effect on the fish (Onoue *et al.*, 1985; Yuki and Yoshimatsu, 1989). Three toxic fractions — neurotoxic, hemolytic, and hemagglutinative — were isolated from *Cochlodinium* sp. (as *Cochlodinium* type '78 Yatushiro). Ichthyotoxicity of the three fractions was tested on juvenile red sea bream, *Pagrus major*. When exposed to 0.02% of the neurotoxic fraction, the fish behaved as though they were anesthetized, and a marked color change or whitening of their bodies was observed. Labored breathing and respiratory arrest resulted in death in 8 to 10 min. When exposed to 0.02% of the hemolytic fraction, fish developed the following symptoms: violent convulsions, loss of balance, labored breathing, edema, hemorrhaging, excess mucus production in the gill lamellae, and respiratory arrest. Fish died in 20 to 30 min. The HD_{50} (hemolytic unit) was estimated to be 0.5 HU per mg in *Cochlodinium*. The reaction of fish to the hemagglutinin fraction was similar to that of fish to the hemolytic fraction. When mice were injected i.v. with the hemagglutinin fraction (20 μg), they died from respiratory paralysis. The lethal dose was 2 to 4 mg/kg (Onoue and Nozawa, 1989a). Two unique paralytic shellfish poisons were also separated from *C. polykrikoides* (as *Cochlodinium* type '78) and were characterized as a zinc complex of carbomoyl-*N*-sulfo-11α-hydroxyneosaxitoxin sulfate (Ic-1) and its 11β epimer (epi-Ic-1). Intraperitoneal injection of Ic-1 into mice resulted in signs characteristic of PSP: ataxia, convulsion, and respiratory paralysis. When exposed to 150-200 ppm Ic-1 in seawater, juvenile red sea bream displayed loss of balance, labored breathing, and respiratory arrest. On mild acid hydrolysis, Ic-1 was converted into GTX1 and epi-Ic-1 into GTX4 (Onoue and Nozawa, 1989b). To my knowledge, since these initial studies there have have been no reports further identifying PSP-like toxins from *C. polykrikoides*. Hemolytic activity produced by *C. polykrikoides* was shown recently to be associated with the fatty acids docosahexaenoicacid (C22:6n3) (25.3%) and eicospentaenoic acid (C20:5n3)(15.3%) (Lee, 1996) (Table 12).

More recently, blooms of *C. polykrikoides* caused fisheries losses amounting to $95.5 million in Korea (Kim, 1998; Kim *et al.*, 1999a). The production of bioactive compounds such as ROS in *C. polykrikoides* and their potential roles in mortalities were investigated (Lee, 1996; Kim *et al.*, 1999a). When live flatfish *Paralichthys olivaceus* were exposed to *C. polykrikoides*, lipid-induced peroxidation was linearly proportional to algal cell density. Edema and histopathological changes in the gills were also observed (Kim *et al.*, 1999a). Because oxygen radicals are generated from *C. polykrikoides*, Kim *et al.* (1999a) suggested that it would be reasonable to assume that lipid peroxidation of fish gill tissue is a result of oxygen-radical-dependent oxidation. Further, lipid peroxidation has been linked to increased solute permeability of the vesicle membranes that control swelling and lysis, which could then account for edema in the gills. Because structural and functional changes in gill cells are induced by ROS, these effects may also reduce the capability for oxygen transfer in the gills. Additionally, because hydroxyl radicals also induce mucus secretion in fish gills, the combination of effects induced by ROS will result in a fish kill (Kim *et al.*, 1999a). The increased susceptibility of pelagic fish such as black scraper, *Thamnaconus septentrionalis*, red seabream, *Pagrus major*, beakperch, *Oplegnathus fasciatus*, and seaperch, *Malakichthys wakiyae*, to the effects of *C. polykrikoides*

when compared to benthic fish such as flounder, *Paralichthys olivaceus*, and rockfish, *Sebastes inermis*, was recently demonstrated. When experimentally exposed to *C. polykrikoides*, the activities of the ion-transport enzymes, carbonic anhydrase and Na^+/K^+-ATPase, in the gills were significantly decreased in relation to increasing algal cell density and exposure time. A drop in blood pH and oxygen partial pressure (pO_2) was also measured in red sea bream and flounder when exposed to *C. polykrikoides* (Kim *et al.*, 2000a).

Blooms of *Cochlodinium* sp. (likely *C. polykrikoides*) caused substantial mortalities of farmed Atlantic salmon, *Salmo salar*, and chinook salmon, *Oncorhynchus kisutch*, in British Columbia that resulted in an economic loss of CAN $2 million. When cells exceeded 5×10^2 cells/ml fish stopped feeding and when concentrations reached more than 2×10^3 cells/ml mortalities occurred. Experimental field bioassays with salmon smolts demonstrated lethality after 120 min exposure with over 90% mortality after 500 min when cell concentrations varied from 2.7 to 10.8×10^3 cells/ml. In fish bioassays at densities of above 1×10^3 cells/ml, fish showed signs of respiratory distress, loss in equilibrium, and an inability to stay in the water column. Pathological change to the gills inlcuded edema and separation of the lamellar epithelium (Whyte *et al.*, 2001).

2. Cyanobacteria

a. Lyngbya majuscula

There have probably been more potentially toxic compounds identified from *Lyngbya majuscula* than from any other microalgal species discussed herein (Table 1 [not all compounds known to be produced by *Lyngbya* are included]). Most of the toxic compounds have been verified through experimental study, and it is unclear to what extent these compounds affect aquatic organisms in the natural environment. It has been speculated that many of the bioactive metabolites produced by *Lyngbya* function in nature as mechanisms that protect this alga from predation by a variety of groups (e.g., crustaceans, herbivorous fish, and gastropods) (Orjala *et al.*, 1995a; Thacker *et al.*, 1997). *Lyngbya majuscula* is common in marine tropical areas and has principally been associated with contact skin dermatitis in humans (Grauer and Arnold, 1961; Moikeha and Chu, 1971; Moikeha *et al.*, 1971); it has caused numerous outbreaks of dermatitis in the Hawaiian Islands and in Japan (Moore, 1984). Apart from laboratory experimentation with small mammals and field observations in humans, it is unclear if contact dermatitis associated with *L. majuscula* is a problem for aquatic animals such as marine mammals or sea turtles. A fatal human intoxication caused by the consumption of meat from a green turtle, *Chelonia mydas*, was recently associated with lyngbyatoxin-a in Madagascar (Yasumoto, 1998; Yasumoto and Satake, 1998). Observed ecological impacts of *L. majuscula* blooms in southeastern Queensland, Australia, include localized seagrass loss and poor harvests of crab and fish (O'Neil *et al.*, 2000).

Several of the compounds isolated from *Lyngbya* have been experimentally demonstrated to be toxic to fish, molluscs, and *Artemia* brine shrimp. Curacin A, kalkipyrone, lyngbyabellin, and tanikolide are potent *Artemia* toxins (Gerwick *et al.*, 1994; Graber and Gerwick, 1998; Singh *et al.*, 1999; Milligan *et al.*, 2000b) with unknown effects on natural zooplankton populations; barbamide is toxic to the

mollusc *Biomphalaria glabrata* at LD_{100} = 100 μg/ml (Orjala and Gerwick, 1996). Toxicity experiments on goldfish, *Carassius auratus*, showed that pure antillatoxin is among the most ichthyotoxic metabolites isolated to date from marine plants (LD_{50} = 0.05 μg/ml) – it is exceeded in potency only by the brevetoxins (LD_{50} = 0.003 μg/ml against the freshwater zebrafish *Danio rerio* [Lin *et al.*, 1981]) (Orjala *et al.*, 1995b). It was demonstrated recently that antillatoxin is neurotoxic in primary cultures of rat cerebellar granule cells, and, like brevetoxin, is an activator of voltage-gated sodium channels (Li *et al.*, 2001). Such activity may have significant implications for natural resources and public health in marine environments.

Malyngamide H was also shown to be toxic to goldfish (LC_{50} = 5 μg/ml), but showed no activity against brine shrimp or molluscs (Orjala *et al.*, 1995a). As well as being toxic to brine shrimp, kalkipyrone and hermitamides are toxic to goldfish (Graber and Gerwick, 1998; Tan *et al.*, 2000).

In addition to other bioactive compounds, *L. majuscula* produces a suite of tumor promoters: aplysiatoxin, debromoaplysiatoxin, bromoaplysiatoxin, and lyngbyatoxins — all of which have been shown to produce erythema, blisters, and necrosis when applied to the skin (Fujiki *et al.*, 1984a, 1984b, 1985, Moore 1984; Fujiki and Suganuma, 1996). Like okadaic acid, lyngbyatoxin-a has been demonstrated experimentally to induce papillomas in two-stage mouse carcinogenesis experiments (Fujiki *et al.*, 1984a). Unlike okadaic acid, nodularins, and microcystins, lyngbyatoxins promote tumor growth through the activation of the protein kinase C, not through protein phosphatase inhibition (Fujiki and Suganuma, 1996). The fact that lyngbyatoxin-a was identified recently in green turtle meat (Yasumoto, 1998) confirms that these toxins, like OA, should also be considered for their potential role as tumor-promoters in sea turtle fibropapillomatosis (Landsberg *et al.*, 1999).

T. SPECIES WITH UNCHARACTERIZED TOXINS OR BIOACTIVE COMPOUNDS

1. Dinoflagellates

a. Alexandrium spp.

Several *Alexandrium* spp. have been implicated in natural aquatic mortality events where toxic compounds other than PST were suspected (Tables 1 and 2). PST are not usually excreted into the surrounding medium, and organisms are generally exposed through ingestion. However, a few case histories of unusual mortality events in conjunction with experimental studies have indicated that additional toxic exudates are also produced by *Alexandrium* spp. Media from *Alexandrium* spp. cultures had hemolytic activity against fish and mammalian erythrocytes (Ogata and Kodama, 1986; Simonsen *et al.*, 1995). Supernatants from cultures of *A. tamarense* and *A. lusitanicum* were also toxic to rat primary neuronal cells (Perovic *et al.*, 2000). The recent demonstration that *A. tamarense* also produces reactive oxygen species such as hydrogen peroxide (Kim *et al.*, 1999a) warrants further investigation of the potential role these bioactive compounds may play in aquatic mortality events.

In March 1982, in Kitaura Bay, Japan, a massive bloom of *A. catenella* resulted in large-scale mortality of cultured yellowtail and red sea bream (Ogata and Kodama,

1986; Table 2). Because these species of fish are not planktivorous, it was suspected that toxins other than PST may have played a role in the mortalities. In experimental studies, surf smelt, *Hypomesus pretiosus japonicus*, were exposed to cell-free filtrates from both *A. catenella* and *A. tamarense* culture media. Test fish died after 3 to 5 h of continuous exposure and had signs of hypoxia. Histologically, the epithelial cells of the gills were swollen and exfoliated from the pillar cells (Ogata and Kodama, 1986). When juvenile greenback flounders, *Rhombosolea taparina*, were exposed to whole cells, cell-free, or lipophilic solvent-extracted culture medium of *A. minutum*, in the first and second treatment death occurred within 3 h. Signs of stress included rapid bursts of uncontrolled swimming, heaving of the operculum and mouth, small rapid convulsive movements of the whole body, and loss of orientation. Gill damage was characterized by severe epithelial swelling. In addition, gills from fish exposed to cell-free medium had lamellar fusion, necrosis, and vacuolated chloride cells. No pathological changes were detected in internal organs (Lush *et al.*, 1998). When milkfish, *Chanos chanos*, were exposed to toxic or nontoxic cells, or cell extracts of *A. minutum*, increased mortalities were observed with increasing concentrations of each treatment. Fingerlings exposed to 1.5 to 3.0×10^4 toxic *A. minutum* cells/ml or to cell extracts at 5.13×10^3 to 2.05×10^4 cells/ml, had noticeable edema, hyperplasia, and necrosis of the secondary gill lamellae. An increase in oxygen consumption rate was also observed in fish exposed to algal extracts (Chen and Chou, 2001).

In July 1984 in Tronisvagur fjord in the Faroe Islands, the appearance of an *A. tamarense* (reported as *A. excavata*) bloom coincided with mortalities of rainbow trout and salmon that resulted in 77% (27 metric tons) of the fish dying. Although shellfish analyzed for PST were shown to contain 9000 MU per 100 g tissue, and four human cases of PSP were reported, the fish behavior and pathology suggest that in this case also, extracellular toxins may have been responsible for the mortality. Two days after the mortalities started, rainbow trout were either swimming randomly with dorsal and caudal fins out of the water or on their sides with their heads above the surface. There were acute histopathological changes to the gills, with necrosis and sloughing of the epithelia of the secondary lamellae, pyknotic nuclei, cytoplasmic vacuolation, cellular hypertrophy, and sometimes hemorrhage associated with breakdown of blood sinuses. No pathological changes were detected in internal organs or were other infectious agents suspected (Mortensen, 1985).

In June 1989 in southern Taiwan, a mass mortality of cultured grass prawns, *Penaeus monodon*, was associated with a bloom of *A. minutum* (reported as *A. tamarense* by Su *et al.*, 1993) (Lush and Hallegraeff, 1996). In enclosed aquaculture facilities, water-quality problems and environmental stressors can sometimes exacerbate the stress effects of *A. minutum* on aquatic animals, and several of these stressors may have been involved. A combination of high temperature, low salinity, low ammonia-N, and a lack of other plankton competitors and predators appeared to be conducive to the development of a heavy *A. minutum* bloom, with concentrations of up to 1×10^4 cells/ml. Prawns and black sea bream, *Acanthopagrus schlegeli*, were experimentally exposed to pond water containing either *A. minutum*, or *A. minutum* filtrate; control fish and prawns were exposed to pond water from three adjacent ponds where no bloom had occurred. After 12 h in pond water, 9 of 10 prawns died; the remaining prawn was moribund, but it recovered when placed in fresh seawater with strong aeration. Dense accumulations of *A. minutum*

cells were observed in the dead prawns' gills or stomach. Toxicity as measured by mouse bioassay was determined to be 1.39×10^4 cells per MU. Prawns became moribund in 1.5, 3, and 9 h when immersed in the mixtures of filtrate of pond water:fresh seawater in ratios of 1:0, 1:1, and 1:3, respectively. Black sea bream became moribund 1.5 hours after immersion in the filtrate. Fish lost equilibrium at first, then became immobile with shallow arrhythmic breathing, and eventually died. Moribund fish recovered if removed and placed into strongly aerated seawater (Su *et al.*, 1993).

There is additional evidence for the production of exudates by *Alexandrium* spp. Nauplii of the harpacticoid copepods *Euterpina acutifrons* became inactive when exposed to cell-free filtrates of *A. minutum* (Bagøien *et al.*, 1996). Both whole cells and a cell-free filtrate of *A. minutum* culture medium were lethal to metanauplii and adults of *Artemia*, whereas pure PSP fractions produced no comparable mortality. The presence of a fast-acting toxin was proposed (Lush and Hallegraeff, 1996). When Farrer's scallop, *Chlamys farreri*, eggs were exposed to *Alexandrium tamarense* cell cultures, hatching rate was 30% when compared with controls, and larval survival decreased significantly (Yan *et al.*, 2001).

Culture filtrate of *Alexandrium lusitanicum* was shown to inhibit the growth of dinoflagellates (Table 11, Blanco and Campos, 1988). *Alexandrium tamarense* (as *A. excavatum*) caused cell death of the ciliate *Favella ehrenbergii* by producing lethal extracellular toxins. The exudate acted on the cell membrane of the ciliate and induced continuous ciliary reversal. After some time, the ciliate swelled and subsequently lysed (Hansen, 1989). Andrasi (1985) also demonstrated the presence of toxins in blue mussels, *Mytilus edulis*, exposed to cell-free filtrate water that had contained *A. catenella* cells.

b. Gymnodinium pulchellum

With the exception of *Gymnodinium pulchellum*, Daugbjerg *et al.* (2000) recently transferred ichthyotoxic *Gymnodinium* species either to the genus *Karenia* or to *Karlodinium*. *Gymnodinium pulchellum* has been implicated in fish mortalities both in aquaculture and in the wild, particularly in Japan and Australia (Table 2). Recently, Steidinger *et al.* (1998b) reported *Gymnodinium pulchellum* for the first time in North America and implicated the species in fish and invertebrate mortalities (Table 2). Onoue and Nozawa (1989a) isolated three toxic fractions — neurotoxic, hemolytic, and hemagglutinative — from *G. pulchellum* (as *Gymnodinium* type 84 k). Ichthyotoxicity of the three fractions was tested on juvenile red sea bream, *Pagrus major*. When exposed to 0.02% of the neurotoxic fraction, fish behaved as though anesthetized, and a marked color change or whitening of the body was observed. The fish labored to breathe and respiratory arrest resulted in death in less than 4 min. When exposed to 0.02% of the hemolytic fraction, fish exhibited violent convulsions; loss of balance; labored breathing; edema, hemorrhaging, and excess mucus production in the gill lamellae; and respiratory arrest. Fish died in 35 to 49 min. Reaction of fish to the hemagglutinin fraction was similar to that of fish to the hemolytic fraction. When mice were injected i.v. with the hemagglutinin fraction (20 μg), they died from respiratory paralysis. The lethal dose was 2 to 4 mg/kg. Further studies of the neurotoxins of *G. pulchellum* (as *Gymnodinium* sp.) by Endo *et al.* (1992) suggested that these toxins were oxidized brevetoxins, but no further information

is available. Exposure of common carp, *Cyprinus carpio*, to neurotoxic fractions of *G. pulchellum* (as *Gymnodinium* sp.) significantly reduced the fishes' heart rates. Fish swam erratically, and the secondary gill lamellae showed very mild hypertrophy and edema (Endo *et al.*, 1992).

c. Gyrodinium corsicum

Gyrodinium corsicum, recently described by Paulmier *et al.* (1995), was associated with fish and shellfish mortalities near both Corsica and the Mediterranean coast of Spain (Paulmier *et al.*, 1995; Garcés *et al.*, 1999) (Table 2). *Gyrodinium corscium* is a small, naked dinoflagellate that is morphologically similar to *Karlodinium micrum* Larsen in Daugbjerg *et al.* (2000) (= *Gymnodinium galatheanum* Braarud). There is little information on its toxins, mode of action, or exact effect on aquatic animals.

In September 1993, a bloom reported as *Gymnodinium* cf. *nagasakiense* was associated with mortalities of sea bass, *Dicentrarchus labrax*, and bogue, *Boops boops*, in the coastal lagoon of Diane, Corsica (Table 2). A maximum density of 2.7×10^3 cells/ml was observed. Histopathological examination of gills from moribund fish showed congestion, hemorrhage, and slight subepithelial edema. Seawater containing 4 cells/ml caused the deaths of 40% of the 9-day-old larvae of great scallops, *Pecten maximus*, that came in contact with the toxic seawater. Filtered seawater contained elevated levels of the toxic PUFA octadecapentaenoic acid (= C18:5n3). Although the species associated with this mortality was reported as *G.* cf. *nagasakiense*, it was not definitively identified as such (Arzul *et al.*, 1994). Therefore, it is unclear whether this mortality could have been attributable to *Gyrodinium corsicum*, which was described from the same location 1 year later and has also been involved in mortalities of the same fish species (Paulmier *et al.*, 1995). If this is the case, then *G. corsicum* may be another species that produces hemolytic fatty acids (C18:5n3) similar to those known in other microalgae (Table 12).

d. Gyrodinium sp.

In early August 1992, a bloom of a novel ichthyotoxic *Gyrodinium* species was considered to be responsible for mass mortalities of cultured finfish in the South Sea of Korea (Kim *et al.*, 1995; Table 2). This *Gyrodinium* sp. appears to be morphologically different from other described ichthyotoxic *Gyrodinium* species. Bloom concentrations measured up to 3.3×10^4 cells/ml. Economic losses were estimated at $12.5 million. Experimental densities of 1.448×10^4 cells/ml were lethal to juvenile bastard halibut, *Paralichthys olivaceus*, after 1 h of exposure and 1.09×10^3 cells/ml after 2 h exposure (Kim *et al.*, 1995).

e. Heterocapsa circularisquama

In September 1988, a harmful bloom of *Heterocapsa circularisquama* (Horiguchi, 1995) was first recorded in Uranouchi Bay, Kochi Prefecture, Japan, and was associated with bivalve mortalities (Table 2). The following year this species was responsible for the mass mortality of Japanese littleneck clams (*Venerupis* [as *Tapes*] *philippinarum*), Mediterranean mussels (*Mytilus galloprovincialis*), Pacific oysters (*Crassostrea gigas*), razor clams (*Solen strictus*), and surfclams (*Mactra chinensis*) in Fukuoka Bay (Yamamoto and Tanaka, 1990). Subsequently, this

species has also been implicated in other mass mortalities of bivalves (Table 2). Economic losses to the shellfish aquaculture industry from the direct killing of marketable products by *H. circularisquama* blooms were estimated to amount to approximately 10 billion yen (= approx. $1 million) in the last decade (Matsuyama, 1999). Detrimental effects to wild or cultured populations of fish or crustaceans or to public health have not been observed (Matsuyama *et al.*, 1996, 1997b). Low oxygen concentrations were observed in the bottom water layer only after the bloom had collapsed in Ago Bay, but the main mortality event occurred during the middle period of the bloom when dissolved oxygen levels were still near saturation.

Caged pearl oysters, *Pinctada fucata*, that were naturally exposed to low (50 to 200 cell/ml) concentrations of *H. circularisquama* closed their valves, periodically "snapped" the valves, and contracted the mantle. When cell densities increased to 5 to 10×10^4 cells/ml, most oysters died within a few days. Dead individuals were characterized by a marked shrinkage of the mantle, decrease of the glycogen lobe attached to the mantle, and gut discoloration (Matsuyama *et al.*, 1996; Matsuyama, 1999). Similar harmful effects were observed on Pacific oysters and Mediterranean mussels during the red tide that occurred in Hiroshima Bay (Matsuyama *et al.*, 1997a). When juvenile pearl oysters were exposed to 5 to 10×10^4 cultured *H. circularisquama* cells/ml, 50% died within 48 h (Nagai *et al.*, 1996), which is comparable to the length of time oysters took to die in the field (Matsuyama *et al.*, 1996). No marked change in behavior was observed when oysters and mussels were exposed to filtrate of *H. circularisquama* (3.7×10^3 cell/ml) (Matsuyama *et al.*, 1997b). When Mediterranean mussels were exposed to *H. circularisquama* at densities exceeding 5×10^1 cell/ml, clearance rates in the mussels were noticeably reduced. Mussels retracted the mantle edges, showed intermittent shrinkage of the exhalent siphon, and were unable to completely close the valves during the 20-min experiment. One hundred percent mortality (N = 20) was noted after 5 days of exposure to 9.8 to 12.3×10^4 cell/ml. Juvenile mussels showed inhibition of byssus production and sustained valve closure 5 to 17 h after the start of the experiment (Matsuyama *et al.*, 1998b). By comparison, there was no effect on clearance when mussels were exposed to *H. triquetra* (whose cells are comparable in size and shape) at a concentration of 8×10^3 cells/ml.

Laboratory exposure studies have demonstrated that in addition to bivalves, organisms such as gastropods, solitary ascidians, jellyfish, and protists (including dinoflagellates) (Tables 10 and 11) are also affected by *H. circularisquama*. No demonstrable effect on mice, finfish, crabs, lobsters, shrimp, starfish, copepods, or diatoms could be found (Matsuyama, 1999). Although current information suggests that there is a direct cytotoxic effect, the toxin has still not been characterized. Toxicity appears to be closely related to the outer components of the cells, and a toxic, proteinaceous substance is probably present on the cell surface (Matsuyama *et al.*, 1996, 1997b). Purification and characterization of toxic fractions have not been successful because of their high lability under neutral conditions (Matsuyama, 1999). Recent studies demonstrate that bioactivity of *H. circularisquama* cells results in hemolysis of mammalian erythrocytes. Oda *et al.* (2001) suggest that the hemolytic toxin may be one of the causes of mollusc mortalities associated with *H. circularisquama*.

f. Karenia brevisculcata

In New Zealand, a sporadic massive mortality of fish and other marine fauna was reported along the central east coast from mid-January 1997 to summer 1998. Major kills of eels and flounders were first noticed in Wellington Harbor; the mortalities then spread to pelagic fish and marine invertebrates (Table 2). More than 200 people suffered from respiratory distress; swimmers, surfers, and beach-goers complained of a dry cough, sore throat, running nose, and eye and skin irritiations (Chang, 1999a, 1999b).

A dominant *Gymnodinium* species (cell concentrations up to 3.33×10^4 cells/ml), now named as *Karenia brevisulcata* Hansen and Moestrup in Daugbjerg *et al.* (2000) (reported as *Gymnodinium brevisulcatum* Chang), was associated with the observed health effects (Chang, 1999a, 1999b). This species is apparently different from that of the *Karenia* sp. producing gymnodimine (see section on gymnodimine) found in the same area of New Zealand (Haywood *et al.*, 1996; Mackenzie *et al.*, 1996a; Chang, 1999a, 1999b). Shellfish collected during the Wellington Harbor bloom tested negative for brevetoxins, but mouse bioassays demonstrated the presence of a "quick action" toxin that is typical of gymnodimine. Mice died very rapidly, within 4 to 6 min. Preliminary tests showed that the toxins extracted from *K. brevisulcata* are more nonpolar than those of gymnodimine and, unlike gymnodimine, were extractable with ether (Chang, 1999a, 1999b).

Toxins (as yet uncharacterized) of *K. brevisulcata* kill a range of marine fauna as well as other phytoplankton and macroalgae. Preliminary tests using *K. brevisulcata* cultures demonstrated lysis of *K. mikimotoi* (Japanese strain) within 2 h and of *K. mikimotoi* (as *G.* cf. *mikimotoi*) (European strain) within 20 min (Chang, 1999b). *Karenia brevisulcat* was toxic to brine shrimp, abalone larvae, tintinnids, amphipods, barnacle nauplii, polychaetes, lobster larvae (phyllosoma stage I and III), and turbot. When the common brown seaweed *Macrocystis pyrifera* was introduced into *K. brevisulcata* cultures, the soft, leafy part of the seaweed collapsed and fell apart in 24 to 48 h. This confirmed the earlier observations of dead *M. pyrifera* (up to 75% of the seaweed cover) during the bloom in the harbor.

g. Karenia digitata

Since the mid-1990s, *K. digitata* has been associated with a series of fish kills in aquaculture facilities in western Japan, southern China, and Hong Kong (Table 2). In March 1998, the bloom affected 22 of Hong Kong's 26 coastal fish farms and killed 90% of the cultured fish at an estimated loss of $32 million. The fish skin and gills were severely damaged with reddened patches. In addition to the wide range of fish species affected, it was also noted that cultured seaweeds *Porphyra tenera* exhibited irregular growth (Baba *et al.*, 1997; Dickman and Tang, 1999; Yang and Hodgkiss, 1999; Yang *et al.*, 2000).

h. Karlodinium micrum (= Gyrodinium galatheanum)

Mass fish mortalities in the region of Walvis Bay, South Africa, in the 1940s were attributed to a *Gymnodinium* species. This species has been classified as *Gyrodinium galatheanum* (Braarud) or *Gymnodinium galatheanum* Braarud (Kite and Dodge) but is now known as *Karlodinium micrum* Larsen in Daugbjerg *et al.* (2000). *Karlodinium micrum* is considered to be ichthyotoxic (Steeman Nielsen, 1953, cited

in Nielsen, 1993). A few reports have associated *K. micrum* with natural mortalities in South Africa (Pieterse and Van der Post, 1967; Pitcher, 1998), and *K. micrum* has been implicated recently in a series of fish kills in aquaculture ponds in the USA (D. Terlizzi, personal communication; Landsberg and Steidinger, unpubl. data).

A concentration of 1.2×10^8 *K. micrum* cells/ml has been demonstrated experimentally to be toxic to and to result in a decrease in the growth rate of mussels (Nielsen and Strømgren, 1991). When juvenile cod, *Gadus morhua*, were exposed to *K. micrum*, the fish stayed close to the surface, often with their heads out of the water. Fish died within 2 days of exposure to cell densities of 1.15×10^8 cells/ml. Dead fish had distended gills, and their mouths were wide open. Blood samples from lethargic or recently dead fish had a significantly higher mean blood osmolality (444 mOsm) than the control fish did (336 mOsm). Fish that were lethargic and had been exposed for less than 2 days showed extensive separation of the respiratory epithelium from the underlying pillar cells of the gills (Nielsen, 1993). Increased gill permeability results in increased plasma osmolality, edema, and impaired osmoregulation.

i. Karlodinium veneficum (= *Gymnodinium veneficum*)

Karlodinium veneficum (= *Gymnodinium veneficum*) Larsen in Daugbjerg *et al.* (2000) was described from Devonport, England (Ballantine, 1956), and when fish were experimentally immersed in cell cultures of the species, it was found to be lethal to dogfish, *Scyllium canicula* (3 h); pollack, *Gadus pollachius* (18 min); the blenny *Blennius gattorugine* (< 45 min); lesser weaver, *Trachinus vipera* (30 min); the gobies *Gobius niger* and *G. virescens* (5 to 15 min); plaice, *Pleuronectes platessa* (30 min); and the wrasse *Ctenolabrus rupestris* (15 to 20 min). All fish showed similar responses when either immersed in cultures, exposed to resuspended cells in seawater or supernatant fluid from cultures, or exposed to toxic extracts. The immediate reaction was a violent attempt to swim away. In gobies, violent swimming either forward or backward continued for about 2 min and then subsided. Intense vasodilation and expansion of the skin chromatophores produced a marked color pattern. Balance control was upset and the fish floated on their side or upside down. Breathing rate slowed down. Soon after immersion, the fish had a spasmodic, violent cough reaction. Death occurs while the gobies are paralyzed, with the gills extended, and is apparently due to respiratory failure. Rapid death was also noted for the following molluscs: waved whelk (*Buccinum undatum*), great scallops (*Pecten maximus*), seahares (*Aplysia punctata*), and the squid *Eusepia officinalis*. The jellyfish *Aurelia aurata* was affected similarly. Other organisms that were slowly affected included the cnidarian anemones *Anemonia sulcata* and *Calliactis parasitica*, the mussels *Mytilus edulis* and *M. galloprovincialis*, the bivalve *Lasaea rubra*, the copepods *Calanus finmarchicus* and *Tigriopus fulvus*, the mysid shrimp *Hemimysis lamornae* and *Macromysis flexuosus*, the shrimp *Palaemon serratus*, the crabs *Carcinus maenus* and *Cancer pagarus*, the starfish *Asterias rubens*, the brittlestars *Ophiothrix fragilis* and *Ophiocomina nigra*, and the cephalochordate *Amphioxus lanceolatus* (Ballantine, 1956; Abbott and Ballantine, 1957). Mice that were injected with toxin were dead within 2 to 4 min and frogs (*Rana temporaria*) within 30 min. Despite the proven experimental toxicity, there have been no documented mortality events in the wild involving *K. veneficu*m.

j. Peridinium polonicum

Few species of freshwater dinoflagellates have been documented to produce toxins. *Peridinium polonicum* was implicated in a large freshwater fish kill in Japan (Hashimoto *et al.*, 1968) (Table 2), and glenodinine and polonicumtoxins were isolated from this dinoflagellate (Hashimoto *et al.*, 1968; Oshima *et al.*, 1989b). Hashimoto *et al.* (1968) suggested that under alkaline conditions glenodinine activity was more lethal than under neutral conditions. During a heavy bloom, pH levels were observed to increase to 8.7 to 9.2 and were accompanied by fish mortalities. When killifish were exposed to i.p. injections of polunicumtoxins A, B, and C, symptoms observed were slight excitement followed by stiffness of the pectoral fins, decrease of response to stimuli, loss of balance, and occasional abrupt jumping before death. Fish died 30 to 40 min after injection with a minimal lethal concentration of 0.13 μg/ml (Oshima *et al.*, 1989b).

k. Pfiesteria spp.

Recently, a series of fish kills and public health threats have highlighted the presence of small, heterotrophic, lightly armored dinoflagellates with life cycles different from those of the more typical planktonic photosynthetic blooming forms. *Pfiesteria piscicida* and *P. shumwayae* are generalist predatory dinoflagellates that target fish and shellfish and are capable of consuming a diverse range of prey, including bacteria, microalgae, and microfauna (Burkholder and Glasgow, 1995, 1996; Burkholder *et al.*, 1998; Cancellieri *et al.*, 2001; Glasgow *et al.*, 2001a). Unlike more typical HABs, *Pfiesteria* spp. may represent a minor component of the plankton community during fish kill events and are not typically associated with the production of discolored water so common to other pigmented species (Burkholder *et al.*, 1998). Aspects of the life cycle, detection, distribution, ecology, taxonomy, and toxicity of *Pfiesteria* spp. and their effects on aquatic organisms and threats to public health have been well reviewed in recent publications (Burkholder *et al.*, 1992, 1995, 1998, 1999, 2001a, 2001b; Noga *et al.*, 1993, 1996; Burkholder and Glasgow, 1995, 1997; Glasgow and Burkholder, 1995; Lewitus *et al.*, 1995; Levin *et al.*, 1997, 1999, 2000; Rublee *et al.*, 1999, 2000, 2001; Bowers *et al.*, 2000; Marshall *et al.*, 2000; Oldach *et al.*, 2000; Silbergeld *et al.*, 2000; Backer *et al.*, 2001; Glasgow *et al.*, 2001b; Morris 2001; Steidinger *et al.*, 2001); only a brief summary is provided here.

Pfiesteria piscicida was first reported as a *Gymnodinium* sp. killing tilapia *Oreochromis* sp. in a North Carolina, USA, aquarium (Smith *et al.*, 1988). Although massive fish kills (mostly of Atlantic menhaden, *Brevoortia tyrannus*) had been particularly prevalent in North Carolina's estuaries for many years, it was not until 1991 that *P. piscicida* was implicated in these mortalities (Burkholder *et al.*, 1992; Noga *et al.*, 1993, 1996) (Table 2). As well as being responsible for mass mortalities of fish, *P. piscicida* has also been reported to kill shellfish, blue crabs (*Callinectes sapidus*), pediveliger eastern oysters (*Crassostrea virginica*), pediveliger bay scallops (*Argopecten irradians*), and northern quahogs (*Mercenaria mercenaria*) (Burkholder *et al.*, 1995; Springer *et al.*, 2000; Springer *et al.*, in press). *Pfiesteria piscicida* was described in 1996 (Steidinger *et al.*, 1996a) and has been documented to occur along the eastern seaboard of the USA and Gulf of Mexico (Burkholder *et al.*, 1992, 1995a, 1995b, 1998, 1999, 2001a, 2001b; Lewitus *et al.*, 1995; Rublee *et al.*, 1999, 2000). A second species of recently described toxic *Pfiesteria*, *P. shumwayae*, has also been

implicated in fish kills along the mid-Atlantic coast and has been demonstrated to be ichthyotoxic in fish bioassays (Glasgow *et al.*, 2001a).

Pfiesteria spp. continue to threaten natural resources, have been implicated in several public health incidents in the eastern USA (Burkholder *et al.*, 1992, 1995; Burkholder and Glasgow, 1997; Grattan *et al.*, 1998; Hudnell *et al.*, 2001; Moe *et al.*, 2001; Morris, 2001; Schmechel and Koltai, 2001; Shoemaker and Hudnell, 2001), and have been responsible for the mortality of millions of fish in North Carolina alone (Burkholder *et al.*, 1995), with significant losses to that state's economy. Outbreaks of *Pfiesteria* and fish kills in Chesapeake Bay in 1997 brought national and international recognition to this genus (Burkholder, 1998). Although there is a widespread distribution of *Pfiesteria* spp. along the eastern seaboard of the USA and (thus far) to a lesser extent in the northern Gulf of Mexico (Bowers *et al.*, 2000; Burkholder *et al.*, 2001a; Rublee *et al.*, 2001), areas of active toxicity where repeated fish kill events occur are in North Carolina and to a lesser extent the eastern shore of Chesapeake Bay (Burkholder *et al.*, 1995, 1997, 2001b; Glasgow *et al.*, 2001b). Additional *Pfiesteria*-like species have been reported from the eastern USA and other areas in the Gulf of Mexico (Burkholder and Glasgow, 1997; Burkholder *et al.*, 2001; Steidinger *et al.*, 2001). The role of *Pfiesteria* in fish disease events is still being investigated (see section on HABs as stressors in disease). An undescribed *Pfiesteria* species, suspected of killing fish in tropical fish tanks but co-occurring with a pathogenic parasitic dinoflagellate of fish (*Amyloodinium ocellatum* Landsberg *et al.*, 1994) (see section on parasites), was characterized from a Florida aquarium (Landsberg *et al.*, 1995). This *Pfiesteria* species has not yet been found in the wild (Landsberg *et al.*, 1995) or was it proven to be ichthyotoxic.

Mice exposed to *Pfiesteria* or cell-free filtrate taken from aquarium-cultured water showed signs of decreased learning ability (Levin *et al.*, 1999). Although the toxins produced by *Pfiesteria* are still being characterized (Ramsdell *et al.*, 2000; Moeller *et al.*, 2001), it is known that there are different strains of *P. piscicida* and that they range from nontoxic to highly toxic (Burkholder *et al.*, 1999, 2001a, 2001b). Recent findings suggest that a putative *Pfiesteria* bioactive compound mimics the neurotransmitter ATP and targets $P2X_7$ receptors on immune cells such as activated macrophages and microglial cells in the brain. Such a mode of action may lead to the neurological effects and inflammatory responses observed in fish and humans (Glasgow *et al.*, 1995; Ramsdell *et al.*, 2000; Burkholder *et al.*, 2001a; Kimm-Brinson *et al.*, 2001; Melo *et al.*, 2001).

l. Prorocentrum minimum

Prorocentrum minimum has a widespread distribution, and most strains are considered to be nontoxic, at least to humans. In Japan in March 1942, a rare shellfish poisoning event (termed Venerupin Shellfish Poisoning [VSP]) occurred in which 114 people died after consuming toxic asari (*Venerupis semidecussata*). Further fatalities resulted after the consumption of toxic Pacific oysters (*Crassostrea gigas*) in March 1943 and asari in March 1949. This event was distinguished from other shellfish poisoning events by the symptomatology of the poisoning outbreak in humans. Symptoms included hemorrhagic diathesis, centrilobular necrosis, and fatty degeneration of the liver, frenzy, unconsciousness, and coma (Akiba and Hattori, 1949). Although toxic shellfish from the same region were associated with *Prorocentrum*

minimum (as *Prorocentrum* sp. or *P. minimum* var. *mariae-lebouriae* [= *Exuviella mariae-lebouriae*]) (Nakazima, 1965a, 1965b, 1965c, 1968; Okaichi and Imatomi, 1979) and partially purified toxins from *P. minimum* cultures were toxic to mice (Okaichi and Imatomi, 1979), conclusive evidence that *Prorocentrum* was involved with VSP has still not been obtained. Other shellfish toxicity events associated with *P. minimum* were documented in the Netherlands in blue mussels, *Mytilus edulis* (Kat, 1979); in Portugal in the cockles *Cardium edule* and *Venerupis decussatus* (Silva, 1985); in Norway (Tangen, 1980); and in China (Chen and Gu, 1993). In the Netherlands, the poisoning event was probably DSP (Quilliam and Wright, 1995), but it is unclear what toxins these other events were attributable to.

More recently, the potential toxicity of some *P. minimum* strains to mice was confirmed, and natural shellfish toxicity was demonstrated in laboratory exposures (Denardou *et al.*, 1995; Grzebyk *et al.*, 1997; Denardou-Queneherve *et al.*, 1999). After injection of *P. minimum* toxic extracts, symptoms in mice (convulsions and spasms with pronounced palpitations) were suggestive of neurotoxic activity. When a sufficient dose was injected, neurotoxic symptoms appeared rapidly and mice died within minutes (Grezebyk *et al.*, 1997). Toxic components of *P. minimum* appear to block calcium channels, and in laboratory exposures toxins could accumulate in nearly equivalent amounts in the hepatopancreas and meat of cultured mussels. The same toxicity was found in samples of wild mussels collected during a *P. minimum* bloom. In 1993, consumption of mussels from the Salses-Leucate Lagoon on the French Mediterranean coast produced neurological symptoms in mice similar to those observed when mice were exposed to *P. minimum* toxins. These results suggest that *P. minimum* could be responsible for shellfish toxicity in the natural environment and thus present a risk for human health. Mediterranean strains of *P. minimum* showed no cytotoxicity on hepatocytes in culture, suggesting that this strain was different from the strain involved in the Japanese poisoning event in 1942 (Denardou-Queneherve *et al.*, 1999) or that this species was not responsible for the hepatotoxic effects noted at that time. The exact role of *P. minimum* has not been confirmed since the earlier poisoning reports from Japan, and venerupin toxins have not yet been characterized (see section on microcystins and hepatotoxic shellfish poisoning).

Although the risk of *P. minimum* to human health has yet to be confirmed, there is increasing evidence that this species affects aquatic organisms. Pathological effects, inhibition of feeding, and mortality occurred in shellfish exposed to *P. minimum* (Bardouil *et al.*, 1993; Luckenbach *et al.*, 1993; Wikfors and Smolowitz, 1993, 1995; Wikfors *et al.*, 1993). Recently, a *Prorocentrum* sp. has been implicated in mass mortalities of flat oysters (*Ostrea rivularis*) in South China. Twenty-five hectares of oyster fields worth more than two million yen were lost between late April and late May 1994. Water samples were dominated by *Prorocentrum* sp. at concentrations of 2.01 to 6.77×10^2 cells/ml. Excess mucus was noted in the gills, and histopathology revealed intense hemocytosis, tissue edema, and atrophy of the digestive tubules (Yomgjia *et al.*, 1995). Tank-conditioned adult oysters frequently do not spawn in the presence of bloom densities of *P. minimum*; early larval development is impaired and oysters die at high rates when *P. minimum* or lysate from ruptured cells is present in culture tanks. All of the juvenile eastern oysters, *Crassostrea virginica*, fed *P. minimum* either at a bloom density of 8.9×10^3 to 2.5×10^5 cell/ml died within 14 days, and 43% of those fed *P. minimum* at 33% of bloom

density died within 22 days. *Prorocentrum minimum* proved to be an unsatisfactory food when present at high concentrations, reducing filtration rates and elevating mortality in juvenile oysters (Luckenbach *et al.*, 1993).

Following observations that experimentally caged northern quahogs, *Mercenaria mercenaria*, held in Long Island Sound grew poorly during a bloom of *Prorocentrum* spp., controlled laboratory feeding exposures were undertaken (Wikfors and Smolowitz, 1993). Hard clams and bay scallops, *Argopecten irradians*, were fed the following: (1) unialgal *Prorocentrum micans*, and (2) and (3) two concentrations of *P. micans* mixed with the standard bivalve food, *Isochrysis*, (4) *P. minimum* mixed with *Isochrysis*, and (5) *Isochrysis* alone. Another group was not fed. Clams survived well in all experiments, but in none of the diets supported adequate growth in bay scallops. Unfed bay scallops showed incremental mortality over a 5-week period, mixed or individual diets of *Isochrysis* and *P. micans* supported 50% survival, and a mixed diet of *Isochrysis* and *P. minimum* caused 100% mortality in one week in one trial and in 4 weeks in the second. Bay scallops ingested *P. minimum*, but histopathological observations showed poorly developed digestive diverticula, attenuation of the epithelium with abnormal vacuolation, and necrosis. Large thrombi were also noted in the open vascular system of the mantle, the digestive diverticula, and tissues of the gill, heart, and kidney. *Prorocentrum minimum* may produce an enterotoxin that systemically affects absorptive cells and produces persistent thrombi throughout the vascular system (Wikfors and Smolowitz, 1993). Additional studies showed that spat of eastern oysters exposed to *P. minimum* had an abnormal accumulation of lipid in the stomach epithelium. Accumulation bodies within absorptive cells of the digestive diverticulum contained dinoflagellate autolysosomal bodies, indicating nutritional interference (Wikfors and Smolowitz, 1995).

An unusual fish kill associated with *P. minimum* was reported in Gwadar Bay, southwestern Pakistan, in November 1987. The bloom extended over 7 km^2 and produced discolored brown water for about 3 days. Maximum cell concentrations of 4.5×10^4 cells/ml coincided with mortalities of nine species of fish (Table 2), mostly pike conger *Congresox* sp. (60%). The mortality event did not appear to be related to low dissolved oxygen. When it appeared at high concentrations, *Prorocentrum minimum* was considered to be sufficiently toxic to affect aquatic species (Rabbani *et al.*, 1990).

These few examples indicate that *P. minimum* does pose a threat to both public health and to natural resources, yet the exact mechanism and possible mode of toxicity is not yet clear.

2. Diatoms

Several genera of diatoms have been shown recently to cause mortality, act as feeding deterrents, or affect the reproductive success of copepods (Ianora and Poulet, 1993; Poulet *et al.*, 1994; Ianora *et al.*, 1995, 1996; Miralto *et al.*, 1995; Shaw *et al.*, 1995a, 1995b; Chaudron *et al.*, 1996; Uye, 1996; Ban *et al.*, 1997) (Table 10), all of which could have harmful consequences for marine food webs (Poulet *et al.*, 1994). Although researchers have debated whether the observed effects on feeding are due to a nutritional insufficiency in the copepod diet (Jónasdóttir and Kiorboe, 1996; Jónasdóttir *et al.*, 1998) or due to diatom toxicity (Ianora *et al.*, 1999), the likely involvement of bioactive compounds has been demonstrated recently. Several apo-

fucoxanthoid pigments produced by *Phaeodactylum tricornutum* and *Thalassiosira pseudonana* are feeding deterrents to the copepod *Tigriopus californicus*. The amounts of apo-fucoxanthinoids necessary to reduce feeding in *T. californicus* by 50% ranged from 2.22 to 20.2 ppm. This range was approximately 1000 times lower than the total apo-fucoxanthinoid concentration in *P. tricornutum*. Additionally, concentrations of apo-fucoxanthinoids ranging from 36.8 to 76.7 ppm caused 50% mortality in a population of *T. californicus*. Researchers considered that these compounds may be ecologically significant in the control of bloom formation and in reducing the amount of copepod grazing on the diatoms (Shaw *et al.*, 1995a, 1995b).

Chemically mediated inhibitory effects of diatoms on egg viability have also been considered (Uye, 1996). When the copepod *Temora stylifera* was fed a diet of *Chaetoceros curvisetum* or *P. tricornutum*, the egg quality was poor and the hatching success rate was as low as 20% (Ianora *et al.*, 1995). It was suggested that the reduced egg production and viability were due to the apo-fucoxanthoid pigments produced by *P. tricornutum* (Shaw *et al.*, 1995a). When adult female *Calanus helgolandicus* were fed *Thalassiosira rotula*, total egg production and hatching success were considerably lower than when they were fed the dinoflagellate *Prorocentrum minimum*. Embryonic development was arrested when eggs were exposed to diatom extracts. Structural anomalies of the eggs included a dark brown, and opaque outer membrane, globular cytoplasm, blockage of pronuclei, and dispersed chromatin scattered in the egg matrix of unhatched eggs (Poulet *et al.*, 1994). Bioassays of embryos of the sea urchin, *Paracentrotus lividus*, that were exposed to extracts of the diatom *Thalassiosira rotula* demonstrated a dose-dependent effect on cell division. The assembly of tubulin necessary for microtubule development was inhibited. The development of eggs and embryos incubated in a water-soluble extract equivalent to 5×10^6 to 5×10^7 cells/ml was totally blocked at the one-cell stage (Buttino *et al.*, 1999). In the presence of the diatom *Skeletonema costatum*, female *Temora stylifera* produced eggs for only 3 to 4 days, after which they became sterile or died (Ianora *et al.*, 1995). Whether these effects were due to bioactive compounds or some other mechanism is currently unknown.

a. Rhizosolenia

One of the few documented cases demonstrating a chronic effect and subsequent mortality of shellfish was that associated with exposure to *Rhizosolenia chunii* (Parry *et al.*, 1989). A bloom of this species occurred in Port Phillip Bay, southeastern Australia, from late August to mid October 1987. Although mussels (*Mytilus edulis planulatus*), scallops (*Pecten alba*), and flat oysters (*Ostrea angasi*) concurrently developed a bitter taste, there was no mortality reported during the bloom. The bitter taste was concentrated in the digestive gland, which also showed extensive inflammation and degeneration. The bitter taste retained in the mussels rendered them unmarketable for 7 months. Digestive gland lesions were evident in mussels in September 1987; these lesions progressively became more severe, and after 3 to 8 months, mortalities began. No other pathogens or pollutants were demonstrated to be responsible for the chronic mortalities. Parry *et al.* (1989) discussed the possibility that scallops exposed to *R. chunii* were more susceptible to parasitism by the protist

Perkinsus sp., which although known to be pathogenic to shellfish (Perkins, 1993), was not implicated in these mortalities.

3. Raphidophytes

a. Fibrocapsa japonica

Low densities of *Fibrocapsa japonica* were reported in the German Wadden Sea in the mid-1990s. In experimental studies, toxin produced by this species killed fish and was determined by mass spectrometry to be of a slightly different structure to that of brevetoxin. The toxin was tentatively named fibrocapsin. Preliminary experiments on isolated nerves showed that fibrocapsin blocks neural conductivity at concentrations as low as 0.01 ng/ml. After mice were given subcutaneous injections they developed tonic-clonic seisures, indicating that the toxin is capable of passing through the blood-brain barrier (Nannen *et al.*, in ICES, 1998).

At the same time that *F. japonica* was observed in the Wadden Sea, two adult and three newborn seals kept in a rehabilitation center adjacent to the sea died. Water samples collected in the center were positive for *F. japonica*. Fibrocapsin was detected in both the water samples and from blood and organ samples from the seals. Whether fibrocapsin played a role in the seal mortality is still unknown, or is it clear whether the animals might have been exposed through direct contact or through the diet (Rademaker *et al.*, in ICES 1998).

4. Prymnesiophytes

a. Phaeocystis globosa

Although *Phaeocystis globosa* is not usually associated with aquatic mortalities, a fish kill involving it was reported in southeastern China in 1997. For approximately 2 months, a bloom of *Phaeocystis globosa* was present along the coast of Fujian and Guangdong provinces. The discoloration caused by the bloom was intense enough to be detected by SeaWIFs imagery. The bloom caused a severe mortality of caged fish — an estimated 60,000 tons of fish, a value of $8 million, were killed (Lu and Huang, 1999).

b. Phaeocystis pouchetii

Phaeocystis pouchetii is a regular component of phytoplankton communities in boreal and arctic environments (Lancelot *et al.*, 1998) and, in general, has not been regarded as a toxic species (Larsen and Moestrup, 1989). Nevertheless, early reports suggested that blooms of this species may have negatively affected the pelagic food web and influenced the migration of herring (Savage, 1930). *Phaeocystis* blooms are now considered to be nuisance blooms that have increased in some areas because of coastal eutrophication (Lancelot *et al.*, 1987). When colonies break up and the bloom collapses, characteristic layers of foam may form long bands along the open coast (Rogers and Lockwood, 1990) or beach and ultimately produce massive unsightly foam banks (Lancelot *et al.*, 1987). High concentrations of mucilaginous colonies of *P. pouchetii* reduce seawater quality (Rogers and Lockwood, 1990) and can lead to reduced bivalve spawning success and poor viability of larvae (Walne,

1974, cited in Rogers and Lockwood, 1990). Concentrations of potentially toxic compounds such as acrylic acid (Sieburth, 1960), methyl bromide (Saemundsdottir and Matrai, 1998), and volatile sulfur compounds such as dimethyl sulfide (Armstrong and Boalch, 1960) were not considered sufficient to cause marine animal mortalities (Rogers and Lockwood, 1990). In New Zealand, blooms of the "Tasman Bay slime" were reported as early as the 1860s and were said to destroy fish and choke fishing nets (Hurley, 1982, cited in Moestrup, 1994).

There is mixed evidence that *P. pouchetii* is toxic, unpalatable, or at least of low nutritional value to copepods (Tande and Båmsted, 1987; Verity and Smayda, 1989; Estep *et al.*, 1990; Nielsen *et al.*, 1990). Egg production of female *Acartia* spp. that were fed *P. pouchetii*, either as gelatinous colonies (>200 μm diameter) or solitary cells (3 to 5 μm), was not significantly different from that of starved females (Verity and Smayda, 1989). Copepods avoided healthy colonies of *Phaeocystis* but actively grazed on senescent colonies (Estep *et al.*, 1990). This would seem to indicate that copepod feeding behavior is not altered by the presence of toxins (Stabell *et al.*, 1999).

In 1988, a heavy bloom of *P. pouchetii* resulted in a mass mortality of numerous benthic invertebrates, particularly lugworms, *Arenicola marina*, in north Wales (Rogers and Lockwood, 1990). Mortalities were attributed to the collapse of the bloom; anoxic conditions developed when dying colonies formed a mucilaginous layer over the sea bed. Immobile fauna were suffocated, whereas mobile fish could leave the area (Rogers and Lockwood, 1990). An enormous bloom of *P. pouchetii* in the western Dutch Wadden Sea in May 1978 harmed the ability of blue mussels, *Mytilus edulis* to collect food, because *Phaeocystis* colonies adhered to the gills. The reduced food intake caused by clogged gills and feeding inhibition contributed to starvation, to reduction in lipid and protein content, to resorption of ripe gametes, and ultimately to reproductive failure (Pieters *et al.*, 1980). Oyster larvae affected by *P. pouchetii* blooms grew 26 to 83% slower than oyster larvae in control groups did (Walne, 1970, cited in Verity and Smayda, 1989), and *P. pouchetii* is an inadequate food source for adult oysters (Gabbott and Walker, 1971, cited in Verity and Smayda, 1989).

It was observed that increased mortalities and the poorest growth of cod, *Gadus morhua*, larvae reported in aquaculture facilities in Norway coincided with the end phase of *P. pouchetii* blooms. A light-induced toxic effect on cod larvae was found recently. *Phaeocystis pouchetii* produces chemical compounds that are lethal to cod larvae, and the production of these compounds appears to be dependent on the level of irradiance. When fish larvae were offered *P. pouchetii* during feeding experiments, acute mortalities were more often observed when *P. pouchetii* had been exposed to high irradiance levels in spring (Eilertsen and Raa, 1995; Aanesen *et al.*, 1998). The toxic effects of filtered seawater on cod larvae during *P. pouchetii* blooms indicate that the toxins are released into the water. It was postulated that toxins entered with the intake water and that high toxin levels coincided with spring bloom characteristics (Eilertsen and Raa, 1995).

The assumed toxic principle of *P. pouchetii* was extracted from cultures by filtering and solid-phase sorbent techniques. The active material from the cultures was found within the chemical fraction previously established for the separation of *Chrysochromulina* and *Prymnesium* sp. toxins. The presence of active material was also found in filtered seawater collected during a bloom, confirming that *Phaeocystis*

pouchetii releases the active material into the natural environment. Hemolytic activity was almost absent in the material tested, demonstrating that the toxic principle in *P. pouchetii* is different from that described for other prymnesiophytes. By the fly-bioassay method, a rapid response to injected material was obtained, resulting in a high proportion of apparently "dead" flies being registered within 1 h. However, an unexpected response was observed: some of the flies that were presumed dead regained motility within 4 hours, and the proportion of recovered flies was inversely proportional to the dose injected. Regained motility was also found when the injected material was obtained from filtered natural seawater. The compounds released by *P. pouchetii* appear to be anesthetizing and may temporarily narcotize fish larvae; in excess doses, they may be toxic (Stabell *et al.*, 1999). Although Aanesen *et al.* (1998) proposed that ingestion of toxic *Phaeocystis* cells and intestinal absorption was the most probable route of intoxication of cod larvae, Stabell *et al.* (1999) suggested that the fact that larvae also died in filtered seawater from which *Phaeocystis* cells had been removed would also indicate other mechanisms: (1) cod larvae may ingest particles that are coated by partly hydrophobic, precipitated material that contains "toxic" compounds, or (2) a toxin absorption (during ionic regulation) resulting from the swallowing of seawater containing harmful material.

5. Cyanobacteria

a. Trichodesmium spp.

Trichodesmium blooms are ubiquitous in tropical, subtropical, and temperate seas and form some of the largest phytoplankton aggregations ever observed (Sellner, 1997). *Trichodesmium* aggregations provide an extremely important habitat for a diverse microheterotrophic community, including cyanobacteria, protists, fungi, bacteria, dinoflagellates, diatoms, copepods, and hydroids. Metazoan herbivory by harpacticoid copepods, salps, zooplankton, and fish on *Trichodesmium* is common (O'Neil and Roman, 1992, 1994; Sellner, 1997), and there were no apparent adverse effects when seagulls, *Larus brunicephalus*, fed on sardines, *Hilsa kanagurta*, and Indian mackerel, *Rastrelliger kanagurta*, with *Trichodesmium* filling 80 to 90% of the fishes' gut volume (Ramamurthy, 1970). Two dominant marine species, *Trichodesmium erythraeum* and *T. thiebautii*, occasionally have been implicated in mortality incidents and negatively affecting marine life (Table 2), but it is still unclear as to whether these are due to poor water quality or to toxicity. A public health incident involving a *Trichodesmium* bloom in Brazil was even held responsible for "Tamandare fever," but the exact etiology of this disease and the role of *Trichodesmium* was unclear (Satô *et al.*, 1963).

Generally, coastal blooms of *T. thiebautii* did not create a problem for farmed pearl oysters and there were no reported mortalities. However, when bloom water was used for experiments on oysters isolated in the laboratory, the *Trichodesmium* began to decay, and oysters subsequently died (Chellam and Alagarswami, 1981). Recently, a highly potent neurotoxic compound that resembles anatoxin-a was isolated from a mixed *T. thiebautii-T. erythraeum* bloom dominated by *T. thiebautii*. Bloom samples collected from St. Thomas, US Virgin Islands, in the Caribbean were highly neurotoxic to mice with an i.p. LD_{50} value ranging from 5- to 85-mg bloom

dry weight/kg body weight. Toxicity in mice was characterized by severe convulsions and then death within 2 to 20 min from respiratory failure. No salivation, lacrimation, or signs typical of hepatotoxic microcystin poisoning were observed (Hawser *et al.*, 1991; Hawser and Codd, 1992). No significant inhibition of cholinesterase was obtained when high levels of the *T. thiebautii* or *T. erythraeum* extracts were used, in contrast to the inhibition noted when neurotoxic extracts of *Oscillatoria agardhii* were used as a positive control.

Trichodesmium thiebautii is toxic to some cyclopoid and calanoid copepods, brine shrimp (*Artemia*), and *Daphnia* spp. (Table 10). However, harpacticoid copepods that are associated with *Trichodesmium* blooms can apparently feed on toxic *T. thiebautii* with no adverse effects and appear to have some undefined adaptive strategy (Hawser *et al.*, 1992; O'Neil and Roman, 1994). By producing toxin(s), *Trichodesmium* may avoid predation by dominant copepod groups (Hawser *et al.*, 1992). Based on the various assays and toxicity tests evaluated, it was suggested that *T. thiebautii* is toxic, whereas *T. erythraeum* was nontoxic (Hawser and Codd, 1992; Hawser *et al.*, 1992). These authors further recommended that axenic cultures be tested because of possible toxicity due to bacteria associated with natural populations of *T. thiebautii*.

Blooms of *T. erythraeum* are not usually considered toxic (Hawser and Codd, 1991; Sellner, 1997), but they have been associated with ciguatera-like outbreaks in Australia (Hahn and Capra, 1992), mortalities of coral polyps (Endean, 1977), avoidance behavior by fish (Nagadhushanam 1967; Eleuterius *et al.*, 1981), and possibly having a role in coral bleaching (Coles, 1994). In India, a wide-scale mortality event involving numerous species of animals was caused by a decaying *T. erythraeum* bloom and associated poor water quality (Chacko, 1942; Table 7). In June 1983, when a bloom was driven to shore along the east coast of Thailand, *Trichodesmium* accumulated into reddish-brown foam patches in the surf. Decomposition of the bloom along a 20-km stretch of beach was associated with respiratory irritation in humans, but no harmful effects to wild marine life were noted. However, the bloom caused extensive damage to fish farms along the coast, and there was an estimated loss of $1.16 million. The fish mortality was attributed to anoxic conditions generated by decomposing *Trichodesmium* (Suvapepun 1989).

Although there was no evidence for toxicity in *T. erythraeum* from the Caribbean (Hawser and Codd, 1992), a strain from Australia contained toxic, water-soluble material that produced symptoms in mice similar to those produced by water-soluble extracts of the flesh of the narrow-barred Spanish mackerel, *Scomberomorus commersoni*, which was implicated in ciguatera poisoning. Extracts of the water-soluble material from the cyanobacterium and the fish were chromatographically indistinguishable. The water-soluble material was lethal to mice within 30 min if injected i.p. at a concentration of 0.25 g/kg mouse. Symptoms in the mice included ataxia, piloerection, quiescence, loss of balance, exophthalmus, labored breathing, and frequently, convulsive spasms. Necropsy revealed markedly swollen livers, distended blood vessels, and engorged sinuses. A lipid-soluble component was also identified that resembled the chromatographic and toxic properties of a scaritoxin-like substance isolated from narrow-barred Spanish mackerel. When the lipid-soluble component was injected into mice it produced signs similar to those produced by classic ciguatoxin, but the ciguatoxin-like material was different from classic ciguatoxin. No epibiotic organisms such as dinoflagellates were observed to

be associated with the *Trichodesmium* filaments, but heterotrophic bacteria may have been present. Ciguatoxin-like compounds from *T. erythraeum* have a possible role in ciguatera outbreaks in Australia and can be accumulated in narrow-barred Spanish mackerel (Endean *et al.*, 1993); snubnose pompano, *Trachinotus blochi*; and the oysters *Pinctada margaritifera*, *Lopha cristagalli*, and *Ostrea nomades* (Hahn and Capra, 1992). It is unclear, however, what potential effects these toxins may have on the health of these species.

When white sea bass, *Lates calarifer*, larvae were exposed to water from a natural *T. erythraeum* bloom, 30% were killed within 24 h when the density of the cyanobacterium exceeded 6.915×10^2 trichomes/ml at 29°C, pH 8.3, NH_4 1.54 ppm, and NO_3 1.46 ppm (Suvapepun *et al.*, 1984, cited in Suvapepun 1992). Mortalities in this case, however, may have been due to poor water quality.

When adult copepods, *Acartia tonsa*, were exposed to intact *Trichodesmium* sp., there were no apparent ill effects, but a high mortality rate was noted when adult copepods were exposed to aged or homogenized cells. This suggests that intracellular toxins were released after cell lysis or disruption. Although *Acartia* ingested healthy cells, egg production could not be supported on a *Trichodesmium* diet, and poor assimilation of food was indicated. After 17 h immersed in aged cultures, *Acartia* survivors were weak, less responsive to probing, and unable to move. Affected copepods also had distended and everted intestines, suggestive of a possible toxic effect (Guo and Tester, 1994).

A *T. erythraeum* bloom in pond culture in Vietnam has been associated with mortality of the shrimp *Penaeus monodon* (Lam and Hai, 1996). Poor survival of the prawn *P. merguiensis* larvae was documented during a bloom of *Trichodesmium* spp. in Albatross Bay, Gulf of Carpentaria, Australia. Prawn larvae reared *in situ* during the bloom failed to develop beyond the first protozoea stage. These *in situ* results were confirmed by the results of laboratory experiments in which none of the larvae that were fed *Trichodesmium* sp. developed beyond the first protozoea stage, whereas 94% of those fed the green flagellate *Tetraselmis suecica* did. Although larvae ingested *Trichodesmium* both in natural blooms and laboratory experiments, the *Trichodesmium* was of no nutritional value to the larvae. The ultrastructure of larval gut cells indicated that the larvae that had ingested *Trichodesmium* filaments were starving. Swollen mitochondria and vesiculated endoplasmic reticulum were observed in the gut cells; these are the typical responses to starvation that have been documented in other crustacean larvae (Preston *et al.*, 1998).

A recent report of an indirect effect of the presence of *Trichodesmium* blooms may be very significant to molluscan and public health. Significant changes in water quality were documented during intensive *Trichodesmium* blooms in the central Great Barrier Reef, near Townsville, Australia. Chemical speciation measurements have established that cadmium, lead, and copper ions in seawater become more bioavailable during the presence of *Trichodesmium*. Coincident with the increased bioavailability of trace elements during the blooms, significant and sustained increases in total iron, zinc, cadmium, copper, silver, and manganese occurred in the black lip oyster, *Saccostrea amassa*. Levels of zinc, cadmium, and copper in these oysters exceeded health guidelines by 8000%, 4000%, and 3000%, respectively (Jones, 1992).

U. HARMFUL SPECIES THAT CAUSE MECHANICAL DAMAGE

1. Diatoms

Mortality and gill lesions in Atlantic salmon, *Salmo salar*, reared in a seawater net pen in British Columbia were associated with a dense bloom of mixed diatoms dominated mostly by *Skeletonema costatum*, *Thalassiosira aestivalis*, and *T. rotula*. A histopathological examination of the gills in moribund fish showed congestion of the central venous sinus at the base of the primary lamellae and diffuse edema at the base of the secondary lamellae. Mucus-containing diatom fragments and sloughed, necrotic epithelial cells were observed between the lamellae. No other pathogens were observed in the gills, and lesions were most severe when directly associated with accumulations of algae (Kent *et al.*, 1995).

An unusual case of mechanical damage associated with several diatom species was reported in a white sucker, *Catostomus commersonii*, that had a granulomatous enteritis. Wolke and Trainor (1971) suggested that the granulomatous response to the diatoms was generated by a cellular response either to the silicon dioxide of the diatom cell wall or to the mineral exoskeleton (= frustule).

a. Chaetoceros spp.

In August 1992, *Chaetoceros convolutus* was implicated in a mortality of red king crabs, *Paralithodes camtschatica*, in Alaska. Although low levels of dissolved oxygen were reported at the same time as the *Chaetoceros* bloom, pathological changes in the gills associated with the penetration of diatom spicules were also a major factor in the mortality (Tester and Mahoney, 1995). *Chaetoceros wighami* (and *C. debile* and *Dictyocha speculum* [see under silicoflagellates] in one incident) were considered responsible for the deaths of up to 550,000 Atlantic salmon, *Salmo salar*, smolts in two separate incidents in Scotland. Histological gill sections showed extensive tissue necrosis and sloughing, with separation of the secondary lamellae and moderate hyperplasia at the base of the filaments. Plankton cells were noted to be in close association with the secondary lamellae. Bruno *et al.* (1989) suggested that the mortalities resulted from direct clogging and abrasion of the delicate gill structures by the silicified diatom frustules. Market value of the Atlantic salmon lost was approximately $1.6 million (Johnson, 1988; Bruno *et al.*, 1989). *Chaetoceros concavicornis* and *C. convolutus* have been implicated in salmonid mortalities in the Pacific Northwest, where fish are cultured in net pens (Taylor, 1988; Rensel *et al.*, 1989; Yang and Albright, 1992, 1994; Albright *et al.*, 1993; Rensel 1993). Short-term laboratory studies on the effects of *C. convolutus* on sockeye and coho salmon smolts indicated that exposure to several million cells/l over a 1- to 7-h period caused total mortality (Bell *et al.*, 1974, in Rensel *et al.*, 1989). Under laboratory conditions, exposure of juvenile chinook salmon, *Oncorhynchus tshawytscha*, and coho salmon, *O. kisutch*, to *C. concavicornis* caused mortality at concentrations as low as 1.5×10^1 cells/ml seawater (Yang and Albright, 1994). Although several theories suggested that the mortalities were due to penetration of the fish gills by the diatom spines, which resulted in excess mucus production, hemorrhaging of damaged tissue, and blood hypoxia or subsequent secondary bacterial infections (Bell, 1961), other mechanisms may also have been operating (Yang and Albright, 1992; Rensel, 1993). Barbed spines of *Chaetoceros* spp. damaged the physical

integrity of the respiratory epithelium of rainbow trout, *O. mykiss*, which led to increased mucus secretion. Accumulation of mucus on and between the secondary lamellae inhibited the oxygen uptake by the gill, resulting in hypoxic conditions, anaerobic metabolism (characterized by increased blood glucose and lactate concentrations as well as haematocrit values), leucopenia (depressed white blood cell count), and subsequent mortality (Yang and Albright, 1992, 1994). Atlantic salmon, *Salmo salar*, experimentally exposed to 4×10^5 *C. concavicornis* cells/ml immediately displayed a cough response and began to die within 3 h. Blood from dying fish was severely hypoxic and hypercapnic (elevated CO_2). There was no evidence that the diatom spines had penetrated the gills. The primary mechanism inducing hypoxia and hypercapnia appears to be mucus production resulting from diatom irritation of the gill epithelium. Excess mucus production resulted in minimal oxygen transfer across the gills, which led to a change in the blood-oxygen partial pressure (Rensel, 1993). There is also compelling evidence that sublethal exposure of salmonids to *Chaetoceros* increases their susceptibility to bacterial disease (Albright *et al.*, 1993) (see section on disease).

b. Corethron sp.

In early October 1987, up to 60,000 40 g coho salmon, *O. kisutch*, began dying within one week after their transfer to saltwater net pens located along the coast of British Columbia. Clinically, the fish hung listlessly near the top and sides of the net pen. Rapid, labored respiration with constant opercular flaring was typical. Some fish had petechial hemorrhages midway along the fin rays. Mortality continued through November and early December, with approximately 10% of the remaining stock dying each week. Surviving fish had extremely poor growth rates, and many subsequently became affected by Bacterial Kidney Disease (see section on disease). Histological and ultrastructural examination of sequential samples of gill tissue revealed a dramatic suppurative branchitis accompanied by extensive fusion of gill lamellae. This dramatic host response and subsequent high rate of mortality appeared to be in response to a bloom of *Corethron*-like diatoms. The setae of *Corethron* did not penetrate host epithelial tissues, except in occasional nonrespiratory areas on the arch. Instead, the impacted diatom apparently became enveloped by the process of lamellar fusion. Extensive lamellar fusion reduced the surface area for oxygen and electrolyte exchange, resulting in reduced respiratory efficiency (Speare *et al.*, 1989).

c. Leptocylindrus minimus

In November 1989, in the center and south of the Chiloe Archipelago, Chile, high concentrations of *L. minimus* were detected, and unusual behavior and mortalities were observed in trout and salmon (Clement and Lembeye, 1993). A similar event occurred in 1993 in the same area. Although it is not clear what mechanisms are involved in the mortality, it is possible that *L. minimus*, like other diatom species, causes mechanical damage. During the bloom, salmon retired to the corners of their cages, and trout swam at the surface with their dorsal fins out of the water. The gills of some of the fish were slightly pale from excess mucus secretion. There was a loss of appetite, especially in trout, but also in coho salmon and Atlantic salmon. These effects were seen at concentrations below 1×10^4 cells/ml — mortalities can occur at higher concentrations (Clement, 1994).

2. Silicoflagellates

a. Dictyocha speculum

Several mortalities of cultured fish in Europe have been associated with mechanical damage due to *Dictyocha speculum* blooms (Table 6). In April 1987, at a rainbow trout farm in Douarnenez, France, an overnight bloom produced turbid water, and caged fish showed signs of distress and asphyxiation. *Dictyocha speculum* densities varied between 1.3×10^2 to 1.3×10^3 cells/ml. Gills were clogged with mucus and many algal cells; histopathology revealed edema and hyperplasia of the lamellae. It was suspected that the siliceous skeleton of *Dictyocha* irritated the gills, which caused the fish to produce more mucus and a reduced gill exchange potential. This effect, coupled with possible low levels of dissolved oxygen overnight due to the bloom, caused the fish to die from asphyxiation (Erard-Le Denn and Ryckaert, 1990). A similar scenario occurred recently in Galicia, northwest Spain, but dissolved oxygen levels there were high. Cell densities of up to 2×10^2 cells/ml were recorded, and fish showed gill irritation and increased mucus production. Almost 5000 cultured Atlantic salmon, *Salmo salar*, died, and it was suggested that the high density of siliceous skeletons was sufficient to cause mortality (Prego *et al.*, 1998).

In Denmark in 1983, a wide-scale mortality of cultured rainbow trout was also associated with a *D. speculum* bloom, but with the naked phase of the life cycle. The absence of a siliceous skeleton in this phase therefore was not responsible for causing mechanical damage. Toxicological assays on the naked stage failed to demonstrate toxicity, and it was considered that low levels of dissolved oxygen was the most likely factor in the mortalities (Henriksen *et al.*, 1993). Cell counts of up to 2.5×10^4 cells/ml were reported (Thomsen and Moestrup, 1985). An organism referred to as "flagellate X" associated with cultured fish mortalities in Ireland and Scotland (Gowen, 1987; Erard-Le Denn, 1991) was considered to be the same as the naked flagellated form of *D. speculum* (K. Tangen, personal communication, in Gowen, 1987; Ø. Moestrup, personal communication, in Erard-Le Denn, 1991).

3. Pelagophytes

Extensive blooms of brown tide caused by *Aureococcus anophagefferens* and *Aureoumbra lagunensis* (Cosper *et al.*, 1987; Buskey and Stockwell, 1993) have resulted in significant effects both on aquatic ecosystems and on individual species. Recent reviews have summarized the major aspects of the ecology and effects of these species (see Buskey *et al.*, 1996; Bricelj and Lonsdale, 1997). Only a brief summary of their impacts is provided here. Although *Aureococcus* and *Aureoumbra* are considered to be nontoxic, the sheer biomass and persistence of monospecific blooms that can last for several months are sufficient to result in numerous direct and indirect effects on aquatic organisms and their habitats. Brown tides have been responsible for dramatic losses in species abundance and diversity (Cosper *et al.*, 1987; Shumway 1990; Buskey and Stockwell, 1993; Montagna *et al.*, 1993; Buskey *et al.*, 1996, 1997; Street *et al.*, 1997).

Although some protists are capable of consuming *Aureococcus*, selective avoidance by most protists has been demonstrated both experimentally and in the field, suggesting that inhibition of grazing by microzooplankton may contribute to brown

tide initiation and maintenance (Bricelj and Lonsdale, 1997). Abundance of meroplanktonic larvae, including those of polychaetes and bivalves, were negatively correlated with brown tide concentration (Smayda and Fofonoff, 1989). *Aureococcus* reduced the feeding activity of filter-feeding shellfish by inhibiting ciliary action, depressed egg-hatching success in red and black drum, and lowered the abundances of zooplankton, shellfish, and other benthic filter feeders (Tracey, 1988; Draper *et al.*, 1990). In 1985 and 1986, *A. anophagefferens* was responsible for the demise of the bay scallop, *Argopecten irradians*, fishery on Long Island, New York, USA, by inducing starvation and subsequent recruitment failure (Tracey, 1988; Tettelbach and Wenczel, 1993). Economic losses to the bay scallop fishery of New York State caused by the reduced landings attributed to brown tide were estimated at $2 million per year (Kahn and Rockel, 1988). Recruitment failure may have been caused by gamete resorption in reproductive adults (Tracey, 1988) or the inability of an *Aureococcus* diet to support gametogenesis (Bricelj and Lonsdale, 1997).

Based on experimental evidence (Tracey, 1988; Bricelj *et al.*, 1989; Gallager *et al.*, 1989; Bricelj and Kuenstner, 1989), Bricelj and Kuenstner (1989) suggested that chronic toxicity of *A. anophagefferens* cells at high densities, rather than indigestibility, small size, or poor nutritional quality may be responsible for the detrimental effects and mortalities observed in bivalves. *In vitro* studies demonstrated that the extracellular, diffuse, polysaccharide layer of *Aureococcus* cells contains a bioactive compound, which is released by amylase digestion (Tracey *et al.*, 1988; Bricelj and Kuenstner, 1989), that is responsible for reduction in the lateral ciliary beat frequency of isolated gills of some bivalves (Draper *et al.*, 1990; Gainey and Shumway, 1991; Bricelj and Lonsdale, 1997). As discussed by Bricelj and Lonsdale (1997), although specific cell toxins have not been identified from *Aureococcus*, several studies (Tracey, 1988; Ward and Targett, 1989; Gallager *et al.*, 1989; Gainey and Shumway, 1991) have demonstrated that inhibitory effects on bivalve feeding require direct cell contact and are not elicited by dissolved metabolites in cell-free filtrates of intact or lysed cells.

Persistent brown tides in Long Island reduced light availability, which resulted in a decline in eelgrass, *Zostera marina* (Dennison *et al.*, 1989). Because eelgrass provides shelter and substrate for numerous estuarine benthic species, a loss in eelgrass habitat may have contributed to poor recruitment of bay scallops and the slow recovery of the stocks (Tettelbach and Wenczel, 1993). A decline of the kelps *Laminaria saccharina* and *L. digitata* was related to mussel mortalities attributed to brown tide because of the loss of suitable molluscan substrate for kelp attachment (Smayda and Fofonoff, 1989)

In Laguna Madre, Texas, a persistent, nearly monospecific bloom of *Aureoumbra lagunensis* has been occurring since January 1990. Zooplankton populations declined following the outbreak of the bloom (Buskey and Hyatt, 1995). Prior to the onset of the Texas brown tide, the dwarf surfclam, *Mulinia lateralis*, was the dominant benthic organism, with densities as high as 6000/m^2, whereas the mean abundance of the species after the bloom declined to 24/m^2 (Street *et al.*, 1997). There is no evidence that the Texas brown tide is toxic to adult invertebrates (Buskey *et al.*, 1996). In Laguna Madre, seagrass-shoot density declined from 8000 to 10,000 shoots/m^2 in 1992 to less than 4000/m^2 in 1994 (K. Dunton, unpublished data cited in Buskey *et al.*, 1996). Light attenuation due to the brown tide bloom was also responsible for declines of the seagrass *Halodule wrightii* (C. Onuf, submitt. in

Buskey *et al.*, 1996). Because seagrasses stabilize sediments, loss of seagrass contributes to resuspension of sediment particles, leading to further light reduction and subsequent further losses of seagrass. There were also noticeable declines in mesozooplankton populations, largely due to reduced feeding, growth, and fecundity of dominant plankters such as the copepod *Acartia tonsa*. Microzooplankton (ciliates, copepod nauplii, and rotifers) population abundance changed from approximately 2.0×10^1 to 2.0×10^2 /ml to less than 3.0×10^1 /ml after the onset of the bloom. Microzooplankton grazing rates on phytoplankton standing stock were reduced from approximately 95% to less than 5% during the bloom (Buskey and Stockwell, 1993; Buskey *et al.*, 1996). Spotted seatrout, *Cynoscion nebulosus*, eggs from laboratory spawns that were placed in brown tide having concentrations of 1 to 1.6×10^6 cells/ml showed significantly reduced hatching rates and 2- to 3-day survival. Only 20% of the fish survived to the third day after hatching. Feeding rates of larval spotted seatrout on rotifers in brown tide water were also considerably reduced when compared to those in nonbloom water (J. Holt, unpublished data cited in Buskey *et al.*, 1996). No adverse effects of brown tide on adult fish or macrobenthic communities were apparent (Buskey *et al.*, 1996).

V. HARMFUL SPECIES AND WATER QUALITY

Any highly concentrated bloom has the potential to reduce water quality. Ultimately, decomposing and respiring cells combined can contribute to anoxic conditions and the subsequent formation of toxic sulfides. Although the discussion of environmentally associated effects of HABs is beyond the scope of this communication, some examples of large-scale mortality events involving nontoxic species are provided below.

1. Dinoflagellates

a. Ceratium spp.

Mass mortalities of aquatic organisms (Table 2) have been blamed on anoxic conditions that developed as a result of blooms of several species of *Ceratium* (Cho, 1979; Mahoney and Steimle, 1979; Nicholls *et al.*, 1980; Onoue, 1990) (and see below under mixed species). In summer 1976 in the New York Bight, USA, a large-scale mortality of marine animals, especially of Atlantic surfclams, *Spisula solidissima*, was associated with the decline and ultimate collapse of a *Ceratium tripos* bloom. Low levels of dissolved oxygen and the subsequent production of hydrogen sulfide contributed to the mortality. Oxygen depletion extended over an area covering 13,000 km^2. An estimated loss of 143,000 metric tons of surfclams was attributed to the bloom. Although some mortalities of benthic fish were reported, the principal effect was to alter established migration and distribution patterns, with recovery of the fish stocks occurring some months after the decline of the bloom (Mahoney and Steimle, 1979).

In August 1987, reports of discolored brown water in Norway were confirmed to be a bloom dominated by *C. furca* (2.8×10^3 cells/ml), but the bloom also included *C. lineatum* (2.72×10^2 cells/ml), *C. tripos* (1.36×10^2 cells/ml), and

Prorocentrum micans (3.4×10^2 cells/ml). There were some reports that farmed salmonids stopped eating, or had a reduced appetite, and when fish were exposed for a longer period, there were reports of mortality of both large (6 to 8 kg) and small fish. Slight lesions were present in the gills. Symptoms were attributed to the algal bloom (Tangen, 1988) (Table 2).

During March 3 to 6, 1990, fish farms in Kagoshima Bay, Japan, were affected by a *C. fusus* red tide. Thirty-nine thousand juvenile yellowtail, *Seriola quinqueradiata*, died when the density of *C. fusus* exceeded 6×10^2 cells/ml (depth 0 to 15 m), resulting in an economic loss of $462,000. In laboratory exposures to 9.8×10^3 to 3.2×10^4 *C. fusus* cells/ml, red seabream died within 56 to 58 min (dissolved oxygen 5 to 6 ppm, temperature 18 to 19°C, salinity 32 ppt), but tilapia survived for more than 3.5 h. At cell densities of 3.6×10^3 cells/ml, red seabream were extremely prostrated, but no death ensued after 1.5 h of exposure. Fish gills became clogged with *C. fusus*, and excess mucus and marked edema were observed in the secondary lamellae. Onoue (1990) suggested that mortalities occurred because of suffocation induced by excess mucus production in response to *Ceratium*.

In April 1997, a large stranding (1500 tons) of rock lobster, *Jasus lalandii*, on the South African west coast followed the decay of a massive bloom of *C. furca* (see also section on mixed species). Exhaustion of nutrients and eventual decay of the bloom inshore led to oxygen depletion throughout the water column. As a consequence, animals concentrated in the shallow surf zone in an attempt to escape anoxic bottom conditions. During the next few weeks, further strandings resulted in a total loss of 2000 tons of rock lobsters valued at $50 million. Because rock lobster are slow-growing and long-lived, recovery of the the regional fishery is likely to be slow (Pitcher, 1998; Pitcher and Cockcroft, 1998).

Although most *Ceratium*-associated aquatic mortalities are attributed to poor water quality, one report (Mijares *et al.*, 1985) indicated the possible role of an uncharacterized toxin from *Ceratium*. In March 1982, 200 tons of ichthyoplanktonic sardines, *Cetengraulis edentulus*, died in Carenero, Venezuela. Analysis of the fish indicated the presence of a high concentration of paralytic toxin that killed mice by i.p. injection. A toxin with the same molecular weight and UV absorbance was isolated from plankton samples collected at the site of the fish kill. The toxic extracts from both fish and plankton were identical to the β fraction isolated from the fire sponge, *Tedania ignis*. Based on the dominance of *Ceratium furca* in the plankton samples and on a feasibility index, *C. furca* was considered to have produced the toxin found in the fish (Mijares *et al.*, 1985). However, other potentially toxic or harmful species, such as *Pseudo-nitzschia seriata* and *Rhizosolenia* sp., were also present in the plankton samples, so it is unclear what species may have been responsible for the kill. Because toxins were only verified from field-tested mixed plankton and not from clonal cultures, this report should be considered inconclusive.

b. Gonyaulax polygramma

Probably the largest-scale mortality ever documented to be associated with *G. polygramma* was that reported in False Bay and Walker Bay, South Africa, in April-May 1962. More than 100 tons of marine organisms, including more than 100 species (Table 2), were killed as a result of the bloom. Cell concentrations were estimated at 1×10^4 cells/ml. The mass mortality was attributed to the large biomass of the bloom, subsequent death and decay

of the plankton, and the severe depletion of oxygen in the water (Grindley and Taylor, 1962, 1964).

In May 1988, large-scale fish kills and two incidents of shellfish mortality in Tolo Harbor, Hong Kong, China, were associated with anoxic conditions caused by a *Gonyaulax polygramma* bloom. The most serious fish kill resulted in a loss of 35 tonnes of fish, estimated at $Hong Kong 7 million. A thick mucus layer was noted on the gills of dead fish. The collapse of the bloom was coupled with the onset of the summer destratification and depletion of oxygen in the bottom waters. Before the fish kills, oxygen levels were virtually zero throughout the water column below a depth of two meters. The bloom declined from 5×10^4 cells/ml to 0.1 cells/ml subsequent to the fish kills. The high water pH (8.85) caused by the photosynthetic activity of the bloom likely contributed to an increase in un-ionized ammonia, which is also known to stress fish (Lam, 1988; Lam and Yip, 1990).

From late August until mid-November 1994, a *G. polygramma* red tide in Uwajima Bay, Japan, caused mass mortalities of cultured and wild fish and shellfish stocks (Table 2) that were worth more than 800 million yen. Maximum cell densities recorded were 6.8×10^4 cells/ml. During the red tide, oxygen-deficient water — and ultimately, anoxic conditions — and the high sulfide and ammonia concentrations caused by bloom decomposition contributed to the large-scale mortalities (Koizumi *et al.*, 1996).

c. Gonyaulax spinifera

During August 1990, a massive bloom of *Gonyaulax spinifera* developed along the west coast of Vancouver Island, British Columbia, Canada. The bloom, which extended alongshore for more than 400 km and stretched offshore as far as 100 km, was at the time the most extensive red tide on record in British Columbia. Recorded surface cell concentrations were as high as 9×10^3 cells/ml. A substantial shellfish mortality believed to be due to hypoxia occurred in Barkley Sound (Forbes, 1990).

d. Noctiluca scintillans

Several mortality events have been attributed to *Noctiluca* blooms (Table 7), and although not considered toxic, these blooms can significantly contribute to adverse water quality. In some cases, such conditions may not result in mortality but in avoidance by fish, leading to localised reductions in fisheries (Bhimachar and George, 1950; Ogawa and Nakahara, 1979; Devassy, 1989). A *Noctiluca* bloom can create a large quantity of mucus, which mechanically damages fish gills or interferes with fish respiration (Subramanian, 1985). In other cases, *Noctiluca* blooms can affect the concentrations of dissolved oxygen or ammonia (Suvapepun, 1989), which indirectly contribute to fish kills. Because *Noctiluca* is heterotrophic, large blooms can consume significant quantities of oxygen, or their subsequent decay and bacterial production can result in severe oxygen depletion (Elbrächter and Qi, 1998). Several fish kills have been attributed to low levels of dissolved oxygen (Subramanian, 1985; Ho and Hodgkiss, 1992). Ammonia production has been associated with older blooms, because when *Noctiluca* cells die and lyse, accumulated ammonia is released (Schaumann *et al.*, 1988, cited in Elbrächter and Qi, 1998) and fish kills occur (Okaichi and Nishio, 1976). In July 1986, a mass mortality of demersal fish and benthic organisms along the east coast of Jakarta Bay, Indonesia, coincided with a bloom of *Noctiluca* at maximum cell densities of 5.3×10^6 cells/m^3. High concentrations of ammonia, nitrogen, and phosphate were measured just

after the mortality (Adnan, 1989). From July to September 1988 in Punta Patilla Bay, Venezuela, an *N. scintillans* bloom that covered an area of approximately 3 km^2 reached population densities as high as 5×10^2 cells/ml. The presence of the bloom resulted in a 100% mortality of mussels, *Perna perna*, that were living in water 0 to 3 m deep. Mouse bioassays revealed that the mussels were not toxic. An examination of the gills showed that they were covered by a mucilaginous substance that likely contributed to suffocation of the animals (La Barbera Sanchez, 1991).

e. Mixed species — Ceratium furca/Prorocentrum micans

In March 1994, the worst marine mortality ever recorded in South Africa occurred along the west coast in St. Helena Bay. The event was caused by the entrapment and subsequent decay of a mixed phytoplankton bloom dominated by nontoxic *Ceratium furca* and *Prorocentrum micans*, with lower concentrations of *Alexandrium catenella* and *Dinophysis acuminata*. Average cell concentration was approximately 1×10^3 cells/ml, although concentrations up to 7×10^3 cells/ml were also recorded. A 30-km stretch of St. Helena Bay was littered with dead and dying marine fauna. Approximately 60 tons of rock lobster, *Jasus lalandii*, and 1500 tons of fish, comprising about 50 species, washed ashore. Mullet, *Liza richardsoni*, made up the bulk of the dead fish (1250 tons), with the remainder being dominated by sharks and bottom-dwelling fish. Surveys of the rocky shores revealed that most mussels, limpets, sea urchins, and other intertidal life had died, except for the false limpet *Siphonaria capensis*, which is capable of switching to anerobic metabolism under anoxic conditions. The mortality was caused by suffocation due to oxygen depletion and toxicity due to hydrogen sulfide poisoning. Oxygen concentrations were maintained at <0.5 ppm in the bottom waters of the bay, and hydrogen sulphide generated by anerobic bacteria was recorded at 50 μmol/l. A complete absence of rock lobsters and other invertebrate life was recorded 1 month after the event, and recruitment of juvenile lobsters did not occur until seven months later (Matthews and Pitcher, 1996).

2. Diatoms

a. Skeletonema costatum

A mass mortality of Atlantic herring, *Clupea harengus*, eggs laid on gravel and marl ridges at a depth of 18 m was noted along the south coast of the Isle of Arran, Scotland, in April 1990. The area of the spawn patch was estimated to be approximately 163,000 m^2. The mortality was associated with a heavy precipitation of organic material largely composed of *Skeletonema costatum* onto the egg layer. The oxygen level of 2.0 ppm measured in water taken from under the egg mat midway through the period of mortality indicated anoxia as the likely cause of death (Morrison *et al.*, 1991).

W. SUSPECTED SPECIES WITH UNIDENTIFIED MECHANISMS

1. Dinoflagellates

a. Akashiwo sanguinea (=Gymnodinium sanguineum)

Akashiwo sanguinea (=*Gymnodinium sanguineum*) Hansen and Moestrup (Daugjberg *et al.*, 2000) occasionally has been associated with fish and shellfish mortalities

(Table 2) or behavioral effects, but the definitive mechanism by which this species may be harmful is unknown. A dense, subsurface bloom (5.1×10^2 cells/ml) of *A. sanguinea* (reported as *G. splendens*) in coastal waters off southern California was actively avoided by macrozooplankton, whose vertical distribution patterns indicated several different patterns of active avoidance of the migrating dinoflagellate layer. Filtration rates of *Paracalanus parvus* and *Calanus pacificus* were significantly lower in water from the *A. sanguinea* layer (24 m depth) than in water from 10 m. Mean gut fullness of *P. parvus*, *C. pacificus*, and *Acartia tonsa* was significantly lower in individuals collected in the bloom layer than in those examined from three other depths (Fiedler, 1982).

On several occasions there have been reports of oyster (*Ostrea lurida* and *Crassostrea virginica*) mortalities and disease outbreaks coinciding with *A. sanguinea* blooms (Table 2) (Nightingale, 1936; Bricelj *et al.*, 1992; Lee *et al.*, 1996). *Akashiwo sanguinea* was reported to be highly toxic to larvae of the Pacific oysters, *Crassostrea gigas*, and Japanese littleneck clams, *Venerupis philippinarum* (reported as *V. japonica*), in Puget Sound (Cardwell *et al.*, 1979, cited in Shumway, 1990). A recent syndrome (juvenile oyster disease) that sometimes coincided with *A. sanguinea* blooms (Bricelj *et al.*, 1992) was partially attributed to vibriosis (Lee *et al.*, 1996), and *A. sanguinea* did not appear to be a primary etiological factor (Lee *et al.*, 1996). *Akashiwo sanguinea* has been considered to have either no effects on oysters (Wikfors and Smolowitz, 1994) or only indirect effects. In field observations during an *A. sanguinea* bloom, it was noted that high *Vibrio* sp. densities in juvenile oysters and in water samples from nursery floats coincided with the bloom. *Akashiwo sanguinea* may therefore influence bacterial loading and contribute to an increase in bacterial pathogens (Lee *et al.*, 1996). The role of microalgae as potential vectors for aquatic animal pathogens is an important aspect in HAB dynamics and is discussed below (see section on HABs as vectors). The recent demonstration that *A. sanguinea* can produce low concentrations of ROS (Kim *et al.*, 1999a) may suggest that a high biomass of the algae may initiate harmful effects and render animals more susceptible to disease.

In June 1984, low-salinity water and a bloom of *A. sanguinea* appeared suddenly off Galveston, Texas, USA. High discharge from the Mississippi-Atchafalaya rivers between March and late May and a strong, wind-driven, downcoast current preceded the appearance of the low-salinity water and its associated bloom. Within a week of the first appearance of the bloom, demersal fish, numerically dominated by Atlantic threadfin, *Polydactylus octonemus* (79%), began dying early in the morning and washing ashore. Mortalities included an estimated 13 million fish, comprising 16 fish species, and blue crabs, *Callinectes sapidus*. The kill was considered to be caused by hypoxic conditions in combination with the hydrogen sulfide produced by the nocturnal metabolism of the bloom and by anaerobic decay of dead dinoflagellate cells (Harper and Guillen, 1989).

b. Prorocentrum micans

Prorocentrum micans has occasionally been associated with human shellfish poisonings or with aquatic mortality events, but potential toxins have not been identified. In 1955, toxic cockles, *Cardium edule*, from the lagoon at Obidos, on

the west coast of Portugal, were associated with one human fatality and numerous poisonings. Neurological symptoms, including loss of sensitivity in the lips and chin, numbness in the arms and hands, paraplegia of the legs, tremors, ataxic walking, and a floating feeling were reported. Cockle extracts were lethal to mice. In addition, blue mussels, *Mytilus edulis*, and palourdes, *Tapes decussatus*, sampled from the same area were also toxic to mice. Prawns (*Palaemon* sp.), crabs (*Portunus* sp.), mullet (*Mugil* sp.), and bass (*Morone* sp.) caught in the lagoon at the same time were nontoxic to mice. A *Prorocentrum micans* bloom (1.5 to 2.7 $\times$ 10^3 cells/ml) was coincidentally present in the lagoon and therefore was suspected to be the major toxin producer (Pinto and Silva, 1956). In October 1968, low-level toxicity in mussels and oysters in Algoa Bay, Port Elizabeth, South Africa, was reported following a *P. micans* bloom (Grindley and Sapeika, 1969). In November 1973 in Dwarskersbos, South Africa, *P. micans* was associated with toxicity in white mussels, *Donax serra*, which caused slight PSP in human consumers (Horstman, 1981). In these human poisoning cases, it is unclear what toxins were involved or what was the relationship with *P. micans* to the symptoms.

Prorocentrum micans was implicated when 40 to 50% of blue mussels were killed in northern Brittany, France, but this mortality event was probably due to low levels of dissolved oxygen (Lassus and Berthome, 1988 in Shumway, 1990). Most studies with *P. micans* have suggested that this species is nontoxic. For example, in feeding experiments, *P. micans* gave no evidence of toxicity or sublethal effects in bivalves (see section on *Prorocentrum minimum*) (Pillet and Houvenhaghel, 1995; Wikfors and Smolowitz, 1995) or to *Artemia* in bioassays (Demaret *et al.*, 1995).

In conjunction with *Ceratium* spp., *P. micans* has been implicated in several marine mortalities (see *Ceratium* spp. and mixed species sections under Harmful Species and Water Quality). Evidence for minimal ROS production (Kim *et al.*, 1999a) may suggest that high cell concentrations could have significant effects on aquatic organisms, but further studies are required.

2. Ciliates

a. Mesodinium rubrum

The ciliate *Mesodinium rubrum* is a cosmopolitan species that occasionally reaches bloom densities and forms red tides in temperate coastal waters, upwelling zones, and estuaries (e.g., Horstman, 1981; Lindholm, 1985; Crawford, 1989; Cloern *et al.*, 1994). Although there is no evidence for toxin production, the possible effects of *Mesodinium* blooms on aquatic organisms have been discussed in some instances. These effects include the association of bacterial pathogens with *Mesodinium* blooms (Romalde *et al.*, 1990a, 1990b; Crawford *et al.*, 1993) (see under section on blooms as vectors), poor water quality and its adverse effects on marine fauna (Horstman, 1981; Hayes *et al.*, 1989; Martin *et al.*, 2000), and discoloration in molluscan digestive glands (due to phycoerythrin accumulation) (Clemens, 1935; Pomeroy *et al.*, 1956; Kat, 1984; Carver *et al.*, 1996), which may indicate a potential role of the blooms as stressors in molluscs (Crawford *et al.*, 1993).

VI. HABS AS POTENTIAL VECTORS FOR PATHOGENS AND STRESSORS IN DISEASE

A. HABS AS POTENTIAL VECTORS

The association of bacteria and other symbionts with HABs has been known for many years, and several components of HAB-microbial interactions play an important role in HAB ecology. Although such a role was postulated in the 1960s (Silva, 1962) and later demonstrated by a few researchers (Kodama *et al.*, 1988, 1989), the real role of bacteria in the production of some microalgal toxins is only now becoming evident (Rausch de Traubenberg and Lassus, 1991; Doucette, 1995; Doucette *et al.*, 1998). In many cases, these bacteria are intracellular symbionts; in other cases, they are extracellular but are strongly associated with dinoflagellate populations.

The presence of HAB-associated bacteria has been documented in several microalgal species known to affect aquatic organisms, including *Alexandrium lusitanicum*, *A. tamarense*, *Amphidinium carterae*, *Gambierdiscus toxicus*, *Karenia brevis*, *Gymnodinium catenatum*, *Heterosigma akashiwo*, *Mesodinium rubrum*, *Ostreopsis lenticularis*, and *Pseudo-nitzschia multiseries* (Buck and Pierce, 1989; Tosteson *et al.*, 1989; Romalde *et al.*, 1990a, 1990b; Bates *et al.*, 1995; Doucette and Trick, 1995; Nayak *et al.*, 1997; Carrasquero-Verde, 1999; Hold *et al.*, 2001). Bacteria are important determinants of bloom population dynamics and toxin production (Doucette, 1995). Recent information has indicated (1) a strong role for interactions between bacteria and HAB species and that toxicity is related to bacterial metabolites (Doucette, 1995) and (2) a synergism between HAB species and their symbiotic bacteria that results in much higher toxin production than occurs in the HAB species alone (Bates *et al.*, 1995; Hold *et al.*, 2001). Under experimental conditions, the toxicity of *Heterosigma akashiwo* (as *H. carterae*) to salmonids depended on the presence of bacteria in cultures — axenic cultures were nontoxic to fish (Carrasquero-Verde, 1999). The role of bacteria in toxin production will not be discussed further here, but the importance of HAB-associated bacteria should always be considered with respect to toxic effects on aquatic organisms.

Aside from the possible role of HAB-associated bacteria in toxin production, there is also the potential for HABs to act as vectors for human pathogens (Doucette, 1995). Attention has been drawn to the potential role of HABs as vectors for vibrios, especially for human pathogens such as *Vibrio cholerae* (Epstein, 1995). However, little attention has been paid to the possibility that some HAB-associated bacteria are also aquatic-animal pathogens (Romalde *et al.*, 1990a; Landsberg, 1997). There is a strong possibility that HABs act as reservoirs and transmission agents for animal pathogens in aquatic systems. In certain cases, there is a possibility that in addition to stressing aquatic animals through physically harmful mechanisms or by toxin exposure, HAB species vector bacterial pathogens that can transfer to compromised animals. An increased biomass of pathogenic bacteria associated with HABs may be able to more readily infect (e.g., through breached skin) stressed animals with external damage caused by HABs. There are documented cases for increased suceptibility of aquatic organisms to bacterial disease during or subsequent to a HAB event (see below), but no study has been done to determine if the same bacterial

species involved in the disease were those vectored by the HAB. Some of the bacterial species isolated from HABs, for example, *Vibrio alginolyticus*, *V. anguillarum*, *V. parahaemolyticus,* and *Aeromonas hydrophila* (Buck and Pierce, 1989; Romalde *et al.*, 1990a), are known fish and shellfish pathogens (see Austin and Austin, 1987; Thune *et al.*, 1993; Riquelme *et al.*, 1996) and have been involved in several HAB-related disease interactions (see below). Some aquatic mortality and disease events therefore may be strongly interrelated with pathogenic microbe and HAB associations, instead of separately triggered by either toxic microalgae or infectious pathogens, the currently accepted model.

B. HABS AS STRESSORS IN DISEASE

There are several documented examples in which either acute or chronic exposure to microalgal toxins or harmful mechanisms associated with HABs were sufficient to increase the susceptibility of aquatic organisms to disease.

Heavy mortalities of more than 20 species of tropical reef fish were considered to be induced by the chronic exposure of fish to toxins produced by benthic dinoflagellates inhabiting coral reef areas (see section on ciguatera). In 1980, 1993 to 1994, and 1997, mass mortalities of tropical fish were widespread in the Caribbean and in Florida, USA (Landsberg, 1995). Over a period of several months in the 1993 to 1994 event in Florida, fish were affected extensively by a number of parasites (*Brooklynella hostilis*, *Uronema marinum*, and amoebae) and bacterial pathogens that are known to induce mortalities in fish. There was no evidence that these pathogens were the principal cause of the disease but rather were secondary invaders of fish whose health had already been compromised. The fish displayed numerous behavioral signs (see ciguatoxins) before dying. The precursor to this disease was postulated to be chronic exposure to microalgal toxins that acted as immunosuppressants and increased the susceptibility of fish to disease. At certain times, when fish are exposed to benthic toxins through dietary consumption, they become weak and susceptible to certain pathogens. In this scenario, it was considered that fish were more than likely exposed to toxins from benthic dinoflagellates, some of which are involved in ciguatera (Landsberg, 1995) (see ciguatoxins).

Pfiesteria and other microalgal species that produce bioactive compounds may have a potential role in aquatic animal diseases. Fish exposed in aquaria directly to *P. piscicida* or *P. shumwayae* cells or to water filtrate (and presumptive toxin) that contained *P. piscicida* showed behavioral changes and sloughing of the fish epithelium, which led to invasion by numerous secondary, opportunistic pathogens (Noga *et al.*, 1996). That *Pfiesteria* causes mechanical damage to fish skin during pedunculate feeding, which could allow for subsequent invasion by secondary opportunistic pathogens, is a possible mode of lesion development (Vogelbein *et al.*, 2001). There has been considerable debate about the role of *Pfiesteria* spp. in the development of fish lesions described as ulcerative mycosis (UM) (Burkholder *et al.*, 1998; Dykstra and Kane, 2000; Noga, 2000; Burkholder *et al.*, 2001a; Glasgow *et al.*, 2001b; Vogelbein *et al.*, 2001). Found predominantly in the Atlantic menhaden, *Brevoortia tyrannus*, along the eastern seaboard of the United States, UM is caused by a fungus, *Aphanomyces invadans* (Blazer *et al.*, 1999; Vogelbein *et al.*, 2001). *Aphanomyces invadans* is a primary pathogen (Kiryu *et al.*, 2000) and is responsible

for UM in other fish species and in other geographical regions (Lilley *et al.*, 1998). Although *Pfiesteria* has been shown to initiate lesions in fish exposed under experimental conditions (Noga *et al.*, 1996; Glasgow *et al.*, 2000, 2001b; Burkholder *et al.*, 2001a; Vogelbein *et al.*, 2001), and is suspected in the development of fish lesions in the field (Burkholder *et al.*, 1998; Glasgow *et al.*, 2001b), the extent to which these lesions are the same as those caused by UM is minimal (Vogelbein *et al.*, 2001). The relationship between *Pfiesteria* and *Aphanomyces* is complicated by an almost coincident geographical distribution of these genera and of fish with UM along the eastern coastal United States. However, there are areas where *Pfiesteria* is nontoxic, or not present, and fish with UM are still found (Landsberg *et al.*, 2000; Lewitus *et al.*, 2000).

During 1989 to 1990, a *Noctiluca scintillans* bloom in the Pei Hai Sea (Northern China Sea) resulted in losses of about $100 million to shrimp (*Penaeus orientalis*) mariculture operations. Poor water quality caused an increase in the susceptibility of prawns to parasitic infections, which led to disease, mortalities, and additional losses valued at $1 million. *Noctiluca* blooms also harmed the commercial farming of *Laminaria* by decreasing frond production and causing the macroalgae to putrefy and spoil (Chen and Gu, 1993).

The harmful diatoms *Chaetoceros concavicornis* and *C. convolutus* have been directly implicated in mortalities of aquatic organisms (see section on harmful mechanisms). In addition, cultured salmonids became noticeably more susceptibile to two major bacterial diseases when they were exposed to low concentrations of these diatoms (Speare *et al.*, 1989; Albright *et al.*, 1993). At sublethal concentrations of 0.4 to 5 cells/ml, *C. concavicornis* and *C. convolutus* increased the mortality rates at which chinook salmon, *Oncorhynchus tshawytscha*, and coho salmon, *O. kisutch*, cultured in seawater in net pens die from vibriosis and/or bacterial kidney disease (BKD). Under laboratory conditions, adding *Vibrio anguillarum* to the water greatly accelerated the mortality rate of coho salmon exposed to sublethal concentrations of *Chaetoceros* spp. None of the 37 untreated control coho salmon or of the 36 coho treated with 2×10^6 cells/ml of *V. anguillarum* for 7 days died. Of the 37 coho maintained in water with 1.4 to 3.7×10^1 cells/ml of *C. concavicornis*, the cumulative mortality was 38% during the same 7-day treatment period. However, 100% of the coho (N = 37) maintained in water with 1.4 to 3.7×10^1 cells/ml of *C. concavicornis* and with 1.7×10^6 cells/ml of *V. anguillarum* added on day three had died by day seven (Albright *et al.*, 1993). Although the mechanism(s) by which *Chaetoceros* spp. increased the susceptibility of salmonids to bacterial diseases was not determined, this critical role as a stressor is clearly another important factor whereby HABs can significantly influence the economic success of aquaculture operations.

Planktonic blooms of *Oscillatoria corakiana* and the presence of *Spirulina* sp., *Lyngbya* sp., *Oscillatoria* sp., and *Nodularia* sp. in the water column, benthic layers, or surface mats were coincident with four mortality episodes of cultured prawns, *Penaeus monodon*, in Australia (Smith, 1996). Prawns started to show symptoms 4 months after stocking. Initially, prawns were lethargic when handled, food consumption decreased, growth slowed, and they had difficulty in molting. By the time the ponds were dominated by benthic or floating mats or planktonic filaments of Oscillatoriales blooms, prawns were found dying at the edge of the ponds. Visually, sick prawns had dark body color, limbs that were often red, muscle that was white, gills that were sometimes fouled (by *Leucothrix mucor*, *Zoothamnium,*

Nitzschia, Oscillatoria), and shells that were thin and covered by fouling organisms (i.e., barnacles, bacteria, and *Nitzschia*). The hepatopancreas was small and pale, and the hind guts were empty or contained watery feces. Affected ponds had higher levels of dissolved phosphorus and ammonia than did estuarine water near the farm. Levels of presumptive *Vibrio* spp. (*V. proteolyticus*, *V. alginolyticus*, *V. harveyi*, *V. vulnificus*, *V. parahaemolyticus*, *V. anguillarum* I, *V. anguillarum* II, and other vibrios) were higher in the hepatopancreas, gills, and muscle tissues of sick prawns than in healthy prawns, indicating that vibriosis was affecting prawns in ponds with blooms of Oscillatoriales. The levels of Vibrionaceae found in prawn tissues indicated that although mortalities were caused by secondary bacterial infection, subacute toxicity due to the Oscillatoriales bloom was the primary cause of the disease. In the first three episodes, mouse bioassays showed that the pond water was clinically nontoxic, although the mice displayed neurotoxic symptoms. Boiled pond water and extracts from a tank culture of benthic Oscillatoriales caused mortalities of *P. monodon* and *P. japonicus*. Immersion of *Artemia* in extracts from the same tank culture also caused mortalities. Smith (1996) demonstrated that the Oscillatoriales blooms produced a water-soluble, heat-labile toxin and that mortalities were possibly caused by a neurotoxin. Supernatant culture tank water, both unfiltered and filtered, was toxic to *Artemia*, and the fact that water was toxic to *Artemia* nauplii before a digestive tract was developed indicated that the toxin was water soluble. Smith (1996) proposed that sublethal levels of toxin(s) weakened the prawns, possibly via a neurotoxic effect that reduces feeding behavior and impairs the immune system, and that the prawns thus were susceptible to secondary infections of pathogenic bacteria such as *Vibrio* spp.

In August 1976, in a fish farm in southern France, extensive algal blooms of *Aphanizomenon flos-aquae* were considered to be the major contributing factor to the development of a disease syndrome of farmed common carp, *Cyprinus carpio*. After the sudden collapse of the bloom, decomposing cells stimulated bacterial activity, and there was a marked decrease in dissolved oxygen and a significant increase in ammonia. About a day after the bloom collapsed, carp were gathered at the inflow to the pond and gasping at the water's surface. Ten days after the bloom collapsed, carp netted from the pond had abdominal distention, excessive mucus on the gills and skin, damaged and clumped gill lamellae, vascular congestion and petechial hemorrhages on the body and fins, and associated internal pathologies in most of the visceral organs. The intestine was soft and transparent, with large quantities of undigested food, gas bubbles, and yellow mucus. Twenty-one days after the bloom, approximately 10 to 20% of the carp had skin lesions, which in some cases penetrated deeply into the skin and muscles and occasionally reached the body cavity. At the time, the disease was considered to be similar to infectious hemorrhagic septicemia, a disease syndrome of carp in Europe that has a multifactored etiology. The disease was considered to be triggered by sublethal levels of unionized ammonia associated with bloom decomposition and the subsequent increased susceptibility of carp to disease (Seymour, 1980).

An unusual case of disease in blue shrimp, *Penaeus stylirostris*, was associated with a cyanobacterial bloom. Epizootics in blue shrimp in tanks or raceways occurred on six different occasions between 1975 and 1977 in Puerto Peñasco, Sonora, Mexico, and resulted in high rates of mortality (up to 85%). Each of the mortalities was preceded by, or concurrent with, a bloom of *Spirulina subsalsa*.

Epizootics of the disease syndrome were not observed in other tanks or raceways in which *S. subsalsa* was absent. Stomach contents of both apparently healthy and moribund shrimp from shrimp populations affected by *S. subsalsa* blooms revealed that the shrimp were ingesting large amounts of this alga. Shrimp dying from septicemic bacterial infections, principally by a strain of *Vibrio alginolyticus*, were documented in every epizootic. Affected shrimp with the disease syndrome in its final stages had whitish, opaque abdominal musculature, a slightly pale cuticular coloration, and often an empty midgut. Many had early or sublethal lesions in the digestive organs. In the most common lesion, there was necrosis of the mucosal epithelium of the midgut and a consequent hemocytic infiltration. Filaments of *S. subsalsa* were often found attached as epibionts on the gill lamellae, accessory gill processes, and the pleopods of shrimp from tanks in which losses, presumed to be due to the *S. subsalsa* bloom, were occurring. Although there was no discernible histopathological effect from the *S. subsalsa* filaments, it was suggested that their presence reduced respiratory efficiency. When healthy shrimp were fed *S. subsalsa* as a dietary supplement for 3 weeks, 2 out of 19 shrimp examined had hemocytic lesions in the anterior midgut. It was concluded that under certain conditions, *S. subsalsa* produces a weak toxin that is only mildly toxic to shrimp, even when relatively large quantities of the alga are consumed. Observations that supported this hypothesis included (1) the occurrence of epizootics of the hemocytic enteritis syndrome in systems in which *S. subsalsa* was blooming but not in tanks in which green algae were dominant and (2) the absence of lesions in tissues protected from potential toxins by a chitinous cuticle, for example, the stomach, esophagus, hindgut, and rectum. Lesions in the midgut that resulted in necrosis and interruption of the lining epthelium allowed a route of entry for *V. alginolyticus*. Because feeds medicated with antibiotics (normally effective against vibrios) were not completely effective in stopping mortality, it was concluded that the vibrios were secondary invaders and not the agents that caused the lesions observed in the digestive tract (Lightner, 1978).

VII. PARASITES AND PATHOGENS

Traditionally, microalgal parasites and pathogens are excluded from most definitions of HABs. For the purposes of this review, they are discussed, but only to refer to those species that have substantial impacts (either ecological or economic) on aquatic resources. These species affect marine fauna, fisheries, or aquaculture operations and include fish and shellfish pathogens such as the dinoflagellates *Amyloodinium ocellatum*, *Piscinoodinium*, and *Hematodinium* and also include the cyanobacteria *Phormidium/Oscillatoria* that are associated with coral diseases. These genera and their association with aquatic mortality events are not included in Table 2.

Hematodinium species are dinoflagellate endoparasites of commerically important macrocrustaceans such as lobsters and crabs (Shields, 1994). *Hematodinium* has been associated with mass mortalities, pathology, decreased swimming performance, or loss in the marketability of fisheries products due to spoilage of the meats (Newman and Johnson, 1975; Meyers *et al.*, 1987; Wilhelm and Mialhe, 1996; Stentiford *et al.*, 2000). Affected Alaskan Tanner crabs, *Chionoecetes bairdi*, have a

pink carapace, chalky-textured meat with a distinctly bitter flavor, and milky hemolymph containing *Hematodinium*. This bitter flavor results in an unmarketable product, which, for example, caused an economic loss of approximately $176,000 to the Alaskan fishery in 1986. The bitter crab disease caused by *Hematodinium* affected as many as 95% of the Tanner crabs in southeastern Alaska (Eaton *et al*., 1991; Meyers *et al*., 1987, 1990; Love *et al*., 1993). In June 1986, unusual mortalities of the velvet swimming crab, *Necora ruber*, in southern Brittany, France, were attributed to heavy infections of *Hematodinium* sp. An examination of dying crabs revealed parasites in the hepatopancreas, gonads, and muscles, as well as heavy infestations in the haemolymph. Between 1984 and 1988, crab catches fell from 1100 tons to 48 tons, a decrease of 96%. Samples of crabs examined between June 1986 and Feburary 1992 showed prevalences of *Hematodinium* infection ranging 0 to 87%. Based on this information, *Hematodinium* sp. was considered to be partially responsible for declines of the *N. ruber* fishery in France (Wilhelm and Mialhe, 1996). Similar conclusions were made with respect to declines in the Norway lobster, *Nephrops norvegicus*, fishery in Scotland (Field *et al*., 1998).

Amyloodinium ocellatum is a nonspecific, marine fish ectoparasite (Brown, 1934; Brown and Hovasse, 1946) that can have devastating effects in aquaculture facilities. There are numerous reports of its incidence and pathogenicity to fish in mariculture and aquarium systems (Lawler, 1977, 1980; Paperna and Baudin-Laurencin, 1979; Paperna, 1980; Baticados and Quinitio, 1984; Aiello and D'Alba, 1986; Noga *et al*., 1991; Landsberg *et al*., 1994, 1995) and, rarely, in the wild (Kuperman and Matey, 1999). The life cycle of *Amyloodinium* consists of three stages: a trophont that feeds while attached to skin and gill surfaces of fish, an encysted tomont that develops after the trophont detaches from the fish, and motile flagellated dinospores that are released after the tomont divides. In closed systems, high concentrations of *Amyloodinium* can build up in several days. Stressed fish congregate on the surface, gasp rapidly for air, lose their appetite rapidly, and can die within several days when heavily infected. Typically, trophonts are found on fish after heavy mortalities (Lawler, 1980; Paperna, 1980, Noga *et al*., 1991; Landsberg *et al*., 1994, 1995, Kuperman and Matey, 1999). Although it has been postulated that cytolytic compounds are produced by the feeding trophont stages (Lom and Lawler, 1973), this has still not been confirmed. Extensive localized damage is caused by the attachment of the trophont to the gills, rhizoid penetration, and feeding on the fish cytoplasm. In heavy infestations with trophonts attached to the gills, the gill epithelium becomes hyperplastic, and there is additional fusion of the secondary lamellae. Cellular damage and necrosis of the gill tissue affect osmoregulation and respiration. With respiratory function considerably impaired, fish die from asphyxiation. The pathological response to the mechanical damage induced by the trophonts ultimately leads to death (Paperna, 1980).

Piscinoodinium pillulare is known from freshwater systems, where occasionally it has been associated with mass mortalities of cultured fish. Like *Amyloodinium ocellatum*, *Piscinoodinium* is a nonspecific dinoflagellate ectoparasite and has a similar life cycle. However, there appear to be differences in the susceptibility of fish species to infestation. In freshwater pond culture in Malaysia, grass carp (*Ctenopharyngodon idella*), jelawat (*Leptobarbus hoevenii*), bighead carp (*Aristhichthys nobilis*), and lampam jawa (*Punitius gonionotus*) were infested by *Piscinoodinium*, but only *P. gonionotus* was highly susceptible and suffered mass mortalities. Clinical

signs included a rust-colored appearance of the skin, a dense covering of mucus, dark head and dorsal regions, petechiae on the body, and fusion of the gill lamellae. If dissolved oxygen reached low levels (2.6 to 5.5 ppm), then 100% mortalities occurred in the ponds (Shaharom-Harrison *et al.*, 1990). In other infestations of aquarium fish, attached *Piscinoodinium* trophonts induced epithelial hypertrophy, focal and diffuse hyperplasia, edema of the respiratory epithelium, lamellar fusion, and reduced respiratory efficiency (Ferraz and Sommerville, 1998).

Microalgae are also causing a series of diseases that negatively affect coral reefs. Numerous disease syndromes affecting several coral reef species throughout the world are often named by the gross macroscopic description of the affected corals, for example, black band, white band, red band, and white pox (Peters *et al.*, 1983; Rutzler and Santavy, 1983; Richardson, 1992). Recent studies suggested that several species of cyanobacteria (Table 1) may be responsible for black and red band diseases (Rutzler and Santavy, 1983; Richardson, 1992). Although it was earlier suggested that *Phormidium corallyticum* is toxic (Rutzler and Santavy, 1983), this has still not been proven, and it is still unknown whether these coral "pathogens" are toxic or produce bioactive compounds. Recent studies have suggested that the chemical environment of the microbial consortium, of which *P. corallyticum* is a major component, contributes to anoxic and sulfidic conditions along the length of the infected coral where the black band occurs (Richardson, 1993).

VIII. CONCLUSIONS

Other than the classical "red tide" fish kills long chronicled by coastal dwellers, the wider role of HAB species in animal mortality and disease events has only just begun to be fully recognized. The broader implications of the presence of these organisms in aquatic systems around the world needs to be elucidated. For this to happen, there must be an integration of new approaches and attitudes. In the next few years it is hoped that the following will exist routinely:

1. Rapid screening techniques that will identify toxins in animal tissues and in water (e.g., molecular probes) and other technologies that will track HABs and provide capabilities for predicting their spatial and temporal appearances. Such information will enable managers to respond quickly and appropriately to situations that endanger public health, wildlife, fisheries, and aquaculture
2. Increased interdisciplinary activity between scientists, diagnosticians, and resource managers, and better integration of HAB knowledge and data among all investigating animal mortalities and disease
3. Strategies that are better integrated and geared toward "managing HABs"
4. Recognition that chronic effects of biotoxins are likely to be very significant in animal health and may be responsible for many currently "unidentified diseases" or "unexplained mortalities." For example, mortalities are often attributed to a virus, when in fact viral expression may have been enhanced by chronic biotoxin exposure. Incidents to consider include morbillivirus

(e.g., Duignan *et al.*, 1996) and potential biotoxin exposure in marine mammals; and oncogenic viruses (e.g., Herbst, 1994) and tumor promoters from dinoflagellates in the expression of fibropapillomas in sea turtles (Landsberg *et al.*, 1999)

5. Recognition that both the acute and chronic interactions of biotoxins and aquatic animal pathogens need to be evaluated, including the potential role of HABs as vectors for aquatic pathogens.

Our natural resources and the health of the general public will continue to be threatened by the impacts of HABs. Anthropogenic changes will continue to enhance the distribution of these blooms and will allow for the appearance of new harmful and toxic species. It is time to acknowledge the extreme range of their effects upon human and natural resources and to begin to minimize the severity of their ecological and economical impacts.

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