Journal of Shellfish Research, Vol. 15, No. 2, 203–230, 1996.

NEOPLASIA AND BIOTOXINS IN BIVALVES: IS THERE A CONNECTION?

JAN H. LANDSBERG
Florida Marine Research Institute
Florida Department of Environmental Protection
100 Eighth Avenue S.E.
St. Petersburg, Florida 33701-5095

ABSTRACT In the past 25 years, there has been an increase in the frequency of two major types of cancer in bivalves: disseminated neoplasia and germinomas, which cause debilitation and mortality in shellfish stocks. Disseminated neoplasia is common in softshell clams, *Mya arenaria;* the cockle, *Cerastoderma edule;* and blue mussels, *Mytilus trossulus;* and less common in edible oysters, *Ostrea edulis;* macomas, *Macoma balthica;* blue mussels, *Mytilus edulis;* and Olympia oysters, *Ostrea conchaphila*. Germinomas occur more frequently in northern quahogs, *Mercenaria mercenaria,* and softshell clams, *Mya arenaria*. Certain geographical locations, especially along the northwest Pacific and northeast Atlantic Coasts of North America and the Atlantic Coast of Europe, are "hot spots" for neoplasia. A genetic susceptibility of bivalves to tumor formation has been suggested, and the etiologies proposed include chemical carcinogens, viruses, and other transmissible agents. However, no clear cause-and-effect relationship has yet been conclusively demonstrated, nor has the potential role of biotoxins as etiological agents been examined. In the past 25 years, there has also been an increase in the frequency with which humans have been poisoned by consuming toxic bivalves. Filter-feeding bivalves accumulate biotoxins produced by toxic microalgal blooms. This study traces the worldwide distribution of paralytic shellfish poisoning (PSP), diarrheic shellfish poisoning, neurotoxic shellfish poisoning, amnesic shellfish poisoning, and venerupin shellfish poisoning and of the microalgae and bivalve species associated with the poisonings and then compares these distributions with the distribution of neoplasia in bivalves. The incidence of disseminated neoplasia in some affected bivalve species appears to parallel, both spatially and temporally, outbreaks of PSP that are associated with the toxigenic dinoflagellates *Alexandrium tamarense, A. minutum, A. fundyense,* and *A. catenella*. Shellfish that have accumulated potent saxitoxin and its derivatives (neosaxitoxin and gonyautoxins) produced by these dinoflagellates are highly toxic to humans. The presence of disseminated neoplasia parallels the presence of certain toxin derivatives in both the bivalve and the *Alexandrium* spp. to which the bivalves are exposed. Disseminated neoplasia is common in softshell clams, *M. arenaria,* that have apparently been exposed to and have accumulated gonyautoxins, (GTX), and in particular GTX1 and GTX4, that are produced by *A. tamarense* or *A. fundyense*. *M. mercenaria* is apparently not affected by disseminated neoplasia and does not usually accumulate toxins associated with *A. tamarense* or *A. fundyense*. Bivalves that accumulate high concentrations of saxitoxin or neosaxitoxin, such as butter clams, *Saxidomus giganteus;* surf clams, *Spisula solidissima;* sea scallops, *Placopecten magellanicus;* and California mussels, *Mytilus californianus,* are apparently not affected by disseminated neoplasia or germinomas. In *M. arenaria,* the incidence of germinomas appears to be related to the distribution of *Alexandrium* spp. blooms. In *M. mercenaria,* however, the distribution of germinomas is not related to those *Alexandrium* spp. that are commonly associated with PSP. The incidence of disseminated neoplasia and germinomas is not correlated with PSP outbreaks associated with *Pyrodinium bahamense* var. *compressum* or *Gymnodinium catenatum*. Although the epizootiological evidence presented here for a correlation between dinoflagellate toxin profiles, the deposition of toxins in bivalve tissues, and the presence of neoplasia in such bivalves is circumstantial, it should be investigated in field and laboratory experiments.

KEY WORDS: Bivalves, cancer, neoplasia, biotoxins, dinoflagellates, *Alexandrium,* epizootiology

NEOPLASIA AND BIVALVES

Occurrence and Type

Since the late 1960s, two main types of neoplasia in bivalves from marine and estuarine locations around the world have been reported with increasing frequency. The first type, disseminated neoplasia, affects some 15 species of bivalves (Tables 1a, 2a, 3a, and 4a) and can cause heavy mortalities (Elston et al. 1992). In disseminated neoplasia, tumor cells are initially found along with normal hemocytes in the circulating hemolymph. As the disease progresses, abnormal cells proliferate throughout the blood sinuses and connective tissue of the visceral mass, muscle, and mantle (Peters 1988). The pathogenesis of disseminated neoplasia is similar to that of vertebrate leukemia in the sense that the circulating tumor cells rapidly divide, ultimately invade the connective tissue, and in advanced stages, kill the host (Miosky et al. 1989). In bivalves, neither the ontogenesis of normal hemocytes nor that of the neoplastic (presumptively hemocytic) cells is known (Elston et al. 1992). Disseminated neoplasia in bivalves was reviewed by Lauckner (1983), Mix (1986a, 1986b), Peters (1988), and Elston et al. (1992) and, except for certain pertinent facts, will not be further discussed. Other types of neoplasia that have been documented, and are often confused with disseminated neoplasia, are gill carcinomas in *Macoma balthica* (L.) (Christensen et al. 1974, Farley 1976a) and epithelioma-like conditions in Australian rock oysters, *Crassostrea commercialis* (Iredale and Roughly) (Wolf 1976).

The second most common type of bivalve neoplasia, germinomas or gonadal tumors, affects 10 species and one hybrid (Table 5a). Tumors result from proliferation of the germinal epithelium, often completely filling the lumen of both male and female gonads (Hesselman et al. 1988, Peters et al. 1994). In germinomas, the affected gonadal follicles are filled with abnormal, hypertrophic cells. Metastasis to the circulatory system occurs in advanced stages (Elston et al. 1992).

Reports discussed here are based on verification of both kinds of neoplasia in the Registry of Tumors in Lower Animals (RTLA, Smithsonian Institution, Washington D.C.) according to Peters (1988) and Peters et al. (1994) and not necessarily as reported in original papers. Rare reports of neoplasia in a particular species, when based on one specimen from many thousands, may need further confirmation (Elston et al. 1992). Consequently, the report

TABLE 1a.

Distribution and prevalence of disseminated neoplasia in oysters with suspected etiology or conditions.

Bivalve Species and Locality	Prevalence (%) (N =)	Date	Etiology	Reference
C. virginica				
Harris Creek	0.02 (5,000)	1960–1967	Genetic	Couch 1969, Farley 1969a, Otto and Farley 1976, Frierman 1976, Frierman and Andrews 1976
York and James River	0.01–0.075 (51,000)	1964–1973		
Chesapeake Bay				
23 sites Chesapeake Bay	0.1 (20,000)	1974–1977		Harshbarger et al. 1979
Apalachicola Bay, FL	0.27 (373)	1978?		Couch and Winstead (1979)
Pensacola Bay, FL	0.04 (4,486)	8/78–8/80		Couch (1985)
Mobile Bay, AL	0.13 (2,336)			
Pascagoula Harbor, MS	0.44 (2,461)			
O. conchaphila				
Yaquina Bay, OR	7.0 (?) 0.0–2.0 (2,349)	1961–1970 ?1975		Farley and Sparks 1970, Mix 1975a, Mix 1975b, Mix et al. 1977
T. chilensis				
Chiloe, Chile	2.0 (4) 1.0 (100)	2/78	Pristine waters	Mix and Breese 1980
New Zealand	1 case?	?		Peters 1988
O. edulis				
Mali-Ston, Croatia	20.0–30.0 (?)	1975	Heavy mortality	Alderman et al. 1977
Galicia, Spain	up to 35.0 (?)	1975		
Brittany, France	0.50 (69,476)	1975–1981	*C. gigas* was −ve (4,500)	Balouet et al. 1986

TABLE 1b.

Corresponding records of dinoflagellate blooms or shellfish toxicity events by nearest location and date.

Toxicity/ Blooms	Site/Date	Bivalve	Reference
?*A. monilatum* *P. minimum*	?Chesapeake Bay 1970, 1971, 1973 Chesapeake Bay		Williams and Ingle 1972, Steidinger 1993, Seliger et al. 1975
?*A. monilatum*	1978 FL, MS		Perry et al. 1979
A. monilatum fish kills	1978 FL, MS		Perry et al. 1979
PSP *A. catenella*	1973 Yaquina Bay, OR	*M. galloprovincialis*	Nishitani and Chew 1988, Taylor 1984
DSP *D. acuta* PSP?	1980, 1984, 1991 Reloncavi estuary, Jacaf fiord, Chonos archipelago	*A. ater, M. chilensis*	Lembeye et al. 1993
L. polyedrum, A. minutum	1980+, 1989		Marasović et al. 1995
PSP *A. minutum*	1976 Galicia	*M. edulis*	Lüthy 1979
P. minimum	1986	*M. edulis, O. edulis*	Berland and Grzebyk 1991, Erard Le-Denn 1991, Belin 1993
PSP *A. minutum*	1988–1990		
DSP *D. acuta, D. acuminata, D. sacculus*	1983–1990 Brittany		

of a germinoma in *Mytilus trossulus* Gould, 1850 in British Columbia (Cosson-Mannevy et al. 1984) and reports of a disseminated neoplasia in *Crassostrea rhizophorae* in Brazil (Nasimento et al. 1986) and in *Crassostrea gigas* (Thunberg) in Japan (Farley 1969a) have not been included.

Neoplasia Distribution in Bivalves

The distribution and prevalence of bivalve neoplasia by type and by species are shown in Tables 1a to 5a. Neoplasia is common mostly in temperate regions (Figs. 1 to 3), particularly in northeastern and northwestern North America, the European Atlantic, the North Sea, and Scandinavia. A few cases have been documented in the Gulf of Mexico. Reports of neoplasia are rare in Australasia and the Mediterranean except for the Adriatic Sea near Croatia. In South America, only one case has been documented (Mix and Breese 1980). In the Middle East, Central America, Africa, and Asia, no reports are known except for one unconfirmed case in Japan (Farley 1969a).

Differences in the predisposition of bivalves to neoplasia are apparent in some families, genera, and species (Tables 1a to 5a). Oysters, mussels, clams, cockles, and macomas are affected, whereas scallops are not (or are rarely) affected. Oysters are heavily affected (*Ostrea edulis* L. and *Ostrea conchaphila* [Carpenter, 1857]), lightly affected (*Crassostrea virginica* and *Tiostrea chilensis*), or unaffected (*C. gigas*) by disseminated neoplasia (Table 1a). Both disseminated neoplasia (Table 1a) and germinomas (Table 5a) have been found in *C. virginica* in the Chesapeake Bay but were more common in the 1960s and 1970s than recently. Among the clams, *Saxidomus giganteus* (Deshayes) and *Spisula solidissima* (Say) are apparently unaffected by either disseminated neoplasia or germinomas. The northern quahog, *Mercenaria mercenaria* (L.), is unaffected by disseminated neoplasia (Table 2a) but is affected by germinomas (Table 5a). *Mya arenaria* L. is heavily affected by both types of neoplasia (Tables 2a and 5a). Blue mussels are affected by disseminated neoplasia in some geographical regions but not in others. Along the Pacific Coast of North America, *M. trossulus* is heavily affected and *Mytilus californianus* (Conrad) is unaffected by disseminated neoplasia (Table 3a). There have been no reports of disseminated neoplasia in *Mytilus edulis* L. from the northeast Atlantic Coast (North America) or in

TABLE 2a.

Distribution and prevalence of disseminated neoplasia in clams with suspected etiology or conditions.

Bivalve Species and Locality	Prevalence (%) (N =)	Date	Etiology	Reference
M. arenaria				
Freeport, Harpswell Neck, ME	10.91 (440)	1967–1977	After oil spill in 1971	Yevich and Barzcsz 1976, Yevich and Barzcsz 1977
Jones Creek Annisquam River, MA	12.0 (50)	9/72	No obvious environmental relationship or viral etiology	Farley 1976a
Bourne, MA; Searsport, ME; Quonset, RI (10 sites)	0.0–64.0 (1,325)	1–9/76	Highest % at oil spill site? Viral	Brown et al. 1976, 1977
Allen Harbor, RI	20.0–40.0 (3,500)	7/77–3/79	*M. mercenaria* and *M. balthica* −ve	Cooper et al. 1982a, Cooper et al. 1982b
New Bedford Harbor (NBH); Little Buttermilk Bay (LBB); Buzzard Bay, MA	73.2 NBH (407) 39.3 NBH (886) 17.0 LBB (881)	1/82–5/83 5/86–10/87	?PCBs* Environmental factors	Reinisch et al. 1984, Leavitt et al. 1990
Long Island Sound (3 sites) Milford Point, CT	45.0–60.0 (3,963) 64.3 (2,121)	6/83–3/84 10/88–12/89	Unresolved	Brousseau 1987, Brousseau and Baglivo 1991a, Brousseau and Baglivo 1991b, Brousseau and Baglivo 1994
Chesapeake Bay, MD (6 sites)	0.0–65.0 (3,584) 0.0–78.0 (?)	12/83–5/85 1990–1995	Was very rare in this location prior to 1984	Farley et al. 1986, McLaughlin et al. 1996
Shrewsbury River, NJ	0.0–19.0 (1,200)	9/86–8/87		Barber 1990
New Brunswick, Nova Scotia (22 sites), Canada	3.1–31.3 (688)	12/85–1/87		Morrison et al. 1993
Mya truncata				
Baffin Is., Canada	1.61 (856)	?1986	oil?	Neff et al. 1987
Ruditapes decussatus				
Galicia, NW Spain	1.3 (360)	2–12/93		Villalba et al. 1995

TABLE 2b.

Corresponding records of dinoflagellate blooms or shellfish toxicity events by nearest location and date.

Toxicity/ Blooms	Site/Date	Bivalve	Reference
PSP *A. tamarense*	1972 York Harbor, ME	*M. edulis* *M. arenaria*	Twarog and Yamaguchi 1975
A. tamarense first reported outbreak of PSP in the region at same time	9/10 1972 Annisquam River, Essex, and Eastham MA	*M. arenaria* *M. edulis* *A. irradians*	Hartwell 1975, Twarog and Yamaguchi 1975, Farley 1976a, Anderson et al. 1982
PSP toxin closed shellfish beds	4–9/76 western ME	*M. edulis*	Hurst 1979
PSP toxin closed shellfish beds	1979 Narragansett Bay, RI	*M. edulis*	Anderson et al. 1982
A. tamarense *P. minimum*	1987–1988 NBH and 7 other stations		Borkman et al. 1993, Pierce and Turner 1994
PSP *A. tamarense* *P. minimum*	1982–1983 Long Island 1986–1989 Long Island Sound, NY	*M. edulis*	Schrey et al. 1984, Nuzzi and Waters 1993, Wikfors and Smolowitz 1993
P. minimum	1978 1992		Seliger et al. 1979, Harding and Coats 1988, Marshall 1995
A. tamarense DSP *D. acuminata*	1987 Atlantic City, NJ 1980, 1983 NJ, NY		Cohn et al. 1988, Freudenthal and Jijina 1988
PSP *A. fundyense* (=*A. excavatum*)	1986 New Brunswick, NS	*M. edulis, M. arenaria*	Martin et al. 1990
DSP *P. lima*	1990 Atlantic NS	*M. edulis*	Marr et al. 1992
DSP *Dinophysis* spp. *A. minutum* *G. catenatum*	1991–1993 Galicia	*M. galloprovincialis*	Blanco et al. 1995, Franco et al. 1994, Anderson et al. 1989

* PCBs, polychlorinated biphenyls.

Mytilus galloprovincialis from the northwest Pacific Coast (North America), whereas there have been a few reports of this cancer in both species in Europe (Table 3a). Four species of macomas and one species of cockle have been reported with disseminated neoplasia (Table 4a). Scallops in the genera *Patinopecten, Placopecten,* and *Argopecten* are apparently unaffected by disseminated neoplasia, and only one case of germinoma has been reported in bay scallops, *Argopecten irradians* (Lamarck) (Table 5a).

TABLE 3a.

Distribution and prevalence of disseminated neoplasia in mussels with suspected etiology or conditions.

Bivalve Species and Locality	Prevalence (%) (N =)	Date	Etiology	Reference
M. trossulus				
Yaquina Bay, OR	7.0 12.0 (100)	9/68 2/69	No virus found. Etiology remains unknown. PAH levels not significant	Farley 1969b, Mix 1983, Elston et al. 1988a, Moore et al. 1991, Cosson-Mannevy et al. 1984, Bower 1989, Emmett 1984
	0.4–9.8 (2,934)	6/76–4/78		
Puget Sound, WA	0.0–40.0 (40)	11/86		
	11.0 (660)	3/89–2/90		
Vancouver Island, BC	0.0–29.2 (166)	12/80–6/81		
	0.0–45.0 (278)	1988?		
Departure Bay BC, Canada	10.0–36.0 (?)	10/83–9/84		
M. edulis				
Plymouth, England	1.61 (994)	1976–1978	Potentially carcinogenic PAHs in sediments*	Lowe and Moore 1978, Green and Alderman 1983
Morecombe Bay, N. Wales and E. England	0.0–4.3 (4,000)	11/78–8/79		
Denmark*	0.2–0.8 (8,720)	10/83–9/84	Viral etiology and multifactorial hypothesis	Rasmussen et al. 1985, Rasmussen 1986
Furuskar, Tvärminne, Finland	0.5 (205)	9/86		Sunila 1987
M. galloprovincialis				
Humboldt Bay, CA	0.0 (40)	1988	—	Elston et al. 1988b,
Rias de Galicia, NW Spain	0.6 (170)	1986		Gutierrez and Sarasquete 1986

TABLE 3b.

Corresponding records of dinoflagellate blooms or shellfish toxicity events by nearest location and date.

Toxicity/ Blooms	Site/Date	Bivalve	Reference
PSP *A. catenella*	1973 Yaquina Bay	*M. trossulus*	Taylor 1984, Anderson 1984, Chiang 1988, Nishitani and Chew 1988
A. catenella	1988 Puget Sound, WA	*M. californianus*	
A. catenella	1980–1982	*S. giganteus, Crassostrea gigas*	
	1985–1987 BC		
PSP *A. tamarense*	1968, 1990 E. England	*M. edulis*	Wyatt and Saborido-Rey 1993
?*P. minimum*			
PSP *A. tamarense*	1987	*M. edulis*	Moestrup and Hansen 1988, Kimor et al. 1985
?*P. minimum*			
DSP *Dinophysis norvegica*	1982		
A. tamarense, D. acuminata, D. acuta, P. minimum, G. catenatum	1984		Kononen et al. 1993
A. catenella	1988	*M. galloprovincialis*	Price et al. 1991, Anderson et al. 1989, Franco et al. 1994, Berland and Grzebyk 1991, Blanco et al. 1985, Blanco et al. 1995
PSP *G. catenatum, A. minutum*	1976, 1981, 1984–1987	*M. galloprovincialis*	
DSP *Dinophysis acuta, D. acuminata, D. sacculus*	1978, 1981, 1983, 1987, 1991–1993	*M. galloprovincialis*	

* Elston et al. 1992 list this record as occurring in *M. trossulus*.

* PAH, polycyclic aromatic hydrocarbons.

The bivalves most commonly affected by disseminated neoplasia and in which prevalences of more than 20% have been consistently recorded are *M. arenaria* in the northeastern United States and Canada, *M. trossulus* in the northwestern United States and *Cerastoderma edule* (L.) in Ireland and France (Tables 2a, 3a, and 4a). Mortalities associated with disseminated neoplasia have been recorded in *O. edulis* (Alderman 1974), *O. conchaphila* (Farley and Sparks, 1970), *M. arenaria* (Cooper et al. 1982a, Farley et al. 1986, Leavitt et al. 1990, Brousseau and Baglivo 1991b), and *M. trossulus* (Cosson-Mannevy et al. 1984). Disseminated neoplasia caused mortalities of up to 78% in *M. arenaria* in New England. The disease may be contributing to recent population declines of *M. arenaria* in New England (Brousseau and Baglivo 1991b) and in the Chesapeake Bay (Brousseau and Baglivo 1991b, McLaughlin et al. 1996).

Prevalences of disseminated neoplasia generally change seasonally and are at their highest between October and March (Cooper et al. 1982a, Cosson-Mannevy et al. 1984, Farley et al. 1986, Rasmussen 1986, Brousseau 1987, McLaughlin et al. 1996), with minimum prevalences from April to August (Leavitt et al. 1990). Biphasic prevalences have also been noted: a second peak may occur from May to July (Cooper and Chang 1982, Cooper et al. 1982a, Barber 1990, McLaughlin et al. 1996) or from January to March (Leavitt et al. 1990). Low water temperatures may suppress the progression of neoplasia (Appeldoorn and Oprandy 1980) and reduce mortality (Brown et al. 1977).

In field studies, some species that were apparently unaffected by disseminated neoplasia have been found in the same location as other species that were heavily affected. For example, in northeastern North America, *M. arenaria* are heavily affected by disseminated neoplasia, whereas *M. mercenaria, M. edulis,* and *C. virginica* are unaffected.

The distribution of germinomas currently appears to be restricted to the East Coast of North America, the southern coast of Ireland, New Zealand, and Arctic Canada (Table 5a). *Mercenaria* spp. and *M. arenaria* are heavily affected by germinomas. Al-

TABLE 4a.

Distribution and prevalence of disseminated neoplasia in macomas and cockles with suspected etiology or conditions.

Bivalve Species and Locality	Prevalence (%) (N =)	Date	Etiology	Reference
M. calcarea				
Baffin Island, Canada	0.19 (519)	?1986	oil?	Neff et al. 1987
*M. balthica**	4.0–15.0	3/82–7/89	No apparent	Pekkarinen 1993
Tvärminne, Finland	(1,748)		correlation with pollution	
Macoma inquinata and *M. nasuta*	5.0 (?)	?1975	PAH?	Farley 1976a
Yaquina Bay, OR				
C. edule				
Cork Harbor and coast, S. Ireland (18 sites)	0.0–72.0 (1,356)	2/83–2/85	Environmental factors/infectious disease	Twomey and Mulcahy 1984, Twomey and Mulcahy 1988a
			M. edulis were −ve	
Brittany, France 4 sites	46.0 (?) 4.1 (752)	?1983	Reference site and site of Amoco oil spill; both had neoplasia	Poder et al. 1983, Poder and Auffret 1986

TABLE 4b.

Corresponding records of dinoflagellate blooms or shellfish toxicity events by nearest location and date.

Toxicity/ Blooms	Site/Date	Bivalve	Reference
A. tamarense, D. acuminata, P. minimum, G. catenatum	1984		Kononen et al. 1993
PSP *A. catenella*	1973 Yaquina Bay, OR	*M. californianus*	Nishitani and Chew 1988
DSP *Dinophysis acuminata, D. acuta, D. norvegica*	1984	*M. edulis*	Jackson and Silke 1995
A. minutum	1987 Cork Harbour		Gross 1988
DSP *D. acuta, D. acuminata, D. sacculus*	1983–1990 Brittany	*M. edulis*	Belin 1993
PSP *Alexandrium minutum*	1988–1990 Brittany	*M. edulis, O. edulis*	Belin 1993
P. minimum	1976, 1986		Berland and Grzebyk 1991

* This reference may not be a disseminated neoplasm but a gill carcinoma.

though *M. mercenaria* are distributed along the Atlantic Coast of North America, those with germinomas are more localized south of Rhode Island and are particularly prevalent along the southeast Atlantic Coast. Germinomas only occur in *M. arenaria* in Maine (Barber 1996). The prevalence of germinomas was highest during the warm summer months (Hessleman et al. 1988, Eversole and Heffernan 1993).

Germinomas are less common (Table 5a) than disseminated neoplasia (Tables 1a to 4a). In some incidences, both types of neoplasia were reported in the same species of bivalve at the same time and from the same location, for example, in *M. arenaria* in northeast North America, in *C. edule* in Ireland, and on rare occasions, in *Macoma calcarea* in northern Canada (Yevich and Barszcz 1976, Cosson-Mannevy et al. 1984, Twomey and Mulcahy 1984, Neff et al. 1987, Peters et al. 1994). In this situation, a common causative agent might be indicated.

Etiology

The etiology of bivalve neoplasia has been postulated to be related to various causative agents, but no clear cause-and-effect relationship or multifactorial sequence of events has yet been established. Tentative links between sublethal exposure to various pollutants and the presence of neoplasia have been postulated but not conclusively demonstrated. A systematic survey of shellfish during the NOAA Status and Trends mussel watch showed that the prevalence of neoplasia was not strongly correlated with chemical contamination (Hillman 1993). Smolowitz and Leavitt (1996) found no correlation between the distribution of disseminated neoplasia in *M. arenaria* and pollution in Boston Harbor and Cape Cod Bay, MA.

Hydrocarbon deposition associated with oil spills was tentatively linked to disseminated neoplasia in New England (Barry and Yevich 1975, Yevich and Barszcz 1976, 1977, Brown et al. 1977, 1979, Gilfillan et al. 1977, Harshbarger et al. 1979, Walker et al. 1981); Yaquina Bay, Oregon, (Mix et al. 1979, Mix 1988); Brittany, France (Auffret and Poder 1986, Poder and Auffret 1986); and northern Canada (Neff et al. 1987). The presence of neoplasia was demonstrated in areas where chemical contaminants were absent (Gilfallan et al. 1977) or were present at low background levels (Brown et al. 1977, Mix 1983, Cosson-Mannevy et al. 1984, Emmett 1984, Twomey and Mulcahy 1988a). Conversely, neoplasia was absent in areas where bivalves were exposed to extremely high concentrations of contaminants (Mix 1988).

Studies attempting to link the occurrence of neoplasia with contaminants have suggested a correlation between the high prevalence of neoplasia and pesticide use (Farley et al. 1991, Gardner et al. 1991b). An increased prevalence of disseminated neoplasia in *M. arenaria* was associated with and statistically correlated to elevated chlordane levels in the tissues (Farley et al. 1991). In recent epizootics, germinomas were observed in *M. arenaria* from Machiasport, Searsport, and Dennysville, ME (Table 5a). Herbicides and other agrochemicals were widely used in the extensive forestry and blueberry industries in the area. Gardner et al. (1991b) indicated that the estuaries at Dennysville had been contaminated by herbicides in a 1979 accidental spray overdrift during the aerial application of Tordon 101® to adjacent forests. Herbicide contamination was the only identified common denominator at all three sites where *M. arenaria* with germinomas were found (Gardner et al. 1991b). Other field studies could not correlate the dis-

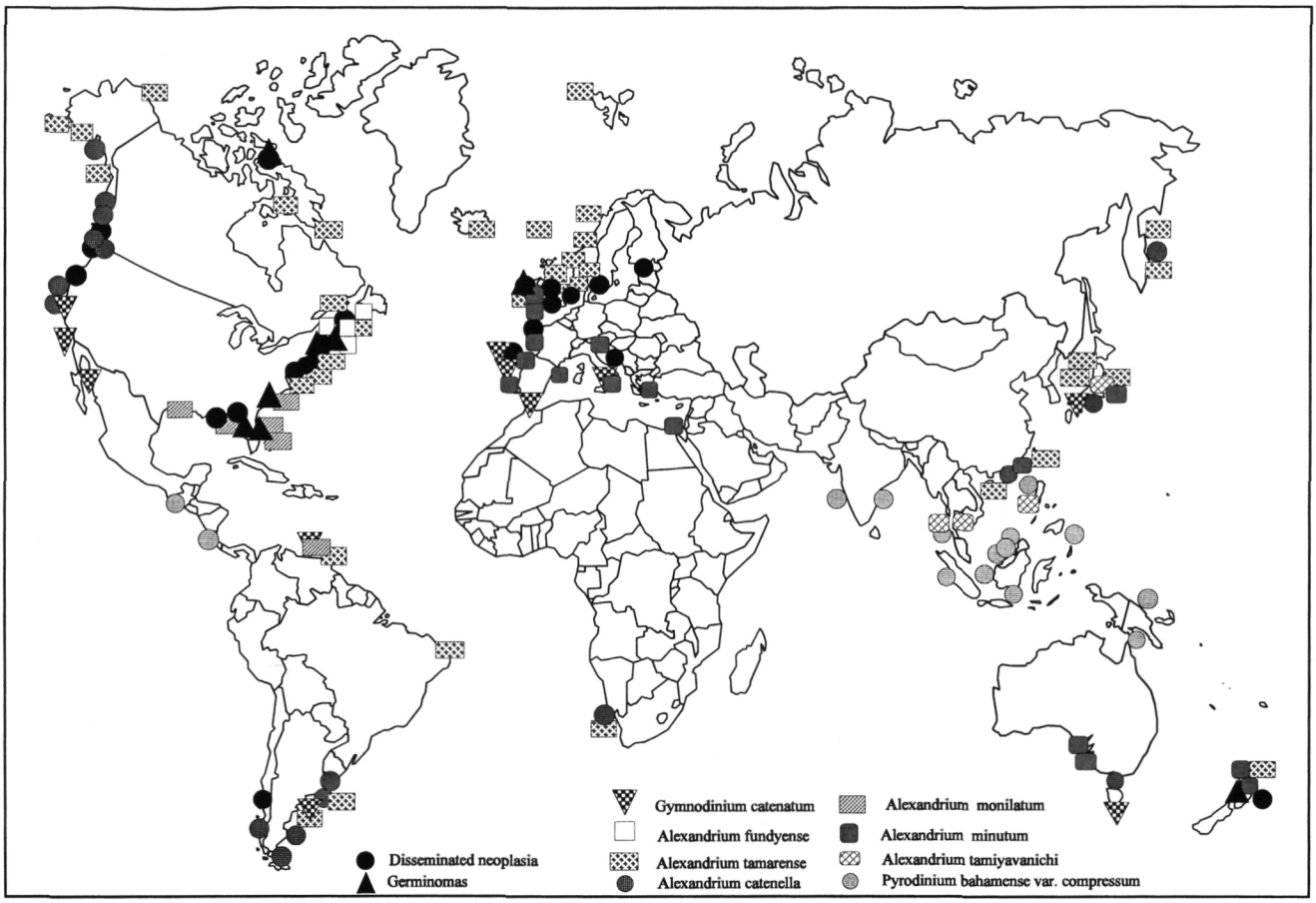

Figure 1. The distribution of dinoflagellates associated with PSP and the distribution of disseminated neoplasia and germinomas in bivalves.

tribution of carcinogenic pollutants with the development of germinomas (Yevich and Barry 1969, Barry and Yevich 1972, Hesselman et al. 1988).

Bivalves have been exposed to various chemical pollutants in laboratory exposures (Rasmussen et al. 1985, Rasmussen 1986), but no disseminated neoplasia or germinomas have been induced (Elston et al. 1992). Exposure to chemicals has induced numerous lesions (Farley 1977, Rasmussen et al. 1985) and, rarely, other types of neoplasia in bivalves. Thirty days after *C. virginica* or *M. edulis* were exposed to particulate suspensions or solid sediments from Black Rock Harbor, Bridgeport, CT, benign tumors were documented in the kidney, gastrointestinal tract, gonad, heart, and neural tissue (Gardner et al. 1991a).

Evidence for a viral etiology for disseminated neoplasia has only been demonstrated in *M. arenaria* (Brown 1980, Oprandy et al. 1981, Oprandy and Chang 1983). Normal *M. arenaria* that were exposed to water that had passed over infected *M. arenaria* developed neoplasia, thus suggesting that a transmissible agent was involved (Brown 1980). When virus-like particles from *M. arenaria* with neoplasia were injected into normal *M. arenaria,* these clams subsequently developed neoplasia. Virus-like particles were then reisolated from the newly induced neoplasia, conforming to Koch's postulates (Oprandy et al. 1981). A virus similar to an RNA tumor virus was isolated from *M. arenaria* with neoplasia, and after the injection of the purified virus into normal *M. arenaria,* neoplasia was induced. Because the virus was not isolated from any of the nonneoplastic samples, it was reasoned that a virus was the etiological agent of disseminated neoplasia (Oprandy and Chang 1983). The chemical 5-bromodeoxyuridine was used to induce retrovirus expression and replication as well as disseminated neoplasia in *M. arenaria*. Oprandy and Chang (1983) suggested that the clam tumor–inducing retrovirus may be endogenous in the cells of normal *M. arenaria*. A retrovirus was also found in the hemocytic cells of *M. arenaria* with disseminated neoplasia (Cooper and Chang 1982). Virus-like particles have been demonstrated in disseminated neoplasia (Rasmussen 1986), and a viral agent has been suggested as the probable cause of neoplasia in mussels (Elston et al. 1988a). However, ultrastructural examinations of tissues from *C. edule* (Auffret and Poder 1986), *O. edulis* (Cahour and Balouet 1984), *M. arenaria* (Farley 1976b, Cooper and Chang 1982, Medina et al. 1993), and *M. trossulus* (Mix et al. 1979) with disseminated neoplasia have failed to reveal the presence of virus. Since the earlier studies demonstrating retrovirus in *M. arenaria,* a viral etiology has not been confirmed despite numerous attempts (Elston et al. 1992).

A viral etiology in the development of germinomas is also unconfirmed. Intranuclear inclusions have been reported in germinoma cells of *M. arenaria* (Harshbarger et al. 1979; Hesselman et al. 1988), but electron microscopy of the same tissue, which is deposited at the RTLA, did not reveal virus (Peters et al. 1994).

An infectious etiology has also been postulated. Disseminated neoplasia appears to be transmissible if neoplastic cells are injected into disease-free bivalves (Farley 1987, Elston et al. 1988b, Twomey and Mulcahy 1988b). However, in several experiments, controls were also diagnosed with neoplasia (Farley 1987, Elston et al. 1988b). Kent et al. (1991) attempted to transfer disseminated

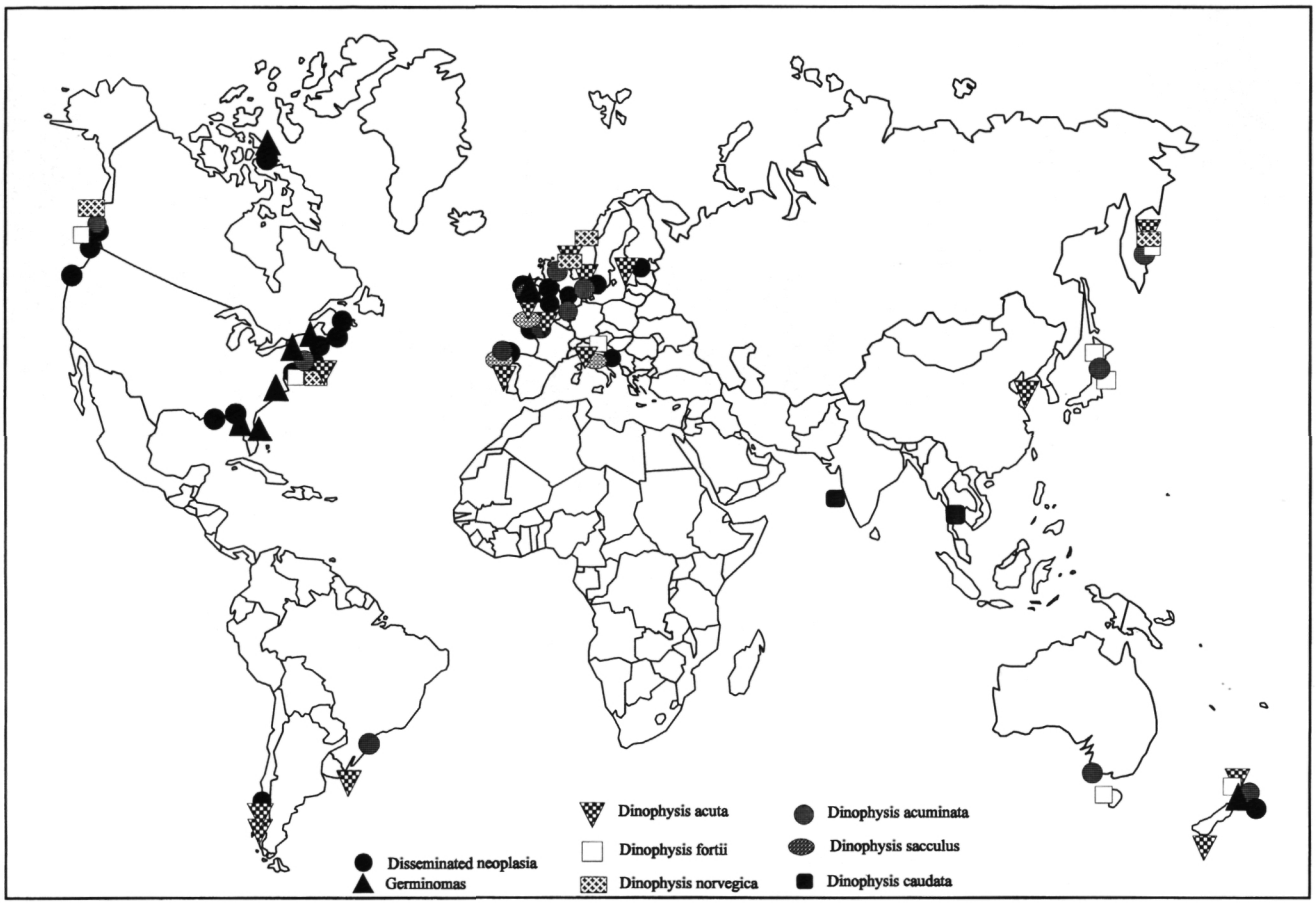

Figure 2. The distribution of dinoflagellates associated with DSP and the distribution of disseminated neoplasia and germinomas in bivalves.

neoplasia by injecting blood from heavily affected *M. trossulus* into *M. arenaria, O. edulis, O. conchaphila,* and other *M. trossulus*. After 152 days, only the injected *M. trossulus* were showing signs of disseminated neoplasia.

BIOTOXINS AND BIVALVES

In coastal areas where toxigenic microalgae occur, bivalves pose a public health risk because they accumulate a variety of biotoxins by filter feeding on phytoplankton. Exposures to toxic microalgae are usually acute, and high levels of toxins in bivalves prone to toxin accumulation can be reached within days or after only a few weeks. Biotoxins in shellfish are transferred to humans (and other predators) through consumption. The most common poisonings of humans from the consumption of shellfish are paralytic shellfish poisoning (PSP), diarrheic shellfish poisoning (DSP), neurotoxic shellfish poisoning (NSP), and more recently, amnesic shellfish poisoning (ASP). Venerupin shellfish poisoning (VSP) has rarely been documented. Biotoxins causing human shellfish poisonings are usually associated with dinoflagellates or, in the case of ASP, with diatoms.

In addition to the public health risk associated with eating toxic bivalves, the bivalves themselves may be affected by toxin exposure. The accumulation of biotoxins in bivalves varies between species, with geography, with the toxicity of specific dinoflagellates, and in the localization of toxins in bivalve tissues. Bivalve feeding behavior may be one of the principal factors controlling toxin levels. Some bivalves show immediate behavioral responses to avoid the consumption of toxic dinoflagellates (Gainey and Shumway 1988, Shumway 1990). Some species typically burrow into and feed on sediments, whereas others filter plankton from the water. Toxigenic dinoflagellates can produce benthic cysts and/or vegetative planktonic stages, so bivalves may be differentially exposed to toxins because of their feeding modes.

Although some studies have evaluated the effects of short-term toxin exposure on bivalve behavioral and physiological responses, other effects of biotoxins on bivalve health are generally unknown. Despite the frequent exposure of bivalves to biotoxins, no apparent associated pathological effects have been reported (Prakash et al. 1971). The detrimental effects of dinoflagellates and their toxins on bivalves have only recently been considered (Shumway 1990, Shumway et al. 1990, Wikfors and Smolowitz 1993, 1995, Smolowitz and Shumway 1996).

The tissues that accumulate toxins and their different components are known to vary both geographically and temporally among bivalve species, but the effects of chronic exposures are unknown. The majority of available information is on dinoflagellates known to be producers of toxins that are lethal or deleterious to mammals. The existence of biotoxins or toxic components that are potentially lethal or sublethal to molluscs should be considered. Recent evidence has shown that dinoflagellates that are apparently not toxic to mammals may be pathogenic to bivalves (Wikfors and Smolowitz 1995).

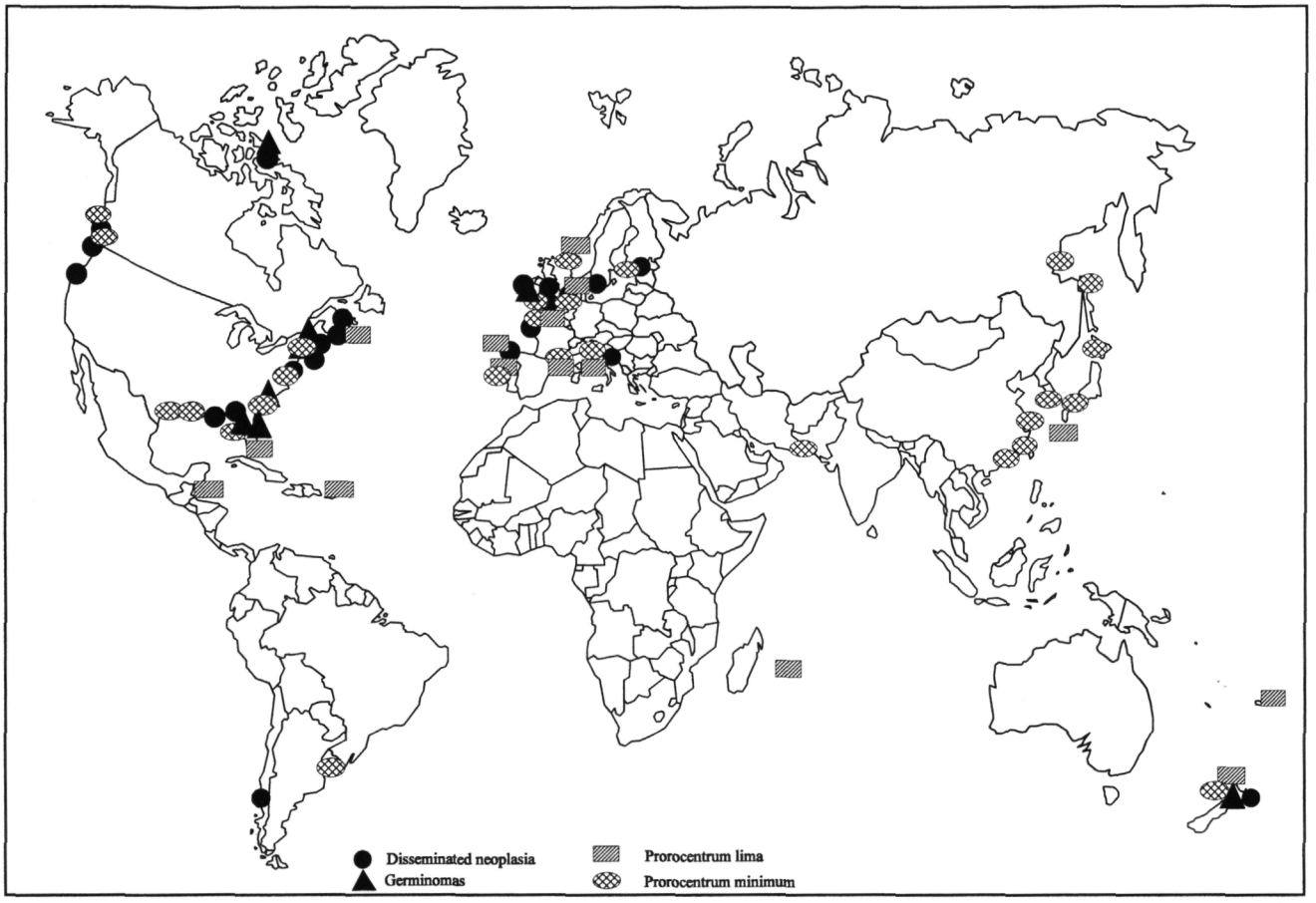

Figure 3. The distribution of *Prorocentrum* spp. implicated in shellfish toxicity and the distribution of disseminated neoplasia and germinomas in bivalves.

ASP

The first outbreak of ASP, in 1987 in Prince Edward Island, Canada, occurred after humans consumed toxic bivalves exposed to a bloom of the diatom *Pseudo-nitzschia multiseries* (Hasle) (Bates et al. 1989). Although the effects of diatoms and their toxins on bivalves have not been well documented, ASP is not considered here to be involved with the initiation of bivalve neoplasia. For the remainder of this article, only biotoxins associated with dinoflagellates will be considered.

NSP

NSP associated with brevetoxins has been documented from the Gulf of Mexico, the eastern United States, and New Zealand and is produced principally by toxins of *Gymnodinium breve* Davis and *Gymnodinium* spp. (Steidinger 1993, Chang 1995). Given that the known distribution of NSP is restricted to these areas, brevetoxins are not considered to play a role in the etiology of bivalve neoplasia. Although brevetoxin is well known for its role in fish kills (Steidinger 1993), its effects on molluscs are less well documented.

PSP

Since the 1970s, there has been a steady increase in the distribution of PSP worldwide (Hallegraeff 1993). Outbreaks of PSP are now common in temperate regions, particularly in North and South America, Europe, South Africa, Japan, and Australasia, and in equatorial regions in the Far East, Central Americas, northern South America, and India (Fig. 1). Outbreaks of PSP are related to a series of factors, including dinoflagellate distributions, environmental conditions favoring high concentrations of cells, population toxicity levels, bivalve distributions, and differential toxin uptake and accumulation by bivalves (Shumway 1990, Hallegraeff 1993). Many bivalve species accumulate PSP toxins, and these species pose a high public health risk during particular seasons and at certain geographical locations.

Dinoflagellate Distribution

Dinoflagellate species associated with the production of paralytic shellfish toxins (saxitoxin [STX] and its derivatives) are *Alexandrium acatenella* (Whedon and Kofoid), *Alexandrium catenella* (Whedon and Kofoid), *Alexandrium fundyense* (Balech), *Alexandrium lusitanicum* (Balech), *Alexandrium minutum* (Halim), *Alexandrium ostenfeldii* (Paulsen), *Alexandrium tamarense* (Lebour), *Alexandrium tamiyavanichi* (Balech), *Gymnodinium catenatum* Graham, *Pyrodinium bahamense* var. *compressum* (Böhm), and possibly, *Alexandrium monilatum* and *Lingulodinium* (=*Gonyaulax*) *polyedrum* (Stein) (Steidinger 1993). Some cyanobacteria are associated with the production of STX (Mahmood and Carmichael 1986), and bacteria have been implicated in paralytic shellfish toxin production (Kodama et al. 1990). How-

TABLE 5a.

Distribution and prevalence of germinomas in bivalves with suspected etiology or conditions.

Bivalve Species and Locality	Prevalence (%) (N =)	Date	Etiology	Reference
Arctica islandica				
Newport, RI	1 case (?)	?		Peters et al. 1994
A. irradians				
Massachusetts	1 case (?)	?		Peters et al. 1994
M. calcarea				
Baffin Island, Canada	1 case	?1986	oil?	Neff et al. 1987, Peters 1988
C. edule				
Cork Harbor, Ireland	0.15 (1,356)	2/83–2/85		Peters et al. 1994
C. virginica				
Delaware Bay, DE; Chesapeake Bay, MD; Black Rock Harbor, CT	2.0 (50) 0.01 (20,000) 0.23 (420)	8/69 1974–1977 1985		Farley 1976a, Harshbarger et al. 1979, Gardner et al. 1986
T. chilensis				
New Zealand	21 cases	?		Peters et al. 1994
M. arenaria				
Searsport, Machiasport, Dennysville, ME; Washington County, ME	6.0–12.5 (2,125) 6.4 (204), <22.0 (?) 32.0–40.0 (300) 10.0–43.0 (?)	1971–1976 1979 1993	oil spill, virus herbicides	Yevich and Barszez 1976, 1977, Brown et al. 1977, Harshbarger et al. 1979, Gardner et al. 1991b, Barber 1996
M. edulis				
New York	1 case	? 1987		Peters et al. 1994
M. mercenaria				
Narragansett Bay, RI; Indian R. Lagoon, FL; Charleston, SC	0.23 (1,300) 2.3–2.7 (539) 3.3–31.5 (1,263) 6.5 (708) 42.0 (?) 58.0–75.0 (440)	summer 68 summer 69/70 5/85–6/87 9/87–8/88 9/87–10/88 1988–1992	No relationship with water quality	Yevich and Barry 1969, Barry and Yevich 1972, Hesselman et al. 1988, Bert et al. 1993, Eversole and Heffernan 1993, Eversole and Heffernan 1966
Mercenaria campechiensis				
Tampa Bay, FL; Indian R. Lagoon, FL; Charleston, SC	7.7 (26) 11.8 (85) 42.0 (?) 58.0–75.0 (440)	9/86 9/87–8/88 9/87–10/88 1988–1992		Hesselman et al. 1988, Bert et al. 1993, Eversole and Heffernan 1993, Eversole and Heffernan 1996
M. campechiensis × *M. mercenaria*				
Indian R. Lagoon, FL; Charleston, SC	21.6 (75) >42.0 (?) 100.0 (440)	9/87–8/88 9/87–10/88 1988–1992		Bert et al. 1993, Eversole and Heffernan 1993, Eversole and Heffernan 1996

TABLE 5b.

Corresponding records of dinoflagellate blooms or shellfish toxicity events by nearest location and date.

Toxins/ Blooms	Site/Date	Bivalve	Reference
DSP *Dinophysis* spp. *A. minutum*	1984 1987	*M. edulis*	Jackson and Silke 1995, Gross 1988
P. minimum *A. tamarense*	1978 1986–1989		Seliger et al. 1975, Nuzzi and Waters 1993
PSP *A. minutum*, *A. tamarense*	1993		Chang et al. 1995
PSP *A. tamarense*	1972 York Harbor, ME	*M. edulis* *M. arenaria*	Twarog and Yamaguchi 1975
A. tamarense	NY 1986–1989		Nuzzi and Waters 1993
D. acuminata *A. monilatum*	1984 1978 Indian R. Lagoon, FL		Maranda and Shimuzu 1987, Norris 1983
A. monilatum	1978 Indian R. Lagoon, FL		Norris 1983
A. monilatum	1978 Indian R. Lagoon, FL		Norris 1983

ever, the majority of outbreaks worldwide have been attributed to dinoflagellates.

The taxonomy of *Alexandrium* has been in flux. Balech (1995) synonymized *Alexandrium excavatum* with *A. tamarense* and synonymized *Alexandrium ibericum* (Balech) with *A. minutum*. Balech (1994) named a new species *A. tamiyavanichi* that had been previously identified as *Alexandrium cohorticula* in the Far East (Kodama et al. 1988, Ogata et al. 1990, Pholpunthin et al. 1990, Wisessang et al. 1991, Han et al. 1992). In this article, the most updated references have been used (Anderson et al. 1994, Balech 1995). I acknowledge that some records that are based on the original authors' descriptions may be inaccurate. When the taxonomy has changed, the original designation has been noted wherever possible.

Figure 1 shows the distribution of blooms of the more common toxic dinoflagellate species associated with PSP. In the majority of cases, PSP outbreaks are associated with *A. tamarense, A. fundyense, A. catenella, A. minutum, G. catenatum,* and *P. bahamense* var. *compressum* (Fig. 1). Particular species have distinct distribution patterns: *P. bahamense* var. *compressum* is tropical and is common in Asia and Central America; *G. catenatum* is common along the West Coast of North America, the European Atlantic, southeastern Australia, New Zealand, southern South America, and Japan; *A. tamarense* is common in northwestern and northeastern North America and in Europe, New Zealand, Argentina, and the Far East; and *A. catenella* is common from Alaska to north-central California, central and southern Chile, southeastern Australia, New Zealand, and South Africa but is rare in southern California and Central America (Taylor 1984, Balech 1995).

Dinoflagellate Toxicity

No natural toxigenic dinoflagellate population has been found to contain all naturally occurring PSP toxin derivatives, so the toxin profile is considered to be characteristic of the dinoflagellate strain (Cembella et al. 1993). Some of the PSP toxin derivatives are highly toxic (as sodium channel–blocking agents in mammals) and include the carbamate toxins, saxitoxin (STX), neosaxitoxin (NEO), and the gonyautoxins (GTX1, GTX2, GTX3, and GTX4). The decarbamoyl analogues (dcSTX, dcNEO, dcGTX1, dcGTX2, dcGTX3, and dcGTX4) and deoxydecarbamoyl analogues (doSTX, doGTX2, doGTX3) are of intermediate toxicity. The least toxic derivatives are the *N*-sulfocarbamoyl toxins B1 (GTX5), B2 (GTX6), C1, C2, C3, and C4 (Sullivan 1988, Oshima 1995). GTX1/GTX4, GTX2/GTX3, C1/C2, and C3/C4 are pairs in an epimeric relationship: GTX1, GTX2, C1, and C3 are the α-epimers, and GTX3, GTX4, C2, and C4 are the β-epimers. Essentially, these pairs are in equilibrium with each other, but different physicochemical conditions can shift the ratio of the α- and β-forms (Shimuzu 1987). In some assays, the epimer pairs are combined because of inconsistent epimerization and are thus represented as a combined mol%.

The toxin profiles of the more common dinoflagellate species associated with PSP are different (Table 6). By species, the individual toxin components (mol%) are quite varied. In *P. bahamense* var. *compressum,* there is a lack of C1 to C4 and GTX1 to GTX4; in *A. minutum,* only GTX is present, with high levels of GTX1 and GTX4 in strains from Spain and Australia and only GTX2 and GTX3 in strains from France (Table 6); in *G. catenatum,* there are zero to trace levels of GTX1 to GTX4; in *A. tamarense,* there are trace to low levels of STX, B1, and B2 and high levels of NEO and GTX1 to GTX4; in *A. fundyense,* there are low levels of GTX1, GTX2, and GTX4 and high levels of GTX3; and in *A. catenella,* there are high levels of NEO, GTX4, B1, and B2 and low levels of GTX1, GTX2, and GTX3 (Table 6). Toxin profiles for *A. monilatum* are unknown (Schmidt and Loeblich 1979).

Toxin composition in dinoflagellate species and strains can vary with geographical range and can be influenced by environmental factors or experimental conditions (Cembella et al. 1988, Anderson et al. 1990, Anderson et al. 1994). *Alexandrium* strains

TABLE 6.

Toxin profiles of dinoflagellates associated with PSP.

Toxin (mol%)	Dinoflagellate species									
	A. tamarense	*A. minutum*	*A. minutum*	*A. catenella*	*A. fundyense*	*A. ostenfeldii*	*A. tamiyavanichi*	*A. lusitanicum**	*G. catenatum*	*P. bahamense var. compressum*
STX	0.0–3.2			trace–2.8	26.8		0.4–23.0		0.2	0.0–15.6
NEO	0.3–30.1			trace–22.8	13.2				0.1–3.8	10.5–68.0
GTX1	0.9–20.3	5.0–45.2	0.0	trace–3.9	0.6		1.1–3.8	26.0–41.0		
GTX2	0.1–23.0	<3.0–15.7	18.0	0.1	1.5	0.6	0.3–3.9	6.0	trace	
GTX3	0.3–86.0	<3.0–10.8	80.0	trace–0.9	50.1	0.1	2.2–10.2	12.0	trace	
GTX4	12.1–80.5	28.3–90.0	0.0	trace–26.2	5.1		36.8–72.8	41.0–53.0	0.8	
B1 (GTX5)	trace			trace–35.5			7.2–13.3		0.3–20.0	26.0–69.4
B2 (GTX6)				trace–57.3		91.6			0.1–36.0	4.0–8.0
C1	1.2–3.2			0.6–3.1	1/2 2.7	1/2 7.7	0.1–7.5		1.2–11.1	
C2	49.0–69.1			15.9–70.9	+	+	0.4–2.2		6.3–52.2	
C3				0.5–2.3			1.9–2.9		6.3–31.3	
C4	0.7–1.8			0.2–10.3			5.1–15.0		30.5–68.4	
dcSTX	0.7–3.0			0.1					0.1–4.0	0.0–4.5
dcGTX2				0.1					2/3 0.1–9.2	
dcGTX3	trace			0.1					+	
Location of isolate	Japan, Korea	Australia, Spain	France	Australia, Korea	USA	Denmark	Thailand Japan	Portugal	Australia, Japan, Spain	Malaysia
Reference	Lassus et al. 1989, Lee et al. 1992, Kim et al. 1993	Hallegraeff et al. 1991, Franco et al. 1994	Erard-Le-Denn 1991	Hallegraeff et al. 1991, Kim et al. 1993	Bricelj et al. 1990	Hansen et al. 1992	Wisessang et al. 1991, Oshima et al. 1990	Mascarenhas et al. 1995	Oshima et al. 1987, 1990, Oshima et al. 1993	Oshima et al. 1987, Usup et al. 1995

* Considered to be a synonym of *A. minutum* by Franco et al. 1995.

can vary from highly toxic to nontoxic (Anderson 1990). The original isolate of *A. tamarense* from the River Tamar, Plymouth, England, and other strains from La Jolla, CA, were found to be nontoxic (Schmidt and Loeblich 1979). The toxicity of *A. tamarense* strains increases northwards along the northeast Atlantic Coast of North America (Maranda et al. 1985, Cembella et al. 1988) and northwards in Japan (Kim et al. 1993). This toxicity gradient in isolates from the more northerly latitudes is a reflection of the increased proportion of the highly potent carbamate toxins (STX, NEO, and GTX1 to GTX4) in *A. tamarense* (Anderson et al. 1982, Anderson et al. 1994). The proportion of the less toxic *N*-sulfocarbamoyl fractions such as C1, C2, B1, and B2 is higher in the more southern areas (Anderson 1990, Anderson et al. 1994). The presence of *A. tamarense* has been documented in southern New England and Long Island, but PSP outbreaks are rarer in these areas than they are in the more northerly regions of New England and Canada (Anderson et al. 1982). Bricelj et al. (1991) also pointed out that blooms of *A. tamarense* are typically less dense in the southern region of its geographical range, which may explain the relative lack of shellfish toxicity in the Long Island area. Analyses of the toxin composition and morphology of 28 strains of *A. tamarense* and *A. fundyense* indicate that although the two species are interspersed geographically from New Jersey to the St. Lawrence estuary and Newfoundland, Canada, only *A. fundyense* occurs in the Gulf of Maine (Anderson et al. 1994). The north-south trend in toxicity in these isolates was not as distinct as that described by Maranda et al. (1985), but this finding can be partially explained by the fact that high-toxicity isolates from northern areas were not tested (Anderson et al. 1994).

The toxin profiles that are discussed in outbreaks of PSP typically refer to those of the bloom-forming vegetative stages. However, the cysts of *Alexandrium* spp. are known to be more toxic than the vegetative cells. When newly formed, the cysts can be up to 1,000 times more toxic than the vegetative cells and are 10 times more toxic even after several months of dormancy (Dale and Yentsch 1978). Benthic bivalves such as *M. arenaria* could therefore be exposed to high levels of toxins at all times if sediments are filtered during feeding.

Toxicity in Bivalves

The distribution of paralytic shellfish toxins in bivalves varies among species and individuals. This variation occurs initially because of differences in dinoflagellate bloom duration, density, and inherent toxicity. The exposure of bivalves to paralytic shellfish toxins can result in increased mucus and pseudofeces production, modification of valve activity, change in filtration rate, impaired burrowing activity, and altered byssus production, cardiac activity, and oxygen consumption (Shumway and Cucci 1987, Gainey and Shumway 1988, Shumway 1990). In the presence of *A. tamarense, M. mercenaria* close the shell valves (Shumway 1990). This response may partly explain the absence or low level of PSP in this species (Table 7). Other species, like *M. arenaria,* retract the siphon (Shumway and Cucci 1987) or, like *C. gigas,* reduce pumping rates (Dupuy and Sparks 1967) when exposed to *A. tamarense* and *A. catenella,* respectively. PSP toxicity levels for *C. gigas* are lower than those of *Placopecten magellanicus* (Gmelin) and *Patinopecten yessoensis* (Jay) (Table 8), and levels for *M. arenaria* are lower than those of *M. edulis* (Tables 7 and 9), which may partly be the result of these behavioral adaptations. Further differences in uptake dynamics and detoxification mechanisms, in anatomical localization, and in physiological breakdown or transformation mechanisms determine the persistence of the toxins in the bivalve tissue (Shimuzu and Yoshioka 1981, Maruyama et al.

TABLE 7.

Selected examples of maximum toxicity levels reported in clams and the associated dinoflagellate species involved in the PSP outbreak.

Bivalve	Date and Location	Toxicity (μg of STXeq 100 g^{-1})	Dinoflagellate	Tissues	Reference
M. mercenaria	1972 Eastham, MA;	0	*A. fundyense*/*A. tamarense*	Whole body	Twarog and Yamaguchi 1975,
	1975 Monhegan Island, ME	1,113	*A. fundyense*/*A. tamarense*	Whole body	Shumway pers. comm.
M. arenaria	1972 York Harbor, ME;	1,726	*A. fundyense*/*A. tamarense*	Whole body	Twarog and Yamaguchi 1975,
	1972 Merrimack River Estuary, MA;	9,600	*A. fundyense*/*A. tamarense*	Whole body	Twarog and Yamaguchi 1975,
	1972 Essex, MA	3,500	*A. fundyense*/*A. tamarense*	Whole body	Twarog and Yamaguchi 1975
S. solidissima	1981 Phippsburg, ME;	7,934	*A. tamarense*	Viscera	Shumway et al. 1988,
	1990 Georges Bank, ME	6,423	?*A. tamarense*	Whole body	White et al. 1993
S. giganteus	1985 British Columbia, Canada	9,600	*A. catenella*	Whole body	Chiang 1988
S. nuttalli	1980 Campbell Cove, CA	14,000	*A. catenella*	Whole body	Price et al. 1991
Meretrix meretrix	1988 Indonesia	1,400	*P. bahamense* var. *compressum*	Whole body	Adnan 1993
Callista chione	1989 Mediterranean Coast, Spain	200	*G. catenatum*	Whole body	Bravo et al. 1990
Arctica islandica	1985 Jonesport, ME;	>1,895	*A. tamarense*	Whole body	Shumway et al. 1988,
	1990 Georges Bank, ME	1,218	?*A. tamarense*	Whole body	White et al. 1993

TABLE 8.

Selected examples of maximum toxicity levels reported in oysters, scallops, and cockles and the associated dinoflagellate species involved in the PSP outbreak.

Bivalve	Date and Location	Toxicity (μg of STXeq 100 g^{-1})	Dinoflagellate	Tissues	Reference
A. irradians	1972 Eastham, MA	2,040	*A. fundyense/A. tamarense*	Whole body	Twarog and Yamaguchi 1975
C. virginica	1972 Eastham, MA;	0	*A. fundyense/A. tamarense*	Whole body	Twarog and Yamaguchi 1975;
	1988 Gulf of St. Lawrence, Canada	214	*A. fundyense/A. tamarense*	Whole body	Worms et al. 1993
C. gigas	1972 British Columbia, Canada;	1,900	*A. catenella*	Whole body	Chiang 1988,
	1980 Marin County, CA;	5,500	*A. catenella*	?Whole body	Nishitani and Chew 1988,
	1986 Okeover Inlet, BC, Canada	9,929	*?A. catenella*	Whole body	Shumway pers. comm.
Crassostrea iridescens	1989 SE Mexico	811	*Pyrodinium bahamense* var. *compressum*	Whole body	Cortés-Altamirano et al. 1993
O. edulis	1986 Harpswell, ME;	1,300	*A. tamarense*	Whole body	Shumway et al. 1990,
	1988 Brittany, France	282	*A. minutum*	Whole body	Belin 1993
Cerastoderma sp.	1986 Obidos Lagoon, Portugal	1,096	*G. catenatum*	Whole body	Franca and Almeida 1989
P. yessoensis	?1984 Japan	220,000	*?A. tamarense*	Digestive gland	Noguchi et al. 1984
P. magellanicus	1978 Bay of Fundy, Canada;	150,000	*A. tamarense* (=*A. excavatum*)	Digestive gland	Jamieson and Chandler 1983,
	1990 Georges Bank, ME;	14,775	*A. tamarense*	Whole body	White et al. 1993,
	1992 Bay of Fundy, Canada	6,180	*A. fundyense*	Digestive gland	Waiwood et al. 1995

1983, Beitler and Liston 1990, Bricelj et al. 1990, Bricelj et al. 1991, Cembella et al. 1993, White et al. 1993, Cembella et al. 1994, Shumway et al. 1994, Cembella and Shumway 1995).

STX was first isolated from toxic butter clams, *S. giganteus* (Schantz et al. 1957, Schantz 1960), and it and at least 20 derivatives (Oshima 1995) in various combinations and concentrations have been associated with PSP. The total toxicity of shellfish meat is usually represented as the integrated potency of all toxins present in the sample and expressed in micrograms of STXeq (STX equivalents) per 100 g (Sullivan et al. 1985, Anderson et al. 1984). Shellfish-monitoring standards have an acceptable safety level of 80 μg STXeq 100 g^{-1} in raw shellfish soft tissues, and toxicities above this level are considered to pose an immediate public health risk (Clem 1975). A range of STX toxicity levels is found in different bivalves (Tables 7–9): *P. yessoensis, P. magellanicus,* and *Mytilus* spp. become highly toxic (Tables 8 and 9); *M. arenaria* have intermediate toxicity levels (Table 7); and *M. mercenaria* and *C. virginica* tend not to accumulate or have low levels of toxin (Tables 7 and 8). In general, toxicity levels in bivalves exposed to the various dinoflagellates can range from high to low: high when exposed to *A. tamarense* and *A. catenella,* medium when exposed to *A. fundyense* and *G. catenatum,* and low when exposed to *A. minutum* and *P. bahamense* var. *compressum* (Tables 7–9). When exposed to *A. catenella,* maximum toxicity levels (in micrograms of STXeq per 100 g) in bivalves varied from 9,929 in *C. gigas,* 14,000 in *Saxidomus nuttalli,* 30,360 in *M. trossulus,* and 127,000 in *Mytilus chilensis* (Tables 7–9).

Bivalve species have different toxin profiles, primarily because of the toxin profile and toxigenicity of the dinoflagellate species to which they are exposed (Tables 10 and 11) and secondarily because of their inherent and differential abilities to accumulate and to bioconvert, depurate, or otherwise modify the various PSP toxins. Bivalves exposed to *P. bahamense* var. *compressum* or *G. catenatum* accumulate very low levels of GTX, whereas some species that are exposed to *Alexandrium* spp. accumulate high GTX levels (Tables 10 and 11). Different bivalve species acquire totally different toxin profiles when exposed to the same dinoflagellate species (e.g., *A. tamarense;* Table 12). Additionally, individuals of the same bivalve species can have totally different toxin profiles, depending on the particular dinoflagellate species and strain to which they are exposed and the location and season of exposure. For example, *M. edulis* accumulate >20 mol% of the derivatives NEO, GTX1, GTX2, GTX4, and C1 when exposed to *A. tamarense;* >20% of the derivatives GTX1, GTX2, GTX3, and GTX4 when exposed to *A. minutum;* and >20 mol% of the derivatives STX and GTX2 when exposed to *A. fundyense* (Table 10).

TABLE 9.

Selected examples of maximum toxicity levels reported in mussels and the associated dinoflagellate species involved in the PSP outbreak.

Bivalve	Date and Location	Toxicity (μg of STXeq 100 g^{-1})	Dinoflagellate	Tissues	Reference
M. edulis	1972 York Harbor, ME;	10,092	*A. fundyense/ A. tamarense*	Whole body	Twarog and Yamaguchi 1975,
	1972 Merrimack River Estuary, ME;	7,392	*A. fundyense/ A. tamarense*	Whole body	Twarog and Yamaguchi 1975,
	1972 Essex, MA;	7,200	*A. fundyense/ A. tamarense*	Whole body	Twarog and Yamaguchi 1975,
	1980 Argentine Sea, Argentina;	50,000	*A. tamarense* (=*A. excavatum*)	?Whole body	Carreto et al. 1985,
	1981 SW Norway;	42,000	*A. tamarense* (=*A. excavatum*)	Whole body	Langeland et al. 1984,
	1986 Harpswell, ME;	2,100	*A. tamarense*	Whole body	Shumway et al. 1990
	1990 Georges Bank, ME;	24,417	?*A. tamarense*	Whole body	White et al. 1993
	1988 Brittany, France	401	*A. minutum*	Whole body	Belin 1993
Mytilus planulatus	1986 S Tasmania, Australia;	8,350	*G. catenatum*	Whole body	Hallegraeff et al. 1989,
	1986/1987 Adelaide, S Australia	2,700	*A. minutum*	Whole body	Hallegraeff et al. 1989
M. trossulus	1978 Puget Sound, WA;	30,360	*A. catenella*	?Whole body	Nishitani and Chew 1988,
	1982 British Columbia, Canada;	30,000	*A. catenella*	Whole body	Chiang 1988,
	1987 Kodiak, AK	>5,000	?*A. catenella*	?Whole body	Nishitani and Chew 1988
M. galloprovincialis	1976 Vigo, Spain;	6,000	*G. catenatum*	Whole body	Lüthy 1979,
	1984 Galicia, Spain	445	*A. minutum*	Whole body	Bianco et al. 1985
M. californianus	1980 Marin County, CA	16,000	*A. catenella*	Whole body	Price et al. 1991
Mytilus sp.	1986 NW Portugal	1,600	*G. catenatum*	Whole body	Sousa et al. 1995
Mytilus chilensis	1992 S Chile	127,200	*A. catenella*	?Whole body	Benavides et al. 1995
Chloromytilus palliopunctatus	1989 SW Mexico	542	*P. bahamense* var. *compressum*	Whole body	Cortés-Altamirano et al. 1993
Perna viridis	1988 Indonesia	1,054	*P. bahamense* var. *compressum*	?Whole body	Adnan 1993
Perna perna	1989 Venezuela	1,309	*G. catenatum*	?Whole body	La Barbera-Sanchez et al. 1993
Modiolus modiolus	1990 Georges Bank, ME	5,016	?*A. tamarense*	Whole body	White et al. 1993

Tissue Deposition of Toxins

Bivalve toxin profiles vary by geographic region (Tables 7–9), by season, and in the distribution of toxic components in different tissues (Beitler and Liston 1990, Cembella et al. 1993, Cembella et al. 1994, Shumway et al. 1994). Some of these differences are reflected in the ability of bivalves to convert toxins both from highly toxic carbamates (STX, NEO, GTX1, GTX2, GTX3, GTX4) to mildly toxic decarbamoyl analogues (dcSTX, dcGTX1, dcGTX2, dcGTX3, dcGTX4) and vice versa or in the ability to store less toxic *N*-sulfocarbamoyl toxins (Tables 10 and 11). The ability to convert carbamates to decarbamoyl derivatives has been demonstrated in *S. solidissima, Protothaca staminea* (Conrad), *Peronidia venulosa,* and *Mactra chinensis* (Sullivan et al. 1983, Bricelj and Cembella 1995, Oshima 1995, Bricelj et al. 1996). Bivalves may therefore have different toxin profiles from those of the dinoflagellate to which they were exposed, and their toxin profiles can vary as a function of time since exposure (Cembella et al. 1994). Depuration times vary between different species. Most species can naturally eliminate PSP toxins within weeks (Shumway 1990). Pacific oysters, *C. gigas,* are able to depurate toxins from their tissues in less than 9 wk (Shumway et al. 1990). However, *S. giganteus, P. magellanicus,* and *S. solidissima* are known to retain high levels of toxins for long periods of time (from months up to 3+ y) (Shumway and Cembella 1993, Shumway et al. 1994, Shumway pers. comm.). In *S. giganteus,* the siphons are the main sites of toxin accumulation (Beitler and Liston 1990), and toxins are stored as STX, NEO, GTX2, and GTX3 (Kitts et al. 1992). In *P. magellanicus* and *P. yessoensis,* the majority of the toxins is concentrated in the digestive gland, with toxicity levels in the gills and gonads typically less than 80 μg of STXeq 100 g^{-1} (Shumway and Cembella 1993). In *S. solidissima,* toxicity levels of more than 20,000 μg of STXeq 100 g^{-1} were recorded in the gills (Shumway et al. 1994). Tissue storage of toxins can vary by season and by concentration (Cembella et al. 1994). Differences in toxin accumulation in individual bivalves exposed to PSP ranged from 40 to 3,213 μg of STXeq 100 g^{-1} in September (White et al. 1993).

The bivalve accumulation of particular toxins and the deposition of these toxins in different tissues have been studied during laboratory-controlled exposures (Lassus et al. 1989, Bricelj and Cembella 1995). Bricelj and Cembella (1995) exposed *S. solidissima* to *A. minutum* even though *S. solidissima* would not typically be exposed to this dinoflagellate, which is rare in North America. The toxins of the *A. minutum* strain to which the bivalves were exposed were exclusively GTX1/GTX4 (96.9 mol%) and GTX2/GTX3 (3.1 mol%). After 40 days, the deposition of GTX1/GTX4 in the gills and viscera of the bivalves had declined to less than 5.0

TABLE 10.

Toxin concentrations (mol%) in dinoflagellate species and clams and mussels associated with PSP outbreaks. Where possible, concentration ranges have been provided to reflect the dynamics of toxin sequestration, conversion, and depuration.

Bivalve/ Dinoflagellate	Carbamates						*N*-sulfocarbamoyls			Decarbamoyls		Reference
	STX	NEO	GTX1	GTX2	GTX3	GTX4	B1/B2	C1/C2	C3/C4	dcSTX	dcGTX2/3	
M. edulis	1.3–9.7	1.4–50.2	2.0–45.7	8.8–36.1	2.1–7.0	2.6–26.3		13.5–42.9				Lee et al.
A. tamarense	0.3–0.5	1.3–2.2	17.7–20.3	7.0–7.5	1.9–2.1	12.5–13.5		43.6–44.1				1992
M. edulis	0.0–0.5	2.0–9.0	2.0–7.0	8.0–13.0	9.0–51.0	0.0–6.0		17.0–24.0				Lassus et
A. tamarense	0.0	0.3–1.1	1.1–2.1	7.0–23.0	70.0–86.0	2.4–4.0		0.8–1.4				al. 1989
M. edulis			38.8–42.4	21.9–30.7	<0.1–30.7	25.9–76.8						Oshima et
A. minutum			40.5	5.2	1.3	52.9						al. 1990
M. edulis	40.0	10.0	1/4 13.0	2/3 48.0				2.7				Bricelj et
A. fundyense	26.8	13.2	0.6	1.5	50.1	5.1						al. 1990
M. trossulus		+	+	+	+	+	+					Shimuzu
?A. catenella												et al.
												1978
M. californianus	60.9	30.4	1–4 8.7									Whitefleet-
A. catenella												Smith et
												al. 1985
M. planulatus	0.1–0.3		0.5–3.0	0.3	0.2	3.6–5.2	1.5–2.7	8.9–18.5	55.9–79.4	5.3–16.2		Oshima et
G. catenatum	0.2			trace	trace	0.8	0.3–0.8	7.5–63.3	36.8–99.7	0.3–1.2		al. 1987
M. galloprovincialis	5.0	0.0	1/4 0.0	2/3 0.0			38.5–42.0	42.0	11.0			Anderson et
G. catenatum	6.0	2.0	1/4 2.0	2/3 0.0				36.0	17.0			al. 1989
M. mercenaria	25.4–30.2	12.2–12.6	1/4	2/3				1.8–3.9				Bricelj et
			9.3–9.6	46.0–49.6								al. 1991
A. fundyense	25.8	13.8	8.9	47.8				3.7				
M. arenaria	+	+	+	+	+	+		+				Martin et
A. fundyense												al. 1990
M. arenaria	23.3	16.2	19.2	17.4	15.6	5.4	0.3	2.7				Hurst et al.
A. tamarense												1985
R. phillipinarum	0.0–2.0	0.0–2.0	0.0–5.0	1.0–17.0	2.5–60.0	0.0–5.0		2.0–13.0				Lassus et
A. tamarense	0.0	0.3–1.1	1.1–2.1	7.0–23.0	70.0–86.0	2.4–4.0		0.8–1.4				al.
												1989
P. viridis	0.2	1.8	30.6	13.4	4.7	49.3						Wisessang
A. tamiyavanichi	0.4	0.0	7.0	0.7	8.5	56.4						et al.
												1987
P. viridis	46.7	8.6					25.5			19.1		Oshima et
P. bahamense var.	15.6	10.5					69.4			4.5		al. 1987
compressum												
Spondylus butleri	+	+					+	+		+		Oshima et
P. bahamense var.												al. 1990
compressum												
Spisula sp.	89.0	9.1	4.6	4.1	2.3		0.6	6.8				Hurst et al.
A. tamarense												1985
Meretrix casta	0.4	0.1	22.8	17.8	5.9	12.9		27.9	0.3		1.2–1.8	Karunasagar
?A. tamiyavanichi												et al. 1990

+, present but no value given.

mol% toxin concentration, and GTX2 and GTX3 had been converted to dcGTX2 and dcGTX3. Exposures of *M. mercenaria* to *A. tamarense* and *A. fundyense* (Bricelj et al.1991) indicated that *M. mercenaria* could accumulate toxins (Table 10), even though toxin accumulation may not occur in the field (Table 7). Cells of the high-toxicity *A. fundyense* isolate were only consumed if supplemented with a nontoxic diatom, *Thalassiosira weissflogii* (Bricelj et al. 1991).

Effects of PSP on Bivalves

In the short term, bivalves are not usually affected by paralytic shellfish toxins (Kao 1993) because their neuromuscular functions operate mainly by voltage-gated calcium channels. STX and its derivatives block only the voltage-gated sodium channels, which function in mammalian nerves and skeletal and cardiac muscle fibers (Kao 1993). High levels of STX are therefore typically not considered to be lethal or pathogenic to bivalves (Prakash et al. 1971). However, the effects of the chronic exposure of bivalves to STX and its derivatives are unknown. Paralysed *M. arenaria* were reported during the PSP outbreak in western Maine and Massachusetts in 1972, whereas toxic *M. arenaria* in eastern Maine and Canada showed no effects (Prakash et al. 1971). Paralysed *M. arenaria* are seen in Maine regularly (Shumway pers. comm.). Morbidity and mortality of shellfish were associated with a PSP outbreak in eastern England in 1968 (Adams et al. 1968, Ingham et al. 1968). Eighty percent of *C. gigas* that had been exposed to 10×10^6 *A. monilatum* cells l^{-1} died within 48 h (Sievers 1969).

The various combinations of the individual toxins described above determine the toxic potential of the shellfish to humans and the physiological damage expected to occur in the bivalves in which they accumulate. The total STX toxicity is the most important measure for public health concerns, yet the relative proportions of these toxic derivatives and their distribution in different tissues are not always considered. The long-term effects of these exposures on molluscan health needs critical evaluation.

TABLE 11.

Toxin concentrations (mol%) in dinoflagellate species in scallops and oysters associated with PSP outbreaks. Where possible, concentration ranges have been provided to reflect the dynamics of toxin sequestration, conversion, and depuration.

Bivalve/ Dinoflagellate	Carbamates						*N*-sulfocarbamoyls			Decarbamoyls		Reference
	STX	NEO	GTX1	GTX2	GTX3	GTX4	B1/B2	C1/C2	C3/C4	dcSTX	dcGTX2/3	
P. magellanicus	20.0	1.0	3.0	58.0	11.0	<1.0						Fix Wichmann
A. tamarense	0.0	11.0	9.0	9.0	41.0	30.0						et al. 1981
(=*A. excavatum*)												
P. magellanicus	11.5	8.4	4.6	39.2	23.8		2.3	7.7	+			Hurst et al.
A. tamarense												1985
P. yessoensis	2.7	34.2		5.4	0.6		0.4	76.8		0.3	2.3–4.8	Oshima et al.
A. catenella												1990
P. maximus	0.0–1.5	0.0–2.0	0.0–5.0	1.5–29.0	4.0–40.0	0.5–3.5		3.0–21.0				Lassus et al.
A. tamarense	0.0	0.3–1.1	1.1–2.1	7.0–23.0	70.0–86.0	2.4–4.0		0.8–1.4				1989
C. gigas	0.0–2.0	2.0–7.0	0.0–3.5	2.0–22.0	1.5–46.0	0.0–4.0		7.0–35.0				Lassus et al.
A. tamarense	0.0	0.3–1.1	1.1–2.1	7.0–23.0	70.0–86.0	2.4–4.0		0.8–1.4				1989
C. gigas	+	+	+	+	+	+	+					Onoue et
A. catenella												al. 1981
C. gigas	0.2	0.0	0.7	0.2	0.1	4.0	3.1	10.0	79.8	2.1		Oshima et al.
G. catenatum				trace	trace	0.8	0.3–0.8	7.5–63.3	36.8–99.7	0.3–1.2		1987
Crassostrea cucullata	0.7	0.0	13.5	52.5	10.1	4.7		14.2		0.0	4.2	Karunasagar
?A. tamiyavanichi												et al. 1990

DSP

DSP is associated with the consumption of shellfish that have been exposed to the dinoflagellates *Dinophysis* spp. (Fig. 2) and *Prorocentrum lima* (Ehrenberg) (Fig. 3). DSP outbreaks are most commonly reported in temperate areas in Europe, the Far East, South America, and Australasia (Fig. 2) (Lassus and Marcaillou-Le Baut 1991, Aune and Yndestad 1993). Recently, DSP was documented in eastern Canada (Quilliam et al. 1993). Bivalves currently implicated in DSP outbreaks are *M. edulis, Mytilus coruscum, M. galloprovincialis, P. yessoensis, Chlamys nipponensis, Tapes japonica, Gomphira melanaegis, M. mercenaria, Aulacomya ater,* and *M. arenaria* (Lassus and Marcaillou-Le Baut 1991, Lembeye et al. 1993).

Dinophysistoxins (DTXs) (DTX-1, DTX-2, and DTX-3) and okadaic acid (OA) are the major toxins currently known to be involved with DSP. DTXs have been found in *Dinophysis acuminata* (Claparède and Lachmann), *Dinophysis acuta* (Ehrenberg), *Dinophysis caudata* (Saville-Kent), *Dinophysis fortii* (Pavillard), *Dinophysis norvegica* (Claparède and Lachmann), *Dinophysis sacculus* (Stein) (Lee et al. 1989), and *P. lima* (Marr et al. 1992). OA, which is found in some benthic dinoflagellates in tropical regions (Steidinger 1993) and is suspected to have a role in ciguatera poisoning, has also been found in the planktonic *P. lima* (Jackson et al. 1993) and *Dinophysis* spp. (Lassus and Marcaillou-Le Baut 1991). OA and DTX-1 have been experimentally shown to induce skin tumors in mice (Fujiki et al. 1988, Suganuma et al. 1988).

TABLE 12.

Comparative toxin profiles of selected bivalves after exposure to *A. tamarense*. Where possible, concentration ranges have been provided to reflect the dynamics of toxin sequestration, conversion, and depuration.

Bivalve	STX (mol%)	GTX1/GTX4 (mol%)	GTX2/GTX3 (mol%)
C. gigas	0.0–2.0	0.0–7.5	3.5–68.0
M. edulis	0.0–9.7	0.0–72.0	17.0–64.0
P. maximus	11.5	0.0–8.5	5.5–69.0
P. magellanicus	11.5–20.0	<1.0–7.6	0.0–81.8
Spisula sp.	89.0	4.6	6.4
R. phillipinarum	0.0–2.0	0.0–10.0	3.5–77.0
M. arenaria	23.3	24.6	33.0

The accumulation and metabolism of DTXs in bivalves have not been well investigated, and the effects on molluscan health are unknown. The exposure of mussels to high concentrations of *P. lima* resulted in reduced filtration rates and was attributed to toxicity associated with inhibitory or cytotoxic effects (Pillet and Houvenaghel 1995). *M. edulis* that were experimentally exposed to *P. lima* accumulated OA and DTX-1 in the hepatopancreas. No mortality was associated with exposure (Pillet et al. 1995). Clearance rates of juvenile and adult *Argopecten irradians* were not inhibited by exposure to toxigenic *P. lima,* and no mortalities were observed. Toxin saturation levels were attained within the first 2 days of exposure, but toxin retention efficiency was low (Bauder et al. 1996).

Dinophysis spp. and *P. lima* are widely distributed (Figs. 2 and 3), and the effects of the exposure of bivalves to low-level concentrations of these dinoflagellates should be investigated. The presence of OA in the planktonic *P. minimum* has not been confirmed (see VSP).

VSP/Prorocentrum minimum

VSP has been associated with the consumption of shortnecked clams, *Venerupis semidecussata,* and Pacific oysters, *C. gigas,* and was coincidental with blooms of the dinoflagellate *Prorocentrum minimum* in Japan (Akiba and Hattori 1949). VSP is rare, and its true role in shellfish poisonings has been the subject of some discussion. Because of its association with VSP, the widespread distribution of *P. minimum* (Fig. 3) will be reviewed here. *P. minimum* is considered to consist of strains that are largely nontoxic to humans (Taylor 1984), but toxins that could be pathogenic to bivalves have been isolated (Okaichi and Imatomi 1979). Other shellfish toxicity events associated with *P. minimum* have been documented in *M. edulis* in Norway (Tangen 1983), in *C. edule* and *Venerupis decussatus* (Silva 1985) in Portugal, and in *M. mercenaria* in northeastern North America (Freudenthal and Jijina

1988). In Chesapeake Bay, blooms of *P. minimum* appear to be fairly common (Sellner et al. 1993) (Tables 1b to 5b) and have recently been associated with shellfish mortalities (Luckenbach et al. 1993).

Recent studies have shown pathological effects, inhibition of feeding, and mortality in shellfish exposed to *P. minimum* (Bardouil et al. 1993, Luckenbach et al. 1993, Wikfors and Smolowitz 1993, Wikfors and Smolowitz 1995). *M. mercenaria* and *A. irradians* were fed *Prorocentrum micans, P. minimum,* and *Isochrysis* sp. in single-species and mixed-species tests (Wikfors and Smolowitz 1993). *M. mercenaria* survived well in all experiments, but in *A. irradians,* none of the diets supported good growth. A mixed diet of *Isochrysis* and *P. minimum* caused 100% mortality in 1–4 wk. *A. irradians* ingested *P. minimum,* but histopathological observations showed poorly developed digestive diverticula, attenuation of the epithelium with abnormal vacuolation and necrosis, and large thrombi in the heart and in the open vascular system of the mantle, digestive diverticula, gill, and kidney tissues (Wikfors and Smolowitz 1993). All juvenile oysters, *C. virginica,* exposed to 100% *P. minimum* bloom density died within 14 days, and 43% exposed to 33% bloom density died within 22 days, but oysters exposed to 5% bloom density had good shell growth and no mortality (Luckenbach et al. 1993). Wikfors and Smolowitz (1993) suggested that *P. minimum* produces an enterotoxin that gradually affects absorptive cells, an effect that was indicated by the development of thrombi throughout the vascular system. Spat of *C. virginica* exposed to *P. minimum* had an abnormal accumulation of lipids in the stomach epithelium (Wikfors and Smolowitz 1995).

A *Prorocentrum* species has recently been implicated in mass mortalities of flat oysters, *Ostrea rivularis,* in southern China (Yomgjia et al. 1995). The pathology was consistent with a systemic toxicosis resulting from the absorption of toxins by the digestive gland. Interestingly, the most intense lesion was formed by hemocytes that accumulated in and around the hemolymph channels, infiltrated the walls of the blood sinus, and formed intravascular thrombi. This pathology appears to be similar to that found in *C. virginica* by Wikfors and Smolowitz (1993). These studies suggest that *Prorocentrum* spp. may induce pathological effects in the hematopoietic system of oysters. If *P. minimum* produces toxins that are important in neoplasia development, could the chronic exposure of oysters to low-level concentrations of *P. minimum* induce neoplasia of the hematopoietic system?

A COMPARISON OF BIVALVE NEOPLASIA AND BIOTOXIN DISTRIBUTION

The epizootiology of disseminated neoplasia and germinomas in bivalves appears to closely parallel, both spatially and temporally, the distribution of blooms of dinoflagellate species associated with PSP or VSP (Tables 1–5; Figs. 1 and 3). The correlations noted here are conservative because they reflect only the coincidences of acute bloom formations and high concentrations of toxins in bivalves. They do not take into account the distribution of low levels of dinoflagellate concentrations and thus do not address the potential effect of chronic exposure of bivalves to toxins. These correlations need to be experimentally and statistically verified. A relationship between the distributions of neoplasia and DSP is not currently indicated (Tables 1–5; Fig. 2).

My working theory that certain dinoflagellate toxins induce neoplasia in bivalves is based on the currently available toxin profiles of bivalves and dinoflagellates. I recognize that there are gaps in the data and inconsistencies between studies in techniques used; dinoflagellate species, strains, and geographical isolates examined; and time elapsed between bivalve exposures to dinoflagellate blooms and subsequent analysis of their toxin profiles. However, patterns and trends in the relationship between biotoxins and neoplasia may still be recognized.

One of the earliest descriptions of disseminated neoplasia in bivalves in North America mentioned that an outbreak of PSP had been going on in the area at the same time (Farley 1976a) (Table 2). During the first red tide that led to a major PSP outbreak from southern Maine to Cape Ann, MA, in September 1972 (Hartwell 1975, Mulligan 1975), *M. edulis* and *M. arenaria* were the most prone to PSP (Tables 7 and 9) and they remained toxic until April 1973 (Hartwell 1975). *M. arenaria* was heavily affected by disseminated neoplasia and germinomas, but *M. edulis* was refractory (Tables 2a, 3a, and 5a), even in locations where *M. arenaria* and *M. edulis* had high toxin levels (Twarog and Yamaguchi 1975) (Tables 7, 9). *M. mercenaria* and *C. virginica* did not accumulate toxin (Tables 7 and 8), and they were also refractory to disseminated neoplasia and germinomas (Tables 1a, 2a, and 5a). PSP outbreaks coincided with several reports of disseminated neoplasia in *M. arenaria* in Maine during 1972–1975 (Table 2) (Farley 1976a). In August 1986, Morrison et al. (1993) found disseminated neoplasia in 3.1% of *M. arenaria* from Lepreau Harbor, New Brunswick, a month after PSP had been found there in the same species (Martin et al. 1990). Numerous parallel temporal and spatial occurrences of PSP and disseminated neoplasia are shown in Tables 1–4.

With the exception of the Gulf of Mexico, it appears that the distribution of disseminated neoplasia in bivalves is restricted to comparatively temperate regions in both the northern and the southern hemispheres. Disseminated neoplasia has not been reported in Asia, California, Africa, the Middle East, central and northern South America, or the tropics (Tables 1a to 4a; Fig. 1). Thus, for the most part, the distribution of disseminated neoplasia in bivalves more closely parallels the distribution of *Alexandrium* spp. associated with PSP (Tables 1–4; Fig. 1) than that of *P. bahamense* var. *compressum* or *G. catenatum*. PSP outbreaks in Asia are usually associated with *P. bahamense* var. *compressum,* and similar associations have recently been reported in Guatemala and Venezuela (Fig. 1). However, toxicity levels in shellfish associated with *P. bahamense* var. *compressum* are typically low (Tables 7–9) and are associated with the toxins STX and NEO and their less potent derivatives (Tables 6 and 10). Unlike some *Alexandrium* spp., this dinoflagellate lacks toxin derivatives such as GTX that might be potential inducers of neoplasia (Table 6). Currently, there are no documented cases of bivalve neoplasia in areas where *P. bahamense* var. *compressum* occurs (Fig. 1).

G. catenatum has trace levels of GTX (Tables 6, 10, and 11). Shellfish toxicity associated with exposure to *G. catenatum* typically tends to be low (Tables 7–10) and is usually associated with high levels of the nontoxic components B1, B2, and C1 to C4 (Tables 10 and 11). PSP outbreaks associated with *G. catenatum* have been reported to occur in Europe, particularly along the Atlantic Coasts of France, Spain, and Portugal, and in Tasmania, Argentina, and California (Fig. 1). In some cases, this distribution of *G. catenatum* parallels that of disseminated neoplasia, but the dinoflagellate has not been reported to occur in northeastern and northwestern North America or in Scandinavia, areas in which there is a high prevalence of disseminated neoplasia. The distri-

butions of neoplasia and *G. catenatum* therefore do not seem to be highly correlated (Fig. 1). In areas where *G. catenatum* and disseminated neoplasia do co-occur, I think that the correlation is more likely to be caused by the presence of *Alexandrium* spp., which co-occurs with *G. catenatum* in those areas (Fig. 1).

Analyses of the toxin compositions of PSP-causing dinoflagellate species (Tables 6, 10, and 11) show a possible connection between the presence of disseminated neoplasia and exposure to the highly toxic GTX. It is postulated here that the combination of specific toxins will, in some cases, initiate neoplastic development in bivalves. Dinoflagellate species with distributions that parallel that of disseminated neoplasia on a worldwide basis and that have toxin profiles with high levels of GTX are *A. tamarense, A. minutum, A. catenella,* and *A. fundyense* (Table 6).

If there is a relationship between disseminated neoplasia in bivalves and their toxin profiles and concentrations, then high STX or NEO levels do not appear to be as important as other combinations of STX derivatives. It generally appears that when >20 mol% of the gonyautoxins GTX1/GTX4 are present, then disseminated neoplasia is also present (Tables 10–13). When >20 mol% STX or NEO is present, then disseminated neoplasia is generally absent (Table 13). In *M. arenaria,* after exposure to *A. tamarense,* >20.0 mol% of STX, GTX1/GTX4, and GTX2/GTX3 are present (Table 12). However, after exposure to *A. fundyense, M. arenaria* had low levels of STX and high levels of GTX1, GTX3, and GTX4 (Martin et al. 1990). In this case, the common toxin derivative associated with the presence of disseminated neoplasia in *M. arenaria* appears to be GTX and not STX. Bivalves such as *M. trossulus* and *M. arenaria* that store highly potent GTXs are affected by disseminated neoplasia, whereas those species that store STX, such as *S. giganteus, S. solidissima, P. magellanicus, P. yessoensis, Spondylus butleri,* and *M. californianus* are unaffected by disseminated neoplasia (Table 13).

Recent appearances of *Alexandrium* spp. with high levels of GTX such as *A. tamarense* and *A. tamiyavanichi* (Balech 1995) (identified as *A. cohorticula*) in Thailand, Korea, and Japan in the 1980s (Ogata et al. 1990, Pholpunthin et al. 1990, Han et al. 1992) and *A. minutum* in Australasia (Hallegraeff et al. 1991) may foreshadow the appearance of disseminated neoplasia in predisposed bivalves in these areas. There is a noticeable absence of dissem-

TABLE 13.

Geographic distribution of neoplasia in various bivalves associated with PSP (high-risk *Alexandrium* spp.), DSP, and VSP and distribution of toxins (at least > 20 mol%).

Bivalve	Germinomas	Distribution	Disseminated Neoplasia	Distribution	PSP					DSP		VSP
					C1/C2	NEO	STX	GTX1/4	GTX2/3	DTX1	OA	
M. edulis	+	NE North America	+ +	Europe	+	+	−*	+	+	+	+	+
M. trossulus	0	NW North America	+ + +	NW North America	?	−	−	+	+	ND	ND	ND
M. galloprovincialis	0		+	Europe	+	−	−	?+	−	+	+	ND
M. californianus	0		0		−	+	+	−	−	ND	ND	ND
M. arenaria	+ + +	NE North America	+ + +	NE North America	−	−	+	+	+	?+	?+	ND
M. truncata	0		+	N Canada	ND	ND	ND	ND	ND	ND	ND	ND
C. gigas	0		0		+	−	−	−	+	ND	+	+
C. virginica	+	E North America	+	E North America, Gulf of Mexico	−	−	−	−	−	ND	ND	?+
T. chilensis	?+	New Zealand	+	SW South America, New Zealand	ND	ND	ND	ND	ND	ND	ND	ND
O. edulis	0		+ +	Europe	ND	ND	ND	ND	ND	ND	ND	ND
O. conchaphila	0		+ +	NW North America	ND	ND	ND	ND	ND	ND	ND	
P. magellanicus	0		0		−	−	+	−	+	ND	+	ND
P. yessoensis	0		0		+	+	−	−	−	+	+	ND
A. irradians	+	NE North America	0		ND	ND	+	ND	ND	ND	ND	ND
Mercenaria mercenaria	+ + +	E/SE North America, Gulf of Mexico	0		−	−	−	−	−	?+	?+	+
C edule	?+	Western Europe	+ + +	Western Europe	ND	ND	ND	ND	ND	ND	+	+
S. solidissima	0		0		−	−	+	−	−	ND	ND	ND
S. butleri	0		0		−	+	+	−	−	ND	ND	ND
A. islandica	+	NE North America	0		ND	ND	ND	ND	ND	ND	ND	ND
M. balthica	0		+ +	Scandinavia	ND	ND	ND	ND	ND	ND	ND	ND
M. casta	0		?		+	−	−	+	+	ND	ND	ND
S. giganteus	0		0		−	−	+	−	−	ND	ND	ND

+ + +, high risk; + +, medium risk; +, low risk; 0, no risk.

* STX values for exposures to *A. fundyense* are >20.0 mol% (Table 10) (ND, no data).

inated neoplasia in bivalves in California, which correlates with and may have been influenced by the absence of *A. tamarense* in this area, by the presence of low-toxicity *G. catenatum,* or by the fact that California mussels, *M. californianus,* retain high STX levels when exposed to *A. catenella* (Fig. 1; Table 10).

From a public health standpoint, the toxicity of individual, nonconsumable bivalve organs is not usually considered because it is the total toxicity value that is important for safety standards. Toxicities that are reported as micrograms of STXeq per 100 g of shellfish meat (Prakash et al. 1971) are a composite of the total toxicity of the shellfish tissues that are typically consumed by humans. Even though the toxicity of individual organs can be much higher than the overall toxicity of the shellfish meat (Martin et al. 1990), these individual values are only relevant from a human health perspective when particular organs, such as adductor muscles from scallops, are consumed (Shumway and Cembella 1993). From a molluscan health perspective, however, the distribution of toxins and derivatives in individual organs may be critical. If neoplastic induction requires a particular period of chronic exposure to one or more toxins, then the deposition of the various toxin derivatives, their concentrations, and their persistence in different organs may play a significant role. At present, both the sites for hematopoiesis and the cellular origin of disseminated neoplasia in bivalves are unknown (Elston et al. 1992). Likely organ sites could include those with open blood sinuses such as the gills, heart, kidney, and brown gland, whereas those such as the adductor muscle and mantle might be less likely.

If there is a correlation between the tissue deposition of the highly toxic carbamate gonyautoxins and the prevalence of neoplasia, then it may be apparent in current bivalve data (Tables 10 and 11). In New England, *M. arenaria* is affected by both disseminated neoplasia and germinomas (Tables 2a and 5a). Martin et al. (1990) showed that the toxicity of whole *M. arenaria* extracts had a typical seasonal pattern, with a maximum of 2,103 μg of STXeq 100 g^{-1} present in July 1986 in Lepreau Harbor, New Brunswick. Toxicities for some individual tissues were far higher than the total maximum toxicity levels reported (Martin et al. 1990). Levels of approximately 10,000 μg of STXeq 100 g^{-1} were present in the digestive gland; 6,500 μg of STXeq 100 g^{-1} in the heart, kidney, and brown gland; 500 μg of STXeq 100 g^{-1} in the gills; 300 μg STXeq 100 g^{-1} in the gonad; and 120 μg of STXeq 100 g^{-1} in the muscle. Could the deposition of PSP toxins, and particularly the gonyautoxins, in tissues such as the gills, kidney, heart, or brown gland trigger the development of disseminated neoplasia? Could the deposition of these same toxins in the gonad trigger germinoma development? After *M. arenaria* were exposed to *A. fundyense* blooms, PSP toxins were transferred rapidly from the digestive gland to the kidney, where they were retained for extensive periods of time (Martin et al. 1990). Morrison et al. (1993) found disseminated neoplasia in *M. arenaria* from the same area (Lepreau Harbor) as those *M. arenaria* studied 1 month previously by Martin et al. (1990). Presumably *M. arenaria* had retained high levels of GTX in susceptible tissues during that period. The presence of disseminated neoplasia appears to be more than coincidental, and verification of such a cause-and-effect scenario is critical.

In contrast, *P. yessoensis* are known to be highly contaminated by toxins during PSP outbreaks (Table 8) but are refractory to disseminated neoplasia. Toxin-profile studies of the scallop *Pecten maximus* show that the accumulation of STX, NEO, and GTX occurs mostly in the digestive gland. The accumulation and subsequent transformation of these toxins in the gonad, kidney, and adductor muscle of the scallop *P. maximus* (L.) lead to an almost complete absence of GTX1 and GTX4 in these tissues 15 days after experimental exposure to *A. tamarense*. However, the digestive glands still contained GTX1 to GTX4 and NEO after 35 days (Lassus et al. 1992). Cembella et al. (1994) reported seasonal variation in toxicity profiles of *P. magellanicus* tissues. In the digestive glands, GTX2 and C1/C2 were the main components; in the gill, NEO; in the mantle, GTX2 and GTX3; and in the gonads, C1/C2, GTX2, GTX3, and NEO. Levels of GTX1 and GTX4 were negligible. The low level or complete absence of GTX1 and GTX4 might again explain the absence of disseminated neoplasia and germinomas in scallops (Cembella et al. 1994). The ability to transform toxic PSP carbamates to their corresponding nontoxic decarbamoyl derivatives, as demonstrated by *S. solidissima, P. staminea, P. venulosa,* and *M. chinensis* (Bricelj and Cembella 1995, Oshima 1995, Bricelj et al. 1996), may also correlate with a lack of neoplasia. Again, species with high STX concentrations and low levels of GTX appear to be unaffected by disseminated neoplasia—or at least less affected by disseminated neoplasia than are those species that retain high levels of GTX.

Although *M. edulis* is heavily affected by PSP in northeastern North America, the incidence of disseminated neoplasia has not been recorded in this species in this region. However, *M. edulis* from northern Europe (England and Scandinavia) are affected by disseminated neoplasia (Table 3a). Several factors could help to explain these geographical differences. In northern Europe, *M. edulis* are more than likely to be exposed to *A. tamarense* or *A. minutum* and, in general, have high GTX levels (>60 mol% GTX1/GTX4) (Table 10). In northeastern North America, *M. edulis* are typically exposed to *A. tamarense* or *A. fundyense*. In Maine, where a high prevalence of disseminated neoplasia and germinomas is documented in *M. arenaria* (Tables 2a and 5a), *M. edulis* are more than likely to be exposed to *A. fundyense* (Anderson et al. 1994). When exposed to *A. fundyense,* more than 40 mol% of STX but only about 13 mol% of GTX1/GTX4 is retained in *M. edulis* (Table 10). In this situation, the high levels of STX and the low levels of GTX may explain the absence of disseminated neoplasia in *M. edulis* in this region. I postulate that high levels of GTX1/GTX4 are required to trigger neoplastic development. If *M. edulis* are usually exposed to *A. fundyense* in Maine and this results in the deposition of low levels of GTX1/GTX4, then the absence of disseminated neoplasia in *M. edulis* in New England can be explained.

The worldwide distribution of germinomas is more localized than that of disseminated neoplasia (Figs. 1–3). If *Alexandrium* spp. are involved in tumor induction, then it might be expected that there would be a parallel distribution of germinomas and disseminated neoplasia in bivalves. In some cases, this situation holds true, as for example, in *M. balthica* in northern Canada, *M. arenaria* in New England, and *C. edule* in Cork, Ireland. However, in most cases, this situation does not occur (Table 13). The absence of germinomas in bivalves from most of Europe and their rare occurrences along the Pacific Coast of North America suggest that in these areas, toxins from the dinoflagellates *A. tamarense, A. fundyense, A. minutum, A. catenella,* and *G. catenatum* are not necessarily involved in germinoma induction. Alternatively, if these dinoflagellates are involved, then the toxin components required for germinoma induction are probably different than those required for the induction of disseminated neoplasia. The high prevalence of germinomas in *M. mercenaria* and the fact that their

exposure to toxic *Alexandrium* spp. under natural conditions may not always result in toxin accumulation (Table 7) suggest an alternative hypothesis for germinoma induction in this species.

There may be a possible correlation between the distribution of neoplasia in bivalves in the Gulf of Mexico and southeastern North America and the distribution of toxigenic *A. monilatum* or *P. minimum*. These dinoflagellates have been documented to occur throughout the Gulf of Mexico, the Caribbean, and southeastern and mid-Atlantic North America as far north as the Chesapeake Bay (Steidinger 1993). A potential relationship between the distribution of *P. minimum* and *A. monilatum* and neoplasia could also be postulated for the bivalves *C. virginica, T. chilensis, M. mercenaria,* and *Mercenaria campechiensis* (Figs. 1 and 3; Tables 1, 5, and 13). The distribution of disseminated neoplasia in oysters appears to be more related to the presence of *P. minimum* or *A. monilatum* than to other toxic dinoflagellates in the genus *Alexandrium* (Table 1). Most accounts of oyster exposure to *Alexandrium* spp. report low or no toxicity (Table 8), whereas toxins from *Prorocentrum* spp. cause pathological effects and have been associated with oyster mortalities (Wikfors and Smolowitz 1993, Wikfors and Smolowitz 1995, Yomgjia et al. 1995). Currently, there is no information on the uptake of toxins from *P. minimum* or *A. monilatum* by, or their toxicity to, *M. mercenaria,* although *P. minimum* cells were found in *M. mercenaria* in Nassau County, NY in 1985 after an outbreak of human shellfish poisoning (Freudenthal and Jijina 1985).

Although there are some incidences of neoplasia that parallel the distribution of DSP (Fig. 2), there are few records of DSP from the East and West Coasts of North America or the Gulf of Mexico, where neoplasia is prevalent. Dinoflagellate species with associated OA and DTX-1 would appear to be likely candidates for causing tumors in bivalves, yet the existing epizootiology of bivalve neoplasia does not appear to parallel the known distribution of these dinoflagellates (Fig. 2). However, the focus of this article has been to review the distribution of toxicity outbreaks typically associated with high-density planktonic blooms and acute exposure to bivalves. Therefore, if the long-term, low-level exposure of bivalves to OA or DTX is occurring through the continual consumption of *Dinophysis* spp. and *P. lima,* then field data comparing high-density bloom distributions and neoplasia incidence may not be pertinent.

The influence of anthropogenic chemical carcinogens on the induction of neoplasia in invertebrates has been well investigated (Mix 1986a). Many bivalves have been exposed to highly contaminated sediments containing chemical carcinogens known or suspected to affect aquatic organisms (Gardner and Yevich 1988). In most cases, a direct cause-and-effect relationship between bivalve exposure to carcinogens and the induction of disseminated neoplasia or germinomas could not be clearly demonstrated (see Etiology). However, in a few examples, benign tumors developed (Gardner et al. 1991a). One could speculate that if there is a connection between bivalve exposure to particular dinoflagellate toxins and neoplasia, then the neoplasia found in chemical carcinogen exposure studies could have been caused by exposure to sedimentary biotoxins. The majority of sediment exposure studies were carried out using sediments from high-risk PSP areas in New England such as Narragansett Bay, RI; Long Island Sound, Blackport, CT; Searsport, Freeport, and Dennysville, ME; and New Bedford Harbor, MA (Yevich and Barscsz 1976, Yevich and Barscsz 1977, Gardner and Yevich 1988) (Table 2b)—all areas where *Alexandrium* spp. cysts are known to be widespread in the sediments (Anderson et al. 1982, Maranda et al. 1985). It has been documented that the total toxin concentration in cysts of *A. tamarense* is six-fold higher than that in the natural population of vegetative cells (Oshima et al. 1992). Further, these cyst toxins comprised approximately 80 mol% of GTX compared with approximately 69 mol% of GTX in vegetative cells (Oshima et al. 1992). Theoretically, if these cysts were present in sediments from high-risk PSP areas during the exposure of bivalves to chemical contaminants, then bivalves could also have ingested toxic cysts along with other contaminated sediment particles.

There is little or no information about the potential role of natural biotoxins in the induction of tumors in aquatic organisms. OA and DTX-1 produced by *Dinophysis* spp. and *P. lima* can, in addition to causing DSP, promote tumors in mammals. The fact that bivalves accumulate toxins associated with *Dinophysis* and *Prorocentrum* is unequivocal, but the role of OA and DTX in inducing tumors in aquatic animals is currently unknown. It remains to be seen as to whether they can trigger neoplasia development in bivalves. Long-term studies to investigate the relationship between toxin exposures and neoplasia should be initiated.

A multifactorial etiology of neoplasia development in bivalves could be hypothesized, but before such a step can be made, the role of biotoxins in tumor induction should be defined and clearly demonstrated. In at least one species of bivalve (*M. arenaria*) known to be affected by disseminated neoplasia, the presence of a retrovirus has been demonstrated (Oprandy et al. 1981). Retroviruses may be endogenous in certain bivalve species and strains such as *M. arenaria* and *Mytilus* spp. The proliferation of these viruses could be triggered by exposure to natural carbamate toxins. Carbamate toxins could act directly as mutagens. Different bivalves may also be predisposed to viral or cellular oncogenes. Genetic differences in species predisposition to neoplasia may be significant (Van Beneden et al. 1993). Genetic susceptibility to germinomas was determined for *M. mercenaria, M. campechiensis,* and their hybrids. Hybrids were more affected by germinomas, which could be explained by decreased genetic fitness (Bert et al. 1993).

Although this concept is highly speculative at present, the geographic association of shellfish toxicity events, dinoflagellates, and neoplasia certainly represents strongly circumstantial evidence. If gonyautoxins induce disseminated neoplasia, then information on the chronic deposition of these toxins in different bivalve species and tissues may be indicative of the differences in species' predisposition to neoplasia. Table 13 shows the geographical distribution of disseminated neoplasia and germinomas, the species affected, and the typically high toxin concentrations (>20 mol%) that some bivalves accumulate. These data can be used to generate a theoretical risk assessment for the geographic distribution of bivalves with disseminated neoplasia (Table 14) and germinomas (Table 15).

Hypotheses

1. Disseminated neoplasia and germinomas can be induced in bivalves by toxins produced by dinoflagellates; a bivalve's predisposition to neoplasms is dependent on genetic, behavioral, physiological, environmental, and geographic factors that may operate in sequence.
2. Certain species, such as the softshell clam, *M. arenaria,* and the cockle, *C. edule,* are affected by both disseminated neoplasia and germinomas, but only in specific geographic locations and at certain times of the year. Other species,

TABLE 14.

Predisposition and theoretical risk of bivalve species to disseminated neoplasia by geographic region and by exposure to dinoflagellate species.

							PSP						
Bivalve	**North America**	**Central/ South America**	**Europe**	**Africa**	**Asia/ Far East**	**Australia/ New Zealand**	***A. tamarense***	***A. catenella***	***A. fundyense***	***A. minutum***	***G. catenatum***	***P. bahamense* var. *compressum***	**VSP *P. minimum***
M. edulis	0		+ +		0		+ +	0	0	? +	0	0	? + +
M. planulatus						? + +	? +			+ +			
M. trossulus	+ + +						+ + +	+ + +			0		?
M. galloprovincialis	0		+				? +	0		+	0		? + +
M. californianus	0							0			0		
M. arenaria	+ + +						+ + +		+ + +				? + +
M. truncata	+						+						
A. ater		0						0					
C. gigas	0		0		0		0	0		0	0	0	0
C. virginica	+						0		0				? + +
T. chilensis		+				+	+ +	? + +		+ + +	0		? + +
O. edulis	0		+ +				0		0	+ +	0		? + +
O. conchaphila	+						+	? +					
P. magellanicus	0						0		0				
P. yessoensis					0		0	0		?0		0	
A. irradians	?0						0			0			
M. mercenaria	0						0			0	0		
C. edule			+ + +				? + + +			+ + +	0		? + +
S. solidissima	0						0		0	0			
S. butleri	0												
A. islandica	+						? +						
M. balthica	0		+				? +						? + +
M. casta					?0							0	
P. viridis					0							0	
S. giganteus	0						0	0					

+ + +, high risk; + +, medium risk; +, low risk; 0, no risk.

such as the blue mussels, *M. edulis* and *M. trossulus,* and the eastern oyster, *C. virginica,* are rarely affected by both types of neoplasia. Some species, such as *M. mercenaria,* are apparently affected only by germinomas, and others, such as *O. edulis,* are affected only by disseminated neoplasia. The butter clam, *S. giganteus;* the Japanese scallop, *P. yessoensis;* the sea scallop, *P. magellanicus;* the surfclam, *S. solidissima;* and the California mussel, *M. californianus,* are apparently unaffected by either disseminated neoplasia or germinomas.

3. The absence of disseminated neoplasia and germinomas in bivalves from particular geographic regions is likely to be correlated with the absence of dinoflagellate species with high-risk toxins, such as GTXs, or with the resistance to neoplasia of particular bivalve species.
4. Disseminated neoplasia is prevalent in most geographic regions where PSP and *Alexandrium* spp. occur, but only in certain species of bivalves. More specifically, only certain species of *Alexandrium,* such as *A. tamarense, A. minutum,* and *A. fundyense,* are potential etiological agents of tumor induction.
5. Even though dinoflagellates such as *P. bahamense* var. *compressum* and *G. catenatum* cause PSP, they are unlikely to induce disseminated neoplasia or germinomas.
6. The decreasing toxicity of *A. tamarense* along a north-to-south gradient in the coastal United States could explain the higher prevalence of disseminated neoplasia in bivalves in more northerly regions.
7. *M. mercenaria* is apparently unaffected by disseminated neoplasia and does not usually accumulate toxins associated with *A. tamarense* or *A. fundyense*. *M. mercenaria* is, however, affected by germinomas. Toxins from known PSP-producing dinoflagellates do not appear to play a role in the development of germinomas in this species. In *M. arenaria,* the incidence of germinomas appears to be related to the distribution of *Alexandrium* spp. blooms.
8. *A. monilatum* and *P. minimum* may be potential etiological agents of neoplasms in some bivalves because of their parallel geographic distributions and their implicated toxicity. The toxin profiles of these dinoflagellate species are unknown.
9. There is a seasonal variation in the prevalence and intensity of neoplasia that parallels the seasonal variation of dinoflagellate blooms and the changing toxin profiles of high-risk toxins in particular tissues. In general, there appears to be a time lag of a few weeks after exposure to dinoflagellate toxins before disseminated neoplasia appears in bivalves.
10. In the development of disseminated neoplasia, bivalves could be sufficiently stressed by toxin exposure to render them susceptible to virus infection. Certain species may have cellular and viral oncogenes that are triggered by toxin exposure.
11. Certain bivalves that were historically affected by neoplasia in particular geographic areas may no longer be affected because the bloom-forming toxic dinoflagellate species are no longer dominant there.

TABLE 15.

Predisposition and theoretical risk of bivalve species to germinomas by geographic region and by exposure to dinoflagellate species.

							PSP							
Bivalve	**North America**	**Central/ South America**	**Europe**	**Africa**	**Asia/ Far East**	**Australia/ New Zealand**	***A. tamarense***	***A. catenella***	***A. fundyense***	***A. minutum***	***G. catenatum***	***A. monilatum***	***P. bahamense* var. *compressum***	**VSP *P. minimum***
M. edulis	+		0		0		?+			?0	0		0	?+
M. planulatus						0	0			?0				
M. trossulus	?+						?+	?0						
M. galloprovincialis	0		+					0		+	0			
M. californianus	0							0			0			
M. arenaria	+ +						+ +		?+					?+ +
M. truncata	+						+							
C. gigas	0		0		0			0					0	
C. virginica	+						0		0			?+		?+
T. chilensis		?0				+ +	0	0		+ +	0			
O. edulis	0		0							0				
O. conchaphila	0						0	0						
P. magellanicus	0						0		0					
P. yessoensis					0		0			0	0		0	
A. irradians	+						?+		?+					
M. mercenaria	+ + +						0		0			?+ +		?+ +
C. edule			+ +				?+ +			?+ +				?+ +
S. solidissima	0						0		0					
A. islandica	+						?+							
M. balthica	0		+ +				?+ +							
S. giganteus	0							0			0			

+ + + = high risk, + + = medium risk, + = low risk, 0 = no risk.

12. There is a strong likelihood that toxic microalgae play a role in both chronic disease and mortality in aquatic organisms.

Future Research

No published surveys have been specifically targeted at evaluating the prevalence of neoplasia in relation to known biotoxin distributions. Evidence presented here suggests that such a study should be conducted. Field data can be obtained through the routine monitoring of both affected and unaffected bivalves from sites where neoplasia is known to be prevalent. In addition to sampling bivalves, water quality and the presence of dinoflagellate species in water and sediment samples should be monitored. There should be comparative studies on bivalve behavior and feeding strategies during dinoflagellate exposure. Toxin profiles and the tissue deposition of toxic derivatives in bivalves should be confirmed for a range of species. Toxin profiles of suspect dinoflagellate species such as *A. monilatum, P. minimum,* and *L. polyedrum* should also be established. This information should be collected on both short- and long-term bases and in parallel with routine diagnostic procedures for monitoring molluscan health, disease, pathologies, and the distribution of neoplasia.

In addition to potential effects on bivalves, consideration should be given to the effects that chronic exposure to dinoflagellate biotoxins may have on other organisms. This consideration should include the evaluation of toxin exposure through dietary transfer and the distribution and epizootiology of neoplasia in organisms that consume molluscs. The long-term effects of biotoxin exposure at all levels of the food chain should be investigated. Criteria for public health exposure may also require reappraisal.

ACKNOWLEDGMENTS

I thank Ruth Reese for her continued patience and critical review of the manuscript and Jim Quinn, Judy Leiby, and Llyn French for their additional review and editorial comments. Special thanks to Karen Steidinger for numerous discussions on the biology of the toxic dinoflagellates, for supporting the concept, and for useful comments on the manuscript. I am especially grateful to Sandy Shumway for providing additional data and for constructive suggestions on the manuscript.

LITERATURE CITED

Adams, J. A., D. D. Seaton, J. B. Buchanan & M. R. Longbottom. 1968. Biological observations associated with the toxic phytoplankton bloom off the east coast. *Nature* 220:24–25.

Adnan, Q. 1993. PSP and red tide status in Indonesia. pp. 199–202. *In:* T. J. Smayda and Y. Shimuzu (eds.). Toxic Phytoplankton Blooms in the Sea. Elsevier Press, Amsterdam.

Akiba, T. & Y. Hattori. 1949. Food poisoning caused by eating asari (*Venerupis semidecussata*) and the oyster (*Ostrea gigas*) and studies on the toxic substance, venerupin. *Jpn. J. Exp. Med.* 20:271–284.

Alderman, D. J. 1974. Foreign diseases hazard British shellfish. *New Sci.* 63:122–124.

Alderman, D. J., P. van Banning & A. Perez-Colomer. 1977. Two European oyster (*Ostrea edulis*) mortalities associated with an abnormal hemocytic condition. *Aquaculture* 10:335–340.

Anderson, D. M. 1984. Shellfish toxicity and dormant cysts in toxic dinoflagellate blooms. pp. 125–138. *In:* R. P. Ragelis (ed.). Seafood Toxins. American Chemical Society, Washington, D.C.

Anderson, D. M. 1990. Toxin variability in *Alexandrium* species. pp. 41–51. *In:* E. Graneli, B. Sundstroem, L. Edler, and D. M. Anderson (eds.). Toxic Marine Phytoplankton. Elsevier Press, New York.

Anderson, D. M., D. M. Kulis, G. J. Doucette, J. C. Gallagher & E. Balech. 1994. Biogeography of toxic dinoflagellates in the genus *Alexandrium* from the northeastern United States and Canada. *Mar. Biol.* 120:467–478.

Anderson, D. M., D. M. Kulis, J. A. Orphanos & A. R. Ceurvels. 1982. Distribution of the toxic dinoflagellate *Gonyaulax tamarensis* in the southern New England region. *Estuarine Coastal Shelf Sci.* 14:447–458.

Anderson, D. M., D. M. Kulis, J. J. Sullivan & S. Hall. 1990. Toxin composition in one isolate of the dinoflagellate *Alexandrium fundyense*. *Toxicon* 28:885–893.

Anderson, D. M., J. J. Sullivan & B. Reguera. 1989. Paralytic shellfish poisoning in northwest Spain: the toxicity of the dinoflagellate *Gymnodinium catenatum*. *Toxicon* 27:665–674.

Appeldoorn, R. S. & J. J. Oprandy. 1980. Tumors in soft-shell clams and the role played by a virus. *Maritimes* 24:4–6.

Armstrong, D. A. & R. E. Millemann. 1974. Pathology of acute poisoning with the insecticide Sevin in the bent-nosed clam, *Macoma nasuta*. *J. Invertebr. Pathol.* 24:201–212.

Auffret, M. & M. Poder. 1986. Sarcomatous lesion in the cockle, *Cerastoderma edule*. II. Electron microscopical study. *Aquaculture* 58:9–15.

Aune, T. & M. Yndestad. 1993. Diarrhetic shellfish poisoning. pp. 87–104. *In:* I. R. Falconer (ed.). Algal Toxins in Seafood and Drinking Water. Academic Press, London.

Balech, E. 1994. Three new species of the genus *Alexandrium* (Dinoflagellata). *Trans. Am. Microsc. Soc.* 11:216–220.

Balech, E. 1995. The genus *Alexandrium* Halim (Dinoflagellata). Sherkin Island Marine Station, County Cork, Ireland. 151 pp.

Balouet, G. M., M. Poder, A. Cahour & M. Auffret. 1986. Proliferative hemocytic condition in European flat oysters: a 6-year survey. *J. Invertebr. Pathol.* 48:208–215.

Barber, B. J. 1990. Seasonal prevalence and intensity and disease progression of neoplasia in soft shell clams, *Mya arenaria,* from the Shrewsbury River, New Jersey. pp. 377–386. *In:* T. O. Perkins and T. C. Cheng (eds.). Pathology in Marine Science. Academic Press, London.

Barber, B. J. 1996. Gonadal neoplasms in *Mya arenaria:* what do we know? *National Shellfisheries Association 1996 Meeting,* Abstracts 52.

Bardouil, M., M. Bohec, M. Cormerais, S. Bougrier & P. Lassus. 1993. Experimental study of the effects of a toxic microalgal diet on feeding of the oyster *Crassostrea gigas* Thunberg. *J. Shellfish Res.* 12:417–422.

Barry, M. M. & P. P. Yevich. 1972. Incidence of gonadal cancer in the quahog *Mercenaria mercenaria*. *Oncology* 26:87–96.

Barry, M. M. & P. P. Yevich. 1975. The ecological, chemical and histopathological evaluation of an oil spill site. III. Histopathological studies. *Mar. Pollut. Bull.* 6:171–173.

Bates, S. S., C. J. Bird, A. S. W. de Freitas, R. Foxall, M. Gilgan, L. A. Hanic, G. R. Johnson, A. W. McCullough, P. Odense, R. Pocklington, M. A. Quilliam, P. G. Sim, J. C. Smith, D. V. Subba Rao, E. C. D. Todd, J. A. Walter & J. L. C. Wright. 1989. Pennate diatom *Nitzschia pungens* as the primary source of domoic acid, a toxin in shellfish from eastern Prince Edward Island, Canada. *Can. J. Fish. Aquat. Sci.* 48:1203–1215.

Bauder, A. G., J. Grant, A. D. Cembella & M. A. Quilliam. 1996. Kinetics of diarrhetic shellfish toxins in the bay scallop, *Argopecten irradians*. *National Shellfisheries Association 1996 Meeting, Abstracts: 35.*

Beitler, M. K. & J. Liston. 1990. Uptake and tissue distribution of PSP toxins in butter clams. pp. 257–262. *In:* E. Graneli, B. Sundstroem, L. Edler and D. M. Anderson (eds.). Toxic Marine Phytoplankton. Elsevier Press, New York.

Belin, C. 1993. Distribution of *Dinophysis* spp. and *Alexandrium minutum* along French coasts since 1984 and their DSP and PSP toxicity levels. pp.469–474. *In:* T. J. Smayda and Y. Shimuzu (eds.). Toxic Phytoplankton Blooms in the Sea. Elsevier Press, Amsterdam.

Benavides, H., L. Prado, S. Díaz & J. I. Carreto. 1995. An exceptional bloom of *Alexandrium catenella* in the Beagle Channel, Argentina. pp. 113–119. *In:* P. Lassus, G. Arzul, E. Erard-Le-Denn, P. Gentien and C. Marcaillou-Le-Baut (eds.). Harmful Marine Algal Blooms. Technique et Documentation, Lavoisier, Paris.

Berland, B. & D. Grzebyk. 1991. Espèces d'apparition recente. pp. 101–113. *In:* A. Sournia, C. Belin, B. Berland, E. Erard-Le-Denn, P. Gentien, D. Grzebyk, C. Marcaillou-Le Baut, P. Lassus and F. Partensky (eds.). Le Phytoplankton Nuisible des Côtes de France: de la Biologie à la Prévention. IFREMER, Centre National de la Recherche Scientifique, Plouzané, France.

Bert, T. M., D. M. Hesselman, W. S. Arnold, W. S. Moore, H. Cruz-Lopez & D. C. Marelli. 1993. High frequency of gonadal neoplasia in a hard clam (*Mercenaria* spp.) hybrid zone. *Mar. Biol.* 117:97–104.

Blanco, J., M. Fernández, J. Mariño, B. Reguera, A. Miguez, J. Maneiro, E. Cacho & A. Martínez. 1995. From *Dinophysis* spp. toxicity to DSP outbreaks: a preliminary model of toxin accumulation in mussels. pp. 777–782. *In:* P. Lassus, G. Arzul, E. Erard-Le-Denn, P. Gentien & C. Marcaillou-Le-Baut (eds.). Harmful Marine Algal Blooms. Technique et Documentation, Lavoisier, Paris.

Blanco, J., J. Mariño & M. J. Campos. 1985. The first toxic bloom of *Gonyaulax tamarensis* detected in Spain (1984). pp. 79–84. *In:* D. M. Anderson, A. W. White and D. G. Baden (eds.). Toxic Dinoflagellates. Elsevier, Amsterdam.

Borkman, D. G., R. W. Pierce & J. T. Turner, 1993. Dinoflagellate blooms in Buzzards Bay, Massachusetts. pp. 211–216. *In:* T. J. Smayda & Y. Shimuzu (eds.). Toxic Phytoplankton Blooms in the Sea. Elsevier Press, Amsterdam.

Bower, S. M. 1989. The summer mortality syndrome and hemocytic neoplasia in blue mussels (*Mytilus edulis*) from British Columbia. *Can. Tech. Rep. Fish. Aquat. Sci.* 1703:65.

Bravo, I., B. Reguera, A. Martinez & S. Fraga. 1990. First report of *Gymnodinium catenatum* Graham on the Spanish Mediterranean coast. pp. 449–452. *In:* E. Graneli, B. Sundstroem, L. Edler and D. M. Anderson (eds.). Toxic Marine Phytoplankton. Elsevier Press, New York.

Bricelj, V. M. & A. D. Cembella. 1995. Fate of gonyautoxins in surfclams, *Spisula solidissima,* grazing upon toxigenic *Alexandrium*. pp. 413–418. *In:* P. Lassus, G. Arzul, E. Erard-Le-Denn, P. Gentien and C. Marcaillou-Le-Baut (eds.). Harmful Marine Algal Blooms. Technique et Documentation, Lavoisier, Paris.

Bricelj, V. M., A. D. Cembella, D. Laby, S. E. Shumway & T. L. Cucci. 1996. Comparative physiological and behavioral responses to PSP toxins in two bivalve molluscs, the softshell clam, *Mya arenaria,* and surfclam, *Spisula solidissima*. Proc. 7th International Conf. on Harmful Algal Blooms, Sendhai, Japan. (In press.)

Bricelj, V. M., J. H. Lee & A. D. Cembella. 1991. Influence of dinoflagellate toxicity on uptake and loss of paralytic shellfish toxins in the northern quahog, *Mercenaria mercenaria*. *Mar. Ecol. Prog. Ser.* 74:33–46.

Bricelj, V. M., J. H. Lee, A. D. Cembella & D. M. Anderson. 1990. Uptake kinetics of paralytic shellfish toxins from the dinoflagellate *Alexandrium fundyense* in the mussel *Mytilus edulis*. *Mar. Ecol. Prog. Ser.* 63:177–188.

Brousseau, D. J. 1987. Seasonal aspects of sarcomatous neoplasia in *Mya arenaria* (soft-shell clam) from Long Island Sound. *J. Invertebr. Pathol.* 50:269–276.

Brousseau, D. J. & J. A. Baglivo. 1991a. Field and laboratory comparisons of mortality in normal and neoplastic *Mya arenaria*. *J. Invertebr. Pathol.* 57:59–65.

Brousseau, D. J. & J. A. Baglivo. 1991b. Disease progression and mortality in neoplastic *Mya arenaria* in the field. *Mar. Biol.* 110:249–252.

Brousseau, D. J. & J. A. Baglivo. 1994. Notes on epizootiological aspects (sex and age) of disseminated neoplasia in *Mya arenaria* from Long Island Sound. *J. Invertebr. Pathol.* 63:214–216.

Brown, R. S. 1980. The value of the multidisciplinary approach to research on marine pollution effects as evidenced in a three-year study to determine the etiology and pathogenesis of neoplasia in the soft-shell clam, *Mya arenaria*. *Rapp. P.-V. Reun. Cons. Int. Explor. Mer* 179: 125–128.

Brown, R. S., R. E. Wolke, C. W. Brown & S. B. Saila. 1979. Hydrocarbon pollution and the prevalence of neoplasia in feral New England soft-shell clams (*Mya arenaria*). pp. 41–51. *In:* E. Scarpelli, S. Nielsen and G. Migaki (eds.). Animals as Monitors of Environmental Pollutants. National Academy of Science, Washington, D.C.

Brown, R. S., R. E. Wolke & S. B. Saila. 1976. A preliminary report on neoplasia in feral populations of the soft-shell clam, *Mya arenaria*, prevalence, histopathology and diagnosis. *Proc. Int. Colloq. Invertebr. Pathol.* 1:151–158.

Brown, R. S., R. E. Wolke, S. B. Saila & C. Brown. 1977. Prevalence of neoplasia in 10 New England populations of the soft-shelled clam (*Mya arenaria*). *Ann. N.Y. Acad. Sci.* 298:522–534.

Cahour, A. & G. Balouet. 1984. Hémocytosarcomas de l'huître plate *Ostrea edulis* L. Observations ultrastructurales. *Rev. Int. Oceanogr. Méd.* 75/76:65–76.

Carreto, J. I., R. M. Negri, H. R. Benavides & R. Akselman. 1985. Toxic dinoflagellate blooms in the Argentine Sea. pp. 147–152. *In:* D. M. Anderson, A. W. White and D. G. Baden (eds.). Toxic Dinoflagellates. Elsevier, Amsterdam.

Cembella, A. D. & S. E. Shumway. 1995. Anatomical and spatio-temporal variation in PSP toxin composition in natural populations of the surf clam *Spisula solidissima* in the Gulf of Maine. pp. 421–426. *In:* P. Lassus, G. Arzul, E. Erard-Le-Denn, P. Gentien and C. Marcaillou-Le-Baut (eds.). Harmful Marine Algal Blooms. Technique et Documentation, Lavoisier, Paris.

Cembella, A. D., S. E. Shumway & R. Larocque. 1994. Sequestering and putative biotransformation of paralytic shellfish toxins by the sea scallop *Placopecten magellanicus:* seasonal and spatial scales in natural populations. *J. Exp. Mar. Biol. Ecol.* 180:1–22.

Cembella, A. D., S. E. Shumway & N. I. Lewis. 1993. Anatomical distribution and spatio-temporal variation in paralytic shellfish toxin composition in two bivalve species from the Gulf of Maine. *J. Shellfish Res.* 12:389–403.

Cembella, A. D., J.-C. Therriault & P. Beland. 1988. Toxicity of cultured isolates and natural populations of *Protogonyaulax tamarensis* from the St. Lawrence Estuary. *J. Shellfish Res.* 7:611–621.

Chang, F. H. 1995. The first records of *Gymnodinium* sp. nov. (cf. *breve*) (Dinophyceae) and other harmful phytoplankton species in the early 1993 blooms in New Zealand. pp. 27–32. *In:* P. Lassus, G. Arzul, E. Erard-Le-Denn, P. Gentien and C. Marcaillou-Le-Baut (eds.). Harmful Marine Algal Blooms. Technique et Documentation, Lavoisier, Paris.

Chang, F. H., L. MacKenzie, D. Till, D. Hannah & L. Rhodes. 1995. The first toxic shellfish blooms in early 1993 in New Zealand. pp. 145–150. *In:* P. Lassus, G. Arzul, E. Erard-Le-Denn, P. Gentien and C. Marcaillou-Le-Baut (eds.). Harmful Marine Algal Blooms. Technique et Documentation, Lavoisier, Paris.

Chiang, R. M. T. 1988. Paralytic shellfish management program in British Columbia, Canada. *J. Shellfish Res.* 7:637–642.

Christensen, D. J., C. A. Farley & F. G. Kern. 1974. Epizootic neoplasms in the clam *Macoma balthica* (L.) from Chesapeake Bay. *J. Natl. Cancer Inst.* 52:1739–1749.

Clem, J. D. 1975. Management of the paralytic shellfish poison problem in the United States. pp. 459–470. *In:* V. R. LoCicero (ed.). Proceedings of the First International Conference on Toxic Dinoflagellate Blooms. Massachusetts Science and Technology Foundation, Wakefield, Massachusetts.

Cohn, M. S., Olsen, P., Mahoney, J. B. & E. Fearst. 1988. Occurrence of the dinoflagellate, *Gonyaulax tamarensis,* in New Jersey. *Bull. N.J. Acad. Sci.* 33:45–49.

Cooper, K. R., R. S. Brown & P. W. Chang. 1982a. The course and mortality of a haematopoietic neoplasm in the soft-shell clam, *Mya arenaria*. *J. Invertebr. Pathol.* 39:149–157.

Cooper, K. R., R. S. Brown & P. W. Chang. 1982b. Accuracy of blood cytological screening techniques for the diagnosis of a possible haematopoietic neoplasm in the bivalve mollusc, *Mya arenaria*. *J. Invertebr. Pathol.* 39:281–289.

Cooper, K. R. & P. W. Chang. 1982. A review of the evidence supporting a viral agent causing a hematopoietic neoplasm in the soft-shelled clam, *Mya arenaria*. *Proc. Int. Colloq. Invertebr. Pathol.* 3:271–272.

Cortés-Altamirano, R., L. Muñoz-Cabrera & O. Sotomayor-Navarro. 1993. Envenenamiento paralítico por mariscos (PSP), causado por el dinoflagelado *Pyrodinium bahamense* var. *compressum* en la costa suroeste de Mexico. *An. Inst. Cienc. Mar Limnol. Univ. Nac. Autón. Méx.* 20:43–54.

Cosson-Mannevy, M. A., C. S. Wong & W. J. Cretney. 1984. Putative neoplastic disorders in mussels (*Mytilus edulis*) from southern Vancouver Island waters, British Columbia. *J. Invertebr. Pathol.* 44:151–160.

Couch, J. A. 1969. An unusual lesion in the mantle of the American oyster, *Crassostrea virginica*. *Natl. Cancer Inst. Monogr.* 31:557–562.

Couch, J. A. 1985. A prospective study of infectious and noninfectious diseases in oysters and fishes in the Gulf of Mexico estuaries. *Dis. Aquat. Org.* 1:59–82.

Couch, J. A. & J. T. Winstead. 1979. Concurrent neoplastic and protistan disorders in the American oyster (*Crassostrea virginica*). *Haliotis* 8: 249–253.

Dale, B. & C. M. Yentsch. 1978. Red tide and paralytic shellfish poisoning. *Oceanus* 21:41–49.

Dupuy, J. L. & A. K. Sparks. 1967. *Gonyaulax washingtonensis,* its relationship to *Mytilus californianus* and *Crassostrea gigas* as a source of paralytic shellfish toxin in Sequim Bay, Washington. *Proc. Natl. Shellfish Assoc.* 58:2.

Elston, R. A., M. L. Kent & A. S. Drum. 1988a. Progression, lethality, and remission of hemic neoplasia in the bay mussel, *Mytilus edulis*. *Dis. Aquat. Org.* 4:135–142.

Elston, R. A., M. L. Kent & A. S. Drum. 1988b. Transmission of hemic neoplasia in the bay mussel, *Mytilus edulis,* using whole cells and cell homogenate. *Dev. Comp. Immunol.* 12:719–727.

Elston, R. A., J. D. Moore & K. Brooks. 1992. Disseminated neoplasia of bivalve mollusks. *Rev. Aquat. Sci.* 6:405–466.

Emmett, B. 1984. The Analysis of Summer Mortality in Cultured Mussels, *Mytilus edulis*. Final Report. British Columbia Science Grant No. 58 (RC-7). 74 pp.

Erard-Le Denn, E. 1991. *Alexandrium minutum* (Dinophycées). pp. 83–90. *In:* A. Sournia, C. Belin, B. Berland, E. Erard-Le-Denn, P. Gentien, D. Grzebyk, C. Marcaillou-Le Baut, P. Lassus and F. Partensky (eds.). Le Phytoplankton Nuisible des Côtes de France: de la Biologie à la Prévention. IFREMER, Centre National de la Recherche Scientifique, Plouzané, France.

Eversole, A. G. & P. B. Heffernan. 1993. Gonadal neoplasia in *Mercenaria mercenaria, M. campechiensis* and their hybrids. *J. Shellfish Res.* 12:150–151.

Eversole, A. G. & P. B. Heffernan. 1996. Gonadal neoplasia in northern and southern quahogs and their hybrids in South Carolina. *National Shellfisheries Association 1996 Meeting, Abstracts:* 52.

Farley, C. A. 1969a. Probable neoplastic disease in the hematopoietic system in oysters, *Crassostrea virginica* and *Crassostrea gigas*. *Natl. Cancer Inst. Monogr.* 31:541–555.

Farley, C. A. 1969b. Sarcomatoid proliferative disease in a wild population of blue mussels (*Mytilus edulis*). *J. Natl. Cancer Res.* 43:509–516.

Farley, C. A. 1976a. Proliferative disorders in bivalve molluscs. *Mar. Fish. Rev.* 38:30–33.

Farley, C. A. 1976b. Ultrastructural observations on epizootic neoplasia and lytic virus infection in bivalve mollusks. *Prog. Exp. Tumor Res.* 20:283–294.

Farley, C. A. 1977. Neoplasms in estuarine mollusks and approaches to ascertain causes. *Ann. N.Y. Acad Sci.* 298:225–232.

Farley, C. A. 1987. Selected aspects of neoplastic progression in mollusks. pp. 1–14. *In:* H. E. Kaiser (ed.). Progressive Stages of Malignant Growth Development. vol. II, part 4. Comparative Aspects of Tumor Progression. Martinus Nijhoff, New York.

Farley, C. A., S. V. Otto & C. L. Reinisch. 1986. New occurrence of epizootic sarcoma in Chesapeake Bay soft shell clams, *Mya arenaria*. *Fish. Bull.* 84:851–857.

Farley, C. A., D. L. Plutschak & R. F. Scott. 1991. Epizootiology and distribution of transmissible sarcoma in Maryland softshell clams, *Mya arenaria,* 1984–1988. *Environ. Health Perspect.* 90:35–41.

Farley, C. A. & A. K. Sparks, 1970. Proliferative diseases of hemocytes, endothelial cells, and connective tissue cells in mollusks. *Bibl. Haematol.* 36:610–617.

Fix Wichmann, C., G. L. Boyer & C. L. Divan. 1981. Neurotoxins of *Gonyaulax excavata* and Bay of Fundy scallops. *Tetrahedron Lett.* 22:1941–1944.

Franca, S. & J. F. Almeida. 1989. Paralytic shellfish poisons in bivalve molluscs on the Portuguese coast caused by a bloom of the dinoflagellate *Gymnodinium catenatum. pp. 93–96. In:* T. Okaichi, D. M. Anderson and T. Nemoto (eds.). Red Tides, Biology, Environmental Science and Toxicology. Elsevier Science Publishing Company, New York.

Franco, J. M., P. Fernández & B. Reguera. 1994. Toxin profiles of natural populations and cultures of *Alexandrium minutum* Halim from Galician (Spain) coastal waters. *J. Appl. Phycol.* 6:275–279.

Franco, J. M., S. Fraga, M. Zapata, I. Bravi, P. Fernández & I. Ramilo. 1995. Comparison between different strains of genus *Alexandrium* of the *minutum* group. pp. 53–58. *In:* P. Lassus, G. Arzul, E. Erard-Le-Denn, P. Gentien and C. Marcaillou-Le-Baut (eds.). Harmful Marine Algal Blooms Technique et Documentation, Lavoisier, Paris.

Freudenthal, A. R. & J. L. Jijina. 1985. Shellfish poisoning episodes involving or coincidental with dinoflagellates. pp. 461–466. *In:* D. M. Anderson, A. W. White and D. G. Baden (eds.). Toxic Dinoflagellates. Elsevier Amsterdam.

Freudenthal, A. R. & J. L. Jijina. 1988. Potential hazards of *Dinophysis* to consumers and shellfisheries. *J. Shellfish Res.* 7:695–701.

Frierman, E. M. 1976. Occurrence of hematopoietic neoplasms in Virginia oysters (*Crassostrea virginica*). *Mar. Fish. Rev.* 38:34–36.

Frierman, E. M. & J. D. Andrews. 1976. Occurrence of hematopoietic neoplasms in Virginia oysters (*Crassostrea virginica*). *J. Natl Cancer Inst.* 56:319–324.

Fujiki, H., M. Suganuma, H. Suguri, S. Yoshizawa, K. Takagi, N. Uda, K. Wakamatsu, K. Yamada, M. Murata, T. Yasumoto & T. Sugimura. 1988. Diarrhetic shellfish toxin, dinophysistoxin-1, is a potent tumor promoter on mouse skin. *Jpn. J. Cancer Res.* 79:1089–1093.

Gainey, L. F. & S. E. Shumway. 1988. A compendium of the responses of bivalve mollusks to toxic dinoflagellates. *J. Shellfish Res.* 7:623–628.

Gardner, G. R. & P. P. Yevich. 1988. Comparative histopathological effects of chemically contaminated sediment on marine organisms. *Mar. Environ. Res.* 24:311–316.

Gardner, G. R., P. P. Yevich, J. C. Harshbarger & A. R. Malcolm. 1991a. Carcinogenicity of Black Rock Harbor, Bridgeport, CT sediment to the American oyster (*Crassostrea virginica*) and trophic transfer of Black Rock Harbor carcinogens from the blue mussel (*Mytilus edulis*) to the winter flounder (*Pseudopleuronectes americanus*). *Environ. Health Perspect.* 90:53–66.

Gardner, G. R., P. P. Yevich, J. Hurst, P. Theyer, S. Benyi, J. C. Harshbarger & R. J. Pruell. 1991b. Germinomas and teratoid siphon anomalies in softshell clams, *Mya arenaria,* environmentally exposed to herbicides. *J. Environ. Health Perspect.* 90:43–51.

Gardner, G. R., P. P. Yevich, A. R. Malcolm, P. F. Rogerson, L. Mills, J. Senecal, A. G. Lee, T. C. Harshbarger & T. P. Cameron. 1986. Tumor development in American oysters and winter flounder exposed to a contaminated marine sediment under laboratory and field conditions. *Aquat. Toxicol.* 11:403–404.

Gilfillan, E. S., S. A. Hanson, D. Page, D. Mayo, J. Cooley, J. Chalfant, T. Archambeault, A. West & J. C. Harshbarger. 1977. Final Report to the Department of Environmental Protection, Contract No. 906439. State of Maine Department of Environmental Protection, Augusta, Maine.

Green, M. & D. J. Alderman. 1983. Neoplasia in *Mytilus edulis* L. from United Kingdom waters. *Aquaculture* 30:1–10.

Gross, J. 1988. A red tide outbreak in Cork Harbour, July, 1987. *Red Tide Newsl.* 1:4.

Gutierrez, M. & M. C. Sarasquete. 1986. Un caso de hemocitosarcoma hialino en el mejillón, *Mytilus edulis* L. (Pelecypoda: Mytiludae) de la costa NO de España. *Invest. Pesq.* 50:265–269.

Hallegraeff, G. M. 1993. A review of harmful algal blooms and their apparent global increase. *Phycologia* 32:79–99.

Hallegraeff, G. M., C. J. Bolch, S. I. Blackburn & Y. Oshima. 1991. Species of the toxigenic dinoflagellate genus *Alexandrium* in southeastern Australian waters. *Bot. Mar.* 34:575–587.

Hallegraeff, G. M., S. O. Stanley, C. J. Bolch & S. I. Blackburn. 1989. *Gymnodinium catenatum* blooms and shellfish toxicity in southern Tasmania, Australia. pp. 77–80. *In:* T. Okaichi, D. M. Anderson and T. Nemoto (eds.). Red Tides, Biology, Environmental Science and Toxicology. Elsevier Science Publishing Company, New York.

Han, M.-S., J.-K. Jeon & Y.-O. Kim. 1992. Occurrence of dinoflagellate *Alexandrium tamarense,* a causative organism of paralytic shellfish poisoning in Chinhae Bay, Korea. *J. Plankton Res.* 14:1581–1592.

Hansen, P. J., A. D. Cembella & Ø. Moestrup. 1992. The marine dinoflagellate *Alexandrium ostenfeldii:* paralytic shellfish toxin concentration, composition, and toxicity to a tintinnid ciliate. *J. Phycol.* 28: 597–603.

Harding, L. W. Jr. & D. W. Coats. 1988. Photosynthetic physiology of *Prorocentrum mariae-lebouriae* (Dinophyceae) during its subpycnocline transport in Chesapeake Bay. *J. Phycol.* 24:77–89.

Harshbarger, J. C., S. V. Otto & S. C. Chang. 1979. Proliferative disorders in *Crassostrea virginica* and *Mya arenaria* from the Chesapeake Bay and intranuclear virus-like inclusions in *Mya arenaria* with germinomas from a Maine oil spill site. *Haliotis* 8:243–248.

Hartwell, A. D. 1975. Hydrographic factors affecting the distribution and movement of toxic dinoflagellates in the western Gulf of Maine. pp. 47–68. *In:* V. R. LoCicero (ed.). Proceedings of the First International Conference on Toxic Dinoflagellate Blooms. Massachusetts Science and Technology Foundation, Wakefield, Massachusetts.

Hesselman, D. M., N. J. Blake & E. C. Peters. 1988. Gonadal neoplasms in hard shell clams *Mercenaria* spp., from the Indian River Lagoon, Florida: occurrence, prevalence, and histopathology. *J. Invertebr. Pathol.* 52:436–446.

Hillman, R. E. 1993. Relationship of environmental contaminants to occurrence of neoplasia in *Mytilus edulis* populations of east and west coast mussel-watch sites. *J. Shellfish Res.* 12:109.

Hurst, J. W. 1979. Shellfish monitoring in Maine. pp. 231–234. *In:* D. L. Taylor and H. H. Seliger (eds.). Toxic Dinoflagellate Blooms. Elsevier, Amsterdam.

Hurst, J. W., R. Selvin, J. J. Sullivan, C. M. Yentsch & R. R. L. Guillard. 1985. Intercomparison of various assay methods for detection of shellfish toxins. pp. 427–432. *In:* D. M. Anderson, A. W. White and D. G. Baden (eds.). Toxic Dinoflagellates. Elsevier, Amsterdam.

Ingham, H. R., J. Mason & E. P. C. Wood. 1968. Distribution of toxin in molluscan shellfish following the occurrence of mussel toxicity in north-east England. *Nature* 220:25–27.

Jackson, A. E., J. C. Marr & J. L. McLachlan. 1993. The production of diarrhetic shellfish toxins by an isolate of *Prorocentrum lima* from Nova Scotia, Canada. pp. 513–518. *In:* T. J. Smayda & Y. Shimuzu (eds.). Toxic Phytoplankton Blooms in the Sea. Elsevier Press, Amsterdam.

Jackson, D. & J. Silke. 1995. *Dinophysis* spp. and the occurrence of diarrhetic shellfish poisons in Ireland. pp. 789–794. *In:* P. Lassus, G. Arzul, E. Erard-Le-Denn, P. Gentien and C. Marcaillou-Le-Baut (eds.). Harmful Marine Algal Blooms. Technique et Documentation, Lavoisier, Paris.

Jamieson, G. S. & R. A. Chandler. 1983. Paralytic shellfish poison in scallops (*Placopecten magellanicus*) in the West Atlantic. *Can. J. Fish. Aquat. Sci.* 40:313–318.

Kao, C. Y. 1993. Paralytic shellfish poisoning. pp. 75–86. *In:* I. R. Falconer (ed.). Algal Toxins in Seafood and Drinking Water. Academic Press, London.

Karunasagar, I., I. Karunasagar, Y. Oshima & T. Yasumoto. 1990. A toxin profile for shellfish involved in an outbreak of paralytic shellfish poisoning in India. *Toxicon* 28:868–870.

Kent, M. L., M. T. Wilkinson, A. S. Drum & R. A. Elston. 1991. Failure of transmission of hemic neoplasia of bay mussels, *Mytilus trossulus,* to other bivalve species. *J. Invertebr. Pathol.* 57:435–436.

Kim, C.-H., Y. Sako & Y. Ishida. 1993. Comparison of toxin composition between populations of *Alexandrium* spp. from geographically distinct areas. *Nippon Suisan Gakkaishi* 59:641–646.

Kimor, B., A. G. Moigis, V. Dohms. & C. Stiemen. 1985. A case of mass occurrence of *Prorocentrum minimum* in the Kiel Fjord. *Mar. Ecol. Prog. Ser.* 27:209–215.

Kitts, D. D., D. S. Smith, M. K. Beitler & J. Liston. 1992. Presence of paralytic shellfish poisoning toxins and soluble proteins in toxic butter clams (*Saxidomus giganteus*). *Biochem. Biophys. Res. Commun.* 184: 511–517.

Kodama, M., T. Ogata, Y. Fukuyo, T. Ishimaru, P. Pholpunthin, S. Wisessang, K. Saitanu, V. Panickyakarn & T. Piyankarnchana. 1988. *Protogonyaulax cohorticula,* a toxic dinoflagellate found in the Gulf of Thailand. *Toxicon* 26:709–712.

Kodama, M., T. Ogata, S. Sakamoto, T. Honda & T. Miwatani. 1990. Production of paralytic shellfish toxins by a bacterium *Moraxella* sp. isolated from *Protogonyaulax tamarensis*. *Toxicon* 28:707–714.

Kononen, K., K. Sivonen & J. Lehtimaki. 1993. Toxicity of phytoplankton blooms in the Gulf of Finland and Gulf of Bothnia, Baltic Sea. pp. 269–273. *In:* T. J. Smayda and Y.Shimuzu (eds.). Toxic Phytoplankton Blooms in the Sea. Elsevier Press, Amsterdam.

La Barbera-Sanchez, A., S. Hall & E. Ferraz-Reyes. 1993. *Alexandrium* sp., *Gymnodinium catenatum* and PSP in Venezuela. pp. 281–285. *In:* T. J. Smayda and Y. Shimuzu (eds.). Toxic Phytoplankton Blooms in the Sea. Elsevier Press, Amsterdam.

Langeland, G., T. Hasselgård, K. Tangen, O. M. Skulberg & A. Hjelle. 1984. An outbreak of paralytic shellfish poisoning in western Norway. *Sarsia* 69:185–193.

Lassus, P., M. Bardouil, M. Ledoux, I. Murail, M. Bohec, P. Truquet. J.-M. Frémy & V. Rohmer. 1992. Paralytic phycotoxin uptake by scallops (*Pecten maximus*). *Aquat. Living Resour.* 5:319–324.

Lassus, P., J.-M. Frémy, M. Ledoux, M. Bardouil & M. Bohec. 1989. Patterns of experimental contamination by *Protogonyaulax tamarensis* in some French commercial shellfish. *Toxicon* 27:1313–1321.

Lassus, P. & C. Marcaillou-Le Baut. 1991. Le genre *Dinophysis* (Dinophycées). pp. 11–61. *In:* A. Sournia, C. Belin, B. Berland, E. Erard-Le-Denn, P. Gentien, D. Grzebyk, C. Marcaillou-Le Baut, P. Lassus and F. Partensky (eds.). Le Phytoplankton Nuisible des Côtes de France: de la Biologie à la Prévention. IFREMER, Centre National de la Recherche Scientifique, Plouzané, France.

Lauckner, G. 1983. Neoplasia. pp. 863–879. *In:* O. Kinne (ed.). Diseases of Marine Animals. II. (Mollusca). Bivalvia to Scaphopoda. Biologische Anstalt Helgoland, Hamburg, Germany.

Leavitt, D. F., J. M. Capuzzo, R. M. Smolowitz, D. L. Miosky, B. A. Lancaster & C. L. Reinisch. 1990. Hematopoietic neoplasia in *Mya arenaria:* prevalence and indices of physiological condition. *Mar. Biol.* 105:313–321.

Lee, J.-S., T. Igarashi, S. Fraga, E. Dahl, P. Hovgaard & T. Yasumoto. 1989. Determination of diarrhetic shellfish toxins in various dinoflagellate species. *J. Appl. Phycol.* 1:147–152.

Lee, J.-S., J.-K. Jeon, M.-S. Han, Y. Oshima & T. Yasumoto. 1992. Paralytic shellfish toxins in the mussel *Mytilus edulis* and dinoflagellate *Alexandrium tamarense* from Jinhae Bay, Korea. *Bull. Korean Fish. Soc.* 25:144–150.

Lembeye, G., T. Yasumoto, J. Zhao & R. Fernandez. 1993. DSP outbreaks in Chilean fiords. pp. 525–529. *In:* T. J. Smayda and Y. Shimuzu (eds.). Toxic Phytoplankton Blooms in the Sea. Elsevier Press, Amsterdam.

Lowe, D. M. & M. N. Moore. 1978. Cytology and quantitative cytochemistry of a proliferative atypical hemocytic condition in *Mytilus edulis* (Bivalvia, Mollusca). *J. Natl. Cancer Inst.* 60:1455–1459.

Luckenbach, M. W., K. G. Sellner, S. E. Shumway & K. Greene. 1993. Effects of two bloom-forming dinoflagellates, *Prorocentrum minimum* and *Gyrodinium uncatenatum,* on the growth and survival of the eastern oyster (Gmelin, 1791). *J. Shellfish Res.* 12:411–415.

Lüthy, J. 1979. Epidemic paralytic shellfish poisoning in western Europe, 1976. pp. 15–22. *In:* D. L. Taylor and H. H. Seliger (eds.). Toxic Dinoflagellate Blooms. Elsevier, Amsterdam.

Mahmood, N. A. & W. W. Carmichael. 1986. Paralytic shellfish poisons produced by the freshwater cyanobacterium *Aphanizomenon flos-aquae* NH-5. *Toxicon* 24:175–186.

Maranda, L., D. M. Anderson & Y. Shimuzu. 1985. Comparison between populations of *Gonyaulax tamarensis* of eastern North American waters. *Estuarine Coast. Shelf Sci.* 21:401–410.

Maranda, L. & Y. Shimuzu. 1987. Diarrhetic shellfish poisoning in Narragansett Bay. *Estuaries* 10:298–302.

Marasović, I., Ž. Ninčević & N. Odžak. 1995. The effect of temperature on blooms of *Lingulodinium polyedra* and *Alexandrium minutum* in Kastela Bay. pp. 187–192. *In:* P. Lassus, G. Arzul, E. Erard-Le-Denn, P. Gentien and C. Marcaillou-Le-Baut (eds.). Harmful Marine Algal Blooms. Technique et Documentation, Lavoisier, Paris.

Marr, J. C., A. E. Jackson & J. L. McLachlan. 1992. Occurrence of *Prorocentrum lima,* a DSP toxin-producing species from the Atlantic coast of Canada. *J. Appl. Phycol.* 4:17–24.

Marshall, H. G. 1995. Succession of dinoflagellate blooms in the Chesapeake Bay, U.S.A. pp. 615–620. *In:* P. Lassus, G. Arzul, E. Erard-Le-Denn, P. Gentien and C. Marcaillou-Le-Baut (eds.). Harmful Marine Algal Blooms. Technique et Documentation, Lavoisier, Paris.

Martin, J. L., A. W. White & J. J. Sullivan. 1990. Anatomical distribution of paralytic shellfish toxins in softshell clams. pp. 379–384. *In:* E. Graneli, B. Sundstroem, L. Edler and D. M. Anderson (eds.). Toxic Marine Phytoplankton. Elsevier Press, New York.

Maruyama, J., T. Noguchi, Y. Onoue, Y. Ueda, K. Hashimoto & S. Kamimura. 1983. Anatomical distribution and profiles of the toxins in highly PSP-infested scallops from Ofunati Bay during 1980–1981. *Bull. Jpn. Soc. Sci. Fish.* 49:233–235.

Mascarenhas, I., P. Alvito, S. Franca, I. Sousa, A. G. Martinez & J. A. Rodriguez-Vazquez. 1995. The dinoflagellate *Alexandrium lusitanicum* isolated from the coast of Portugal: observations on toxicity and ultrastructure during growth phases. pp. 71–76. *In:* P. Lassus, G. Arzul, E. Erard-Le-Denn, P. Gentien and C. Marcaillou-Le-Baut (eds.). Harmful Marine Algal Blooms. Technique et Documentation, Lavoisier, Paris.

McLaughlin, S. M., A. C. Farley, & C. C. Judy. 1996. An update on softshell clam (*Mya arenaria*) sarcoma in the Chesapeake Bay and the declining fishery. *National Shellfisheries Association 1996 Meeting, Abstract:*53.

Medina, D., G. E. Paquette, E. C. Sadasiv & P. W. Chang. 1993. Isolation of infectious particles having reverse transcriptase activity and producing hematopoietic neoplasia in *Mya arenaria*. *J. Shellfish Res.* 12:112–113.

Miosky, D. L., R. M. Smolowitz & C. L. Reinisch. 1989. Leukemia cell specific protein of the bivalve mollusc, *Mya arenaria*. *J. Invertebr. Pathol.* 53:32–40.

Mix, M. C. 1975a. Neoplastic disease of Yaquina Bay bivalve molluscs. *Proc. 13th Annu. Hanford Biol. Symp.* 1:369–386.

Mix, M. C. 1975b. Proliferative characteristics of atypical cells in native

oysters (*Ostrea lurida*) from Yaquina Bay, Oregon. *J. Invertebr. Pathol.* 26:289–298.

Mix, M. C. 1983. Haemic neoplasms of bay mussels, *Mytilus edulis,* from Oregon: occurrence, prevalence, seasonality and histopathological progression. *J. Fish Dis.* 6:239–248.

Mix, M. C. 1986a. Cancerous diseases in aquatic animals and their association with environmental pollutants: a critical literature review. *Mar. Environ. Res.* 20:1–141.

Mix, M. C. 1986b. Topics related to neoplasms in shellfish. *Mar. Environ. Res.* 20:83–141.

Mix, M. C. 1988. Shellfish diseases in relation to toxic chemicals. *Aquat. Toxicol.* 11:29–42.

Mix, M. C. & W. P. Breese. 1980. A cellular proliferative disorder in oysters (*Ostrea chilensis*) from Chiloe, Chile, South America. *J. Invertebr. Pathol.* 36:123–124.

Mix, M. C., J. W. Hawkes & A. K. Sparks. 1979. Observations on the ultrastructure of large cells associated with putative neoplastic disorders of mussels, *Mytilus edulis,* from Yaquina Bay, Oregon. *J. Invertebr. Biol.* 34:41–56.

Mix, M. C., H. J. Pribble, R. T. Riley & S. P. Tomasovic. 1977. Neoplastic disease in bivalve mollusks from Oregon estuaries with emphasis on research on proliferative disorders in Yaquina Bay oysters. *Ann. N.Y. Acad Sci.* 298:356–373.

Moestrup, Ø. & P. J. Hansen. 1988. On the occurrence of the potentially toxic dinoflagellates *Alexandrium tamarense* (=*Gonyaulax excavata*) and *A. ostenfeldii* in Danish and Faroese waters. *Ophelia* 28:195–213.

Moore, J. D., R. A. Elston, A. S. Drum & M. T. Wilkinson. 1991. Alternate pathogenesis of systemic neoplasia in the bivalve mollusc *Mytilus*. *J. Invertebr. Pathol.* 58:231–243.

Morrison, C. M., A. R. Moore, V. M. Marryatt & D. J. Scarratt. 1993. Disseminated sarcomas of soft-shell clams, *Mya arenaria* Linnaeus 1758, from sites in Nova Scotia and New Brunswick. *J. Shellfish Res.* 12:65–69.

Mulligan, H. F. 1975. Oceanographic factors associated with New England red tide blooms. pp. 23–40. *In:* V. R. LoCicero (ed.). Proceedings of the First International Conference on Toxic Dinoflagellate Blooms. Massachusetts Science and Technology Foundation, Wakefield, Massachusetts.

Nascimento, I. A., D. H. Smith, F. Kern II & S. A. Pereira. 1986. Pathological findings in *Crassostrea rhizophorae* from Todos os Santos Bay, Bahias, Brazil. *J. Invertebr. Pathol.* 47:340–349.

Neff, J. M., R. E. Hillman, R. S. Carr, R. L. Buhl & J. I. Lahey. 1987. Histopathologic and biochemical responses in Arctic marine bivalve molluscs exposed to experimentally spilled oil. *Arctic* 40(suppl 1):220–229.

Nishitani, L. & K. Chew. 1988. PSP toxins in the Pacific coast states: monitoring programs and effects on bivalve industries. *J. Shellfish Res.* 7:653–669.

Noguchi, T., Y. Ueda, Y. Onoue, M. Kono, K. Koyama, K. Hashimoto, Y. Seno & S. Mishima. 1984. Toxicity of the adductor muscle of markedly PSP-infested scallop *Patinopecten yessoensis*. *Bull. Jpn. Soc. Sci. Fish.* 50:517–520.

Norris, D. R. 1983. The occurrence of a toxic dinoflagellate in the Indian River system. *Florida Sci.* 46:150–153.

Nuzzi, R. & R. M. Waters. 1993. The occurrence of PSP toxin in Long Island, New York, USA. pp. 305–310. *In:* T. J. Smayda and Y. Shimuzu (eds.). Toxic Phytoplankton Blooms in the Sea. Elsevier Press, Amsterdam.

Ogata, T., P. Pholpunthin, Y. Kukuyo & M. Kodama. 1990. Occurrence of *Alexandrium cohorticula* in Japanese coastal water. *J. Appl. Phycol.* 2:351–356.

Okaichi, T. & Y. Imatomi. 1979. Toxicity of *Prorocentrum minimum* var. *mariae-lebouriae* assumed to be a causative agent of short-necked clam poisoning. pp. 385–388. *In:* D. L. Taylor and H. H. Seliger (eds.). Toxic Dinoflagellate Blooms. Elsevier, Amsterdam.

Onoue, Y., T. Noguchi, J. Maruyama, K. Hashimoto & T. Ideda. 1981. Comparison of PSP compositions between toxic oysters and *Protogonyaulax catenella* from Senzaki Bay, Yamaguchi Prefecture. *Bull. Jpn. Soc. Sci. Fish.* 47:1347–1350.

Oprandy, J. J. & P. W. Chang. 1983. 5-bromodeoxyuridine induction of hematopoietic neoplasia and retrovirus activation in the soft-shell clam, *Mya arenaria*. *J. Invertebr. Pathol.* 42:196–206.

Oprandy, J. J., P. W. Chang, A. D. Pronovost, K. R. Cooper, R. S. Brown & V. J. Yates. 1981. Isolation of a viral agent causing hematopoietic neoplasia in the soft-shell clam, *Mya arenaria*. *J. Invertebr. Pathol.* 38:45–51.

Oshima, Y. 1995. Chemical and enzymatic transformation of paralytic shellfish toxins in marine organisms. pp. 475–480. *In:* P. Lassus, G. Arzul, E. Erard-Le-Dunn, P. Gentien and C. Marcaillou-Le-Baut (eds.). Harmful Marine Algal Blooms. Technique et Documentation, Lavoisier, Paris.

Oshima, Y., S. I. Blackburn & G. M. Hallegraeff. 1993. Comparative study on paralytic shellfish toxin profiles of the dinoflagellate *Gymnodinium catenatum* from three different countries. *Mar. Biol.* 116:471–476.

Oshima, Y., C. J. Bolch & G. M. Hallegraeff. 1992. Toxin composition of resting cysts of *Alexandrium tamarense* (Dinophyceae). *Toxicon* 30:1539–1544.

Oshima, Y., M. Hasegawa, T. Yasumoto, G. Hallegraeff & S. Blackburn. 1987. Dinoflagellate *Gymnodinium catenatum* as the source of paralytic shellfish toxins in Tasmanian shellfish. *Toxicon* 25:1105–1111.

Oshima, Y., K. Sugino, H. Itakura, M. Hirota, T. Yasumoto. 1990. Comparative studies on paralytic shellfish toxin profile of dinoflagellates and bivalves. pp. 391–396. *In:* E. Graneli, B. Sundstrom, L. Edler and D. M. Anderson (eds.). Toxic Marine Phytoplankton. Elsevier Science Publishing, New York.

Oshima, Y., T. Yasumoto, G. Hallegraeff & S. Blackburn. 1987. Paralytic shellfish toxins and causative organisms in the tropical Pacific and Tasmanian waters. pp. 423–428. P. *In:* P. Gopalakrishnakone and C. K. Tan (eds.). Progress in Venom and Toxin Research. Singapore, National University of Singapore.

Otto, S. V. & C. A. Farley. 1976. Neoplasms in bivalve mollusks from Upper Chesapeake Bay and adjoining tributaries. *In:* Proceedings of the First International Colloquium on Invertebrate Pathology. Kingston, Canada. p. 159.

Pekkarinen, M. 1993. Neoplastic diseases in the Baltic *Macoma balthica* (Bivalvia) off the Finnish coast. *J. Invertebr. Pathol.* 61:138–146.

Perry, H. M., K. C. Stuck & H. D. Howse. 1979. First record of a bloom of *Gonyaulax monilata* in coastal waters of Mississippi. *Gulf Res. Rep.* 6:313–316.

Peters, E. C. 1988. Recent investigations on the disseminated sarcomas of marine bivalve molluscs. *AFS Spec. Publ.* 18:74–92.

Peters, E. C., P. P. Yevich, J. C. Harshbarger & G. E. Zaroogian. 1994. Comparative histopathology of gonadal neoplasms in marine bivalve molluscs. *Dis. Aquat. Org.* 20:59–76.

Pholpunthin, P., S. Wisessang, T. Ogata, Y. Fukuyo, M. Kodama, T. Ishimaru & T. Piyakarnchana. 1990. Coexistence of toxic and nontoxic strains of *Alexandrium tamarense* in the Gulf of Thailand. pp. 903–906. *In:* R. Hirano and I. Hanyu (eds.). The Second Asian Fisheries Forum. Asian Fisheries Society, Manila, Philippines.

Pierce, R. W. & J. T. Turner. 1994. Plankton studies in Buzzards Bay, Massachusetts, USA. III. Dinoflagellates, 1987 to 1988. *Mar. Ecol. Prog. Ser.* 112:225–234.

Pillet, S. & G. Houvenaghel. 1995. Influence of experimental toxification by DSP producing microalgae, *Prorocentrum lima,* on clearance rate in blue mussels, *Mytilus edulis*. pp. 481–486. *In:* P. Lassus, G. Arzul, E. Erard-Le-Denn, P. Gentien and C. Marcaillou-Le-Baut (eds.). Harmful Marine Algal Blooms. Technique et Documentation, Lavoisier, Paris.

Pillet, S., A. Pereira, J.-C. Braekman & G. Houvenaghel. 1995. Patterns in the long-term accumulation of okadaic acid and DTX1 in blue mussels, *Mytilus edulis,* experimentally fed with the DSP-containing alga *Prorocentrum lima* pp. 487–492. *In:* P. Lassus, G. Arzul, E. Erard-

Le-Denn, P. Gentien and C. Marcaillou-Le-Baut (eds.). Harmful Marine Algal Blooms. Technique et Documentation, Lavoisier, Paris.

Poder, M., M. Auffret & G. Balouet. 1983. Etudes pathologiques et épidémiologiques de lésions parasitaires chez *Ostrea edulis* L. Premiers résultats d'une recherche prospective comparative chez principales espèces de Mollusques des zones ostréicoles de Bretagne Nord. *IFREMER Actes de Colloq.* 1:125–138.

Poder, M. & M. Auffret. 1986. Sarcomatous lesion in the cockle *Cerastoderma edule*. I. Morphology and population survey in Brittany, France. *Aquaculture* 58:1–8.

Prakash, A., J. C. Medcof & A. D. Tennant. 1971. Paralytic shellfish poisoning in eastern Canada. *Fish. Res. Board Can. Bull.* 177:1–87.

Price, D. W., K. W. Kizer, K. H. Hansgen. 1991. California's paralytic shellfish poisoning prevention program, 1927–89. *J. Shellfish Res.* 10:119–145.

Quilliam, M. A., M. W. Gilgan, S. Pleasance, A. S. W. de Freitas, D. Douglas, L. Fritz, T. Hu, J. C. Marr, C. Smyth & J. L. C. Wright. 1993. Confirmation of an incident of diarrhetic shellfish poisoning in eastern Canada. pp. 547–552. *In:* T. J. Smayda and Y. Shimuzu (eds.). Toxic Phytoplankton Blooms in the Sea. Elsevier Press, Amsterdam.

Rasmussen, L. P. D. 1986. Occurrence, prevalence and seasonality of neoplasia in the marine mussel *Mytilus edulis* from three sites in Denmark. *Mar. Biol.* 92:59–64.

Rasmussen, L. P. D., E. Hage & O. Karlog. 1985. Light and electronmicroscopic studies of the acute and long-term toxic effects of N-nitrosodipropylamine and N-methylnitrosurea on the marine mussel *Mytilus edulis*. *Mar. Biol.* 85:55–65.

Reinisch, C. L., A. M. Charles & A. M. Stone. 1984. Epizootic neoplasia in soft shell clams collected from New Bedford Harbor. *Hazard. Waste* 1:73–81.

Schantz, E. J. 1960. Biochemical studies on paralytic shellfish poisons. *Ann. N.Y. Acad. Sci.* 89:843–855.

Schantz, E. J., J. D. Mold, D. W. Stanger, J. Shavel, F. J. Riel, J. P. Bowden, J. M. Lynch, R. S. Wyler, B. Reigel & H. Sommer. 1957. Paralytic shellfish poison. VI. A procedure for the isolation and purification of the poison from toxic clams and mussel tissues. *J. Am. Chem. Soc.* 78:5230–5235.

Schmidt, R. J. & A. R. Loeblich III. 1979. Distribution of paralytic shellfish poison among Pyrrhophyta. *J. Mar. Biol. Assoc. U.K.* 59:479–487.

Schrey, S. E., E. J. Carpenter & D. M. Anderson. 1984. The abundance and distribution of the toxic dinoflagellate, *Gonyaulax tamarensis,* in Long Island estuaries. *Estuaries* 7:472–477.

Seliger, H. H., M. E. Loftus & D. V. Subba Rao. 1975. Dinoflagellate accumulations in Chesapeake Bay. pp. 181–205. *In:* V. R. LoCicero (ed.). Proceedings of the First International Conference on Toxic Dinoflagellate Blooms. Massachusetts Science and Technology Foundation, Wakefield, Massachusetts.

Seliger, H. H., M. A. Tyler & K. R. McKinley. 1979. Phytoplankton distributions and red tides resulting from frontal circulation patterns. pp. 239–248. *In:* D. L. Taylor and H. H. Seliger (eds.). Toxic Dinoflagellate Blooms. Elsevier, Amsterdam.

Sellner, K. G., P. Sawangwong, R. Dawson, W. R. Boynton, W. M. Kemp & J. H. Garber. 1993. Fate of dinoflagellates in Chesapeake Bay: is sedimentation likely? pp. 825–830. *In:* T. J. Smayda and Y. Shimuzu (eds.). Toxic Phytoplankton Blooms in the Sea. Elsevier Press, Amsterdam.

Shimuzu, Y. 1987. Dinoflagellate toxins. pp. 282–315. *In:* F. J. R. Taylor (ed.). The Biology of Dinoflagellates. Blackwell Scientific Publications, Oxford, England.

Shimuzu, Y., W. E. Fallon, J. C. Wekell, D. Gerber Jr. & E. J. Gauglitz, Jr. 1978. Analysis of toxic mussels (*Mytilus* sp.) from the Alaskan Inside Passage. *J. Agric. Food Chem.* 26:878–881.

Shimuzu, Y. & M. Yoshioka. 1981. Transformation of paralytic shellfish toxins as demonstrated in scallop homogenates. *Science* 212:546–547.

Shumway, S. E. 1990. A review of the effects of algal blooms on shellfish and aquaculture. *J. World Aquacult. Soc.* 21:65–104.

Shumway, S. E., J. Barter & S. Sherman-Caswell. 1990. Auditing the impact of toxic algal blooms on oysters. *Environ. Audit.* 2:41–56.

Shumway, S. E. & A. D. Cembella. 1993. The impact of toxic algae on scallop culture and fisheries. *Rev. Fish. Sci.* 1:121–150.

Shumway, S. E. & T. L. Cucci. 1987. The effects of the toxic dinoflagellate *Protogonyaulax tamarensis* on the feeding and behaviour of bivalve molluscs. *Aquat. Toxicol.* 10:9–27.

Shumway, S. E., S. A. Sherman, A. D. Cembella & R. Selvin. 1994. Accumulation of paralytic shellfish toxins by surfclams, *Spisula solidissima* (Dillwyn, 1897) in the Gulf of Maine: seasonal changes, distribution between tissues, and notes on feeding habits. *Nat. Toxins* 2:236–251.

Shumway, S. E., S. Sherman-Caswell & J. W. Hurst. 1988. Paralytic shellfish poisoning in Maine: monitoring a monster. *J. Shellfish Res.* 7:643–652.

Sievers, A. M. 1969. Comparative toxicity of *Gonyaulax monilata* and *Gymnodinium breve* to annelids, crustaceans, molluscs and fish. *J. Protozool.* 16:401–404.

Silva, E. S. 1985. Ecological factors related to *Prorocentrum minimum* blooms in Obidos Lagoon (Portugal). pp. 251–256. *In:* D. M. Anderson, A. W. White and D. G. Baden (eds.). Toxic Dinoflagellates. Elsevier, Amsterdam.

Smolowitz, R. & D. Leavitt. 1996. Neoplasia and other pollution associated lesions in *Mya arenaria* from Boston Harbor. *National Shellfisheries Association 1996 Meeting, Abstracts:*54.

Smolowitz, R. & S. E. Shumway. 1996. Possible cytotoxic effects of the dinoflagellate *Gyrodinium aureolum* on juvenile bivalve molluscs. *Aquacult. Int.* (In press.)

Sousa, I., P. Alvito, S. Franca, M. A. de Sampayo, A. G. Martinez & J. A. Rodriguez-Vazquez. 1995. Data on paralytic shellfish toxins related to recent *Gymnodinium catenatum* blooms in Portugal coastal waters. pp. 825–829. P. Lassus, G. Arzul, E. Erard-Le-Denn, P. Gentien and C. Marcaillou-Le-Baut (eds.). Harmful Marine Algal Blooms. Technique et Documentation, Lavoisier, Paris.

Steidinger, K. A. 1993. Some taxonomic and biological aspects of toxic dinoflagellates. pp. 1–28. *In:* I. R. Falconer (ed.). Algal Toxins in Seafood and Drinking Water. Academic Press, London.

Suganuma, H., H. Fujiki, H. Suguri, S. Yoshizawa, M. Hirota, M. Nakayasu, M. Ojika, K. Wakamatsu, K. Yamada & T. Sugimura. 1988. Okadaic acid: an additional non-phorbol-12-tetradecanoate-13-acetate-type tumor promoter. *Proc. Natl. Acad. Sci. USA* 85:1768–1771.

Sullivan, J. J. 1988. Methods of analysis for DSP and PSP toxins in shellfish: a review. *J. Shellfish Res.* 7:587–595.

Sullivan, J. J., W. T. Iwaoka & J. Liston. 1983. Enzymatic transformation of PSP toxins in the littleneck clam (*Protothaca staminaea*). *Biochem. Biophys. Res. Commun.* 114:465–472.

Sullivan, J. J., M. M. Wekell & L. L. Kentala. 1985. Application of HPLC for the determination of PSP toxins in shellfish. *J. Food Sci.* 50:26–29.

Sunila, I. 1987. Histopathology of mussels (*Mytilus edulis* L.) from the Tvärminne area, Gulf of Finland (Baltic Sea). *Ann. Zool. Fenn.* 24: 55–69.

Tangen, K. 1983. Shellfish poisoning and the occurrence of potentially toxic dinoflagellates in Norwegian waters. *Sarsia* 68:1–7.

Taylor, F. J. R. 1984. Toxic dinoflagellates: taxonomic and biogeographic aspects with emphasis on *Protogonyaulax*. pp. 77–97. *In:* E. P. Ragelis (ed.). Seafood Toxins. American Chemical Society, Washington, D.C.

Twarog, B. M. & H. Yamaguchi. 1975. Resistance to paralytic shellfish toxins in bivalve molluscs. pp. 381–393. *In:* V. R. LoCicero (ed.). Proceedings of the First Conference on Toxic Dinoflagellate Blooms. Massachusetts Science and Technology Foundation, Wakefield, Massachusetts.

Twomey, E. & M. F. Mulcahy. 1984. A proliferative disorder of possible

hemic origin in the common cockle, *Cerastoderma edule*. *J. Invertebr. Pathol*. 44:109–111.

Twomey, E. & M. F. Mulcahy. 1988a. Epizootiological aspects of a sarcoma in the cockle, *Cerastoderma edule*. *Dis. Aquat. Org*. 5:225–238.

Twomey, E. & M. F. Mulcahy. 1988b. Transmission of a sarcoma in the cockle *Cerastoderma edule* (Bivalvia: Mollusca) using cell transplants. *Dev. Comp. Immunol*. 12:195–200.

Usup, G., D. Kulis & D. M. Anderson. 1995. Toxin production in a Malaysian isolate of the toxic dinoflagellate *Pyrodinium bahamense* var. *compressum*. pp. 519–524. *In:* P. Lassus, G. Arzul, E. Erard-Le-Denn, P. Gentien and C. Marcaillou-Le-Baut (eds.). Harmful Marine Algal Blooms, Technique et Documentation, Lavoisier, Paris.

Van Beneden, R. J., G. R. Gardner, N. J. Blake & D. G. Blair. 1993. Implications for the presence of transforming genes in gonadal tumors in two bivalve mollusk species. *J. Cancer Res*. 53:2976–2979.

Villalba, A., E. C. Peters, M. Carmen Lopez & M. J. Caraballal. 1995. Disseminated sarcoma in the clam *Ruditapes decussatus* in Galicia (NW Spain). *J. Invertebr. Pathol*. 65:76–78.

Waiwood, B. A., K. Haya & J. L. Martin. 1995. Depuration of paralytic shellfish toxins by giant scallops from the Bay of Fundy, Canada. pp. 525–530. *In:* P. Lassus, G. Arzul, E. Erard-Le-Denn, P. Gentien and C. Marcaillou-Le-Baut (eds.). Harmful Marine Algal Blooms. Technique et Documentation, Lavoisier, Paris.

Walker, H. A., E. Lorda & S. B. Saila. 1981. A comparison of the incidence of five pathological conditions in soft-shell clams, *Mya arenaria*, from environments with various pollution histories. *Mar. Environ. Res*. 5:109–123.

White, A. W., S. E. Shumway, J. Nassif & D. K. Whitaker. 1993. Variation in levels of paralytic shellfish toxins among individual shellfish. pp. 441–446. *In:* T. J. Smayda and Y. Shimuzu (eds.). Toxic Phytoplankton Blooms in the Sea. Elsevier Press, Amsterdam.

Whitefleet-Smith, J. L., C. L. Divan, E. J. Schantz & H. K. Schnoes. 1985. Distribution of paralytic shellfish toxins in California shellfish. *Toxicon* 23:346–349.

Wikfors, G. H. & R. M. Smolowitz. 1993. Detrimental effects of a *Prorocentrum* isolate upon hard clams and bay scallops in laboratory feeding studies. pp. 447–452. *In:* T. J. Smayda and Y. Shimuzu (eds.). Toxic Phytoplankton Blooms in the Sea. Elsevier Press, Amsterdam.

Wikfors, G. H. & R. M. Smolowitz. 1995. Experimental and histological studies of four life-history stages of the eastern oyster, *Crassostrea virginica*, exposed to a cultured strain of the dinoflagellate *Prorocentrum minimum*. *Biol. Bull*. 188:313–328.

Williams, J. & R. M. Ingle. 1972. Ecological notes on *Gonyaulax monilata* (Dinophyceae) blooms along the west coast of Florida. *Fla. Dept. Nat. Resour. Leafl*. Ser. 1, No. 5. 12 pp.

Wisessang, S., T. Ogata, M. Kodama, Y. Fukuyo, T. Ishimaru, K. Saitanu, T. Yongvanich & T. Piyakarnchana. 1991. Accumulation of paralytic shellfish toxins by green mussel *Perna viridis* by feeding on cultured cells of *Alexandrium cohorticula* isolated from the Gulf of Thailand. *Nippon Suisan Gakkaishi* 57:127–131.

Wolf, P. H. 1976. Studies on the geographical distribution, etiology, and transmission of integumentary epitheliomas in rock oysters from Australian estuaries. *Prog. Exp. Tumor Res*. 20:295–303.

Worms, J., N. Bouchard, R. Cormier, K. E. Pauley & J. C. Smith. 1993. New occurrences of paralytic shellfish poisoning toxins in the southern Gulf of St. Lawrence, Canada. pp. 353–358. *In:* T. J. Smayda and Y. Shimuzu (eds.). Toxic Phytoplankton Blooms in the Sea. Elsevier Press, Amsterdam.

Wyatt, T. & F. Saborido-Rey. 1993. Biogeography and time series analysis of British PSP records, 1968 to 1990. pp. 73–78. *In:* E. Graneli, B. Sundstroem, L. Edler and D. M. Anderson (eds.). Toxic Marine Phytoplankton. Elsevier Press, New York.

Yevich, P. P. & M. M. Barry. 1969. Ovarian tumours in the quahog *Mercenaria mercenaria*. *J. Invertebrate Pathol*. 14:266–267.

Yevich, P. P. & C. A. Barszcz. 1976. Gonadal and haematopoietic neoplasms in *Mya arenaria*. *Mar. Fish. Rev*. 38:42–43.

Yevich, P. P. & C. A. Barszca. 1977. Neoplasia in soft-shell clams (*Mya arenaria*) collected from oil-impacted sites. In: *Aquatic Pollutants and Biologic Effects with emphasis on neoplasia*. H. F. Kraybill, C. J. Dawe, J. C. Harshbarger & R. G. Tardiff, eds., *Ann. N.Y. Acad. Sci*. 298:409–426.

Yomgjia, Z., B. Munday & J. Handlinger. 1995. Mass mortality of flat oysters (*Ostrea rivularis*) associated with a bloom of *Prorocentrum* sp. in the port of Zhanjiang, South China. *Bull. Eur. Assoc. Fish Pathol*. 15:61–63.