Literature Review of Florida Red Tide: Implications for Human Health Effects

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Abstract

Florida red tides are a natural phenomenon caused by dense aggregations of single cell or several species of unicellular organisms. Patches of discolored water, dead or dying fish, and respiratory irritants in the air often characterize these algal blooms. In humans, two distinct clinical entities, depending on the route of exposure, are associated with exposure to the Florida red tide toxins (particularly the brevetoxins). With the ingestion of brevetoxin-contaminated shellfish, neurotoxic shellfish poisoning (NSP) presents as a milder gastroenteritis with neurologic symptoms compared with other marine toxin diseases such as paralytic shellfish poisoning (PSP) or Ciguatera fish poisoning. With the inhalation of the aerosolized red tide toxins (especially the brevetoxins) from the sea spray, respiratory irritation and possibly other health effects are reported in both humans and other mammals (Baden 1995, Fleming 1998a, Fleming 1998b, Fleming 1999a, Bossart 1998, Asai 1982, Eastaugh 1989, Pierce 1986, Music 1973, Temple 1995, Anderson 1994).

This paper reviews the published and available literature on the known and possible human health effects of exposure to the Florida red tides and their toxins. The review includes discussion of the red tide organisms and their toxins, as well as the effects of these toxins on both wild and laboratory animals as they relate to possible human health effects and exposures.

Background

Toxic red tides have been observed in Florida since the 1840s. Since that time, there have been multiple episodes with significant fish kills, as well as cases of NSP, reported from the Gulf of Mexico (including the East coast of Mexico), the East Coast of Florida, and up to the North Carolina coast; toxic blooms occur almost annually on the West Coast of Florida. Recently, these and other red tides appear to be increasing in incidence, time length and geographic spread

(Viviani 1992, Smayda 1990, Van Dolah 2000, Tester 1991, Tester 1997). Anthropogenic influences (such as nutrient run-off inducing red tides blooms, and the transport of dinoflagellate cysts in ballast water of ships, etc) have been suggested as possible causes. However, it should be noted that these red tides in Florida occurred even prior to significant pollution and development by human populations: between 1844 and 1971, red tides and their sequellae were noted along the West Coast of Florida at least 24 times prior to the major industrial and agricultural development of that area. Alternative explanations (such as the effects of changing ocean temperatures, currents and weather patterns associated with global warming, as well as atmospheric transport of Sahara dust) are being investigated (Tester 1997, Tester 1991, Viviani 1992, Tibbetts 1998, Morris 1991, Ishida 1996, Anderson 1994, Sierra Beltran 1998, Cortes Altamirano 1995, Tommasi 1983, Epstein 1994, NRC 1999, Epstein 1998, Steidinger 1972, Kin Chung 1991, Smayda 1990, Walsh 2001).

Recent prolonged red tides in the Gulf of Mexico have been associated with significant environmental, human health and economic impacts, as discussed below. Beaches in Texas have been closed, as well as shellfish beds from Florida to Mexico. Significant die-offs of fish, endangered manatees, and double-crested cormorants, as well as reported human health effects, have resulted annually secondary to the red tide toxin exposure along the coastline of the Gulf of Mexico (Bossart 1998, Hopkins 1997, Kreuder 1998, Trainer 1999).

Organisms

The dinoflagellates are very ancient, single celled, eukaryotic organisms that can exist in benthic, parasitic, symbiotic, and free-living forms; the latter can be transported easily via ocean currents. Many of the dinoflagellates include in their life cycle at least one resting form or cyst. The cysts may serve as the seeds for the red tides as they are the renewal of the motile phase of the dinoflagellate when the environmental conditions are appropriate; it is the motile forms that create the blooms and the natural toxins (Anderson 1994, de M Sampayo 1997, Baden 1995, Baden 1983).

The classic causative organism of Florida red tides is Karenia brevis (formerly known as Gymnodinium breve and Ptychodiscus brevis). K. brevis is a dinoflagellate restricted to the Gulf of Mexico and the Caribbean, although it has been carried by ocean currents around Florida and up the East coast of the US as far as North Carolina. Other species producing the same or similar toxins occur throughout the world, particularly in New Zealand (Ishida 1996, MacLean 1979, Hermes 1984 Chang 1998, Temple 1995, Morohashi 1999, Anderson 1994, , Anderson 1994, Sierra Beltran 1998, Cortes Altamirano 1995, Tommasi 1983, , Horstman 1991, Khan 1997, Steidinger 1983). K. brevis red tide blooms usually occur in the late summer and autumn months, almost every year off the West Coast of Florida, causing massive fish and bird kills.

The K. brevis organism is relatively fragile because it is unarmored. Therefore, particularly in wave action along beaches, the organism is easily broken open, releasing the toxins. During an active in-shore red tide, the aerosol of contaminated salt spray will contain the toxins and organism fragments, both in the droplets and attached to salt particles; these can be carried inland depending on wind and other environmental conditions (Pierce 1990, Pierce 1989, Sakamoto 1987, Music 1973, Backer submitted, Pierce 1986, Horstman 1991, ILO 1984).

Toxins

Associated with these algal bloom episodes of K. brevis, a variety of phytoplankton-related natural toxins have been identified. There are reportedly hemolytic components and even cardiotoxic anti-cholinesterase phosphorus-containing compounds (Mazumder 1997), however

the most important group is the neurotoxic brevetoxins (Ptychodiscus brevis toxin, ie. PbTx). As a group, the brevetoxins are lipid soluble, cyclic polyethers with molecular weights around 900. Over 9 different brevetoxins have been isolated in sea water blooms and K. brevis cultures, as well as multiple analogs and derivatives from the metabolism of shellfish and other organisms (Morohashi 1999, Baden and Trainer 1993, Baden 1995, Mazumder 1997, Mattei 1999, Pierce and Kirkpatrick, 2001). In red tides, the major brevetoxin produced by concentration is PbTx-2, as well as lesser amounts of PbTx-1 and PbTx-3 (Baden 1989, Pierce et al., 1992).

As with many of the known marine toxins, the brevetoxins are tasteless, odorless, and heat and acid stable. These toxins cannot be easily detected, nor removed by food preparation procedures (Baden 1982a, Baden 1993, Baden 1995, Sakamoto 1987).

These brevetoxins are depolarizing substances that open voltage gated sodium (Na+) ion channels in cell membranes, leading to uncontrolled Na+ influx into the cell (Baden 1983, Purkerson 1999). This alters the membrane properties of excitable cell types in ways that enhance the inward flow of Na+ ions into the cell; this current can be blocked by external application of tetrodotoxin, a Na+ ion channel blocker (Gallagher 1980, Baden 1983, Halstead 1988, Poli 1986, Viviani 1992, Trainer 1991, Jeglitsch 1998). Recent work by Purkerson et al (1999) and others using electrophysiology studies of single sodium channel of rat central nervous system cells suggest that PbTx 3 may cause hyper excitability as well as inhibitory effects in the intact brain (Apland 1993, Templeton 1989a, Templeton 1989b). As a consequence of their lipid solubility, these toxins are expected to easily pass through cell membranes including the blood brain barrier, as well as buccal mucosa and skin (Mehta 1991, Kemppainen 1991, Apland 1993).

The massive fish kills associated with Florida red tides are due to the neurotoxin exposure, with possible contribution of the hemolytic fraction. In particular, PbTx 3 is believed to be responsible for the respiratory irritation associated with toxin inhalation (Baden 1982a, Baden 1982b). The brevetoxins ionically depolarize nerve cells and lead to the characteristic disruptions of respiratory and cardiac function known as neurotoxic shellfish poisoning (NSP). When Borison et al (1985) and Koley et al (1995) studied brevetoxin in cats, the authors concluded that brevetoxin exerts its major toxic effects on the circulation and respiration through reflex and central actions, largely sparing peripheral motor mechanisms. These toxins are also directly cardiotoxic and hepatotoxic in various in vitro and in vivo systems (Templeton 1989a, Templeton 1989b, Rodriguez Rodriguez 1996, Bossart 1998, Rodgers 1984)

It is believed that the respiratory problems associated with the inhalation of aerosolized Florida red tide toxins are due in part to the opening of sodium channels of nerve cell membranes by the brevetoxin (Baden 1982a, Baden 1993, Asai 1982, Borison 1980, Franz 1989, Baden 1989). These effects can be blocked by atropine (muscarinic blocker) as well as tetrodotoxin (sodium channel blocker), but not by the interruption of vagal nerve stimulation or by diaphragm dissection in experimental animals (Baden 1982a, Gallagher 1980, Asai 1982, Trainer 1991, Baden 1989, Tsai 1991, Watanabe 1988). In isolated canine tracheal smooth muscle, neostigmine as an acetylcholinesterase inhibitor potentiated the brevetoxin-induced contraction; mepyramine, phentolamine, methysergide, and chlorisondamine did not effect the contraction (Asai 1982). In isolated human bronchial smooth muscle, Shimoda et al (1988) found similar results as well as attenuation by verapamil (calcium and sodium channel blockers). Therefore, brevetoxin produces contraction of the lower airway smooth muscle via stimulation of the cholinergic nerve fiber sodium channels with acetylcholine release. However, additional pathways may be important for brevetoxin's physiological effects. For example, in the rat vas deferens, Sakamoto et al (1985)

found that brevetoxin stimulated sodium channels on adrenergic nerve fibers, releasing norepinephrine from the nerve endings.

In addition, there appears to be a role for mast cells in the brevetoxin-associated respiratory effects. Watanabe et al (1988) noted that brevetoxin can combine with a separate site on the h gates of the sodium channel, causing the release of neurotransmitters from autonomic nerve endings. In particular, this can release acetylcholine, leading to smooth tracheal muscle contraction, as well as massive mast cell degranulation. The mast cell contribution to the adverse airway effects of brevetoxin is supported by studies in a sheep model of asthma. In this model, aerosolized brevetoxin causes bronchoconstriction that can be blocked by the mast cell stabilizing agent cromolyn and the histamine H1 antagonist chlorpheniramine (Singer 1998). Thus, in addition to the direct neural component, brevetoxin appears to induce the release histamine from mast cells and the combination of these actions results in adverse airway effects. Furthermore, because brevetoxin exposure by the respiratory route results in systemic distribution of brevetoxin, the initial bronchoconstriction may only be part of the overall consequences associated with toxin inhalation, including the central nervous system (Benson 1999, Apland 1993).

Of note, based on computer modeling, brevetoxin is a possible enzymatic binding inhibitor of cysteine cathepsins. Cathepsins are powerful lysosomal proteinases and epitope presenting enzymes, found within cytosol or lysosomes of macrophages cells, lymphoid tissues and other cells (Bossart 1998, Sudarsanam 1992). Bossart et al (1998) postulated that the effects of aerosolized brevetoxins may be chronic not just acute. These chronic effects would begin with the initial phagocytosis by macrophages, inhibition of cathepsins, and apoptosis of these cells, followed by the phagocytosis of the debris by new macrophages, ultimately resulting in chronic neuro-intoxication, hemolytic anemia, and/or immunologic compromise.

Brevetoxins undergo biotransformation in rodents and fish (Poli 1990a, Poli 1990b, Kennedy 1992). In fish, the brevetoxins induce both cytochrome P4501A, and glutathione S transferase with a variety of pathways for metabolism (Washburn 1996, Washburn 1994). Based on their evaluations of PbTx3 on the sodium channels of rat sensory neurons, Jeglitsch et al (1998) suggested that PbTx3 metabolites may be more potent than PbTx3 parent compound in affecting sodium channels. Work by Poli et al (2000) evaluating metabolites in both the urine of 3 persons suffering from NSP and from the contaminated shellfish supported this conclusion; the authors suggested that these toxic metabolites from both the shellfish and the humans may be an additional cause of NSP, and should be taken into account during regulatory testing.

Animals

The major seafoods contaminated by brevetoxins are shellfish, although there is no definitive evidence of any health effects to the shellfish, with possible exception of scallops (Cummins 1971, Sakamoto 1987, Steidinger 1972, Summerson 1990, Ellis 1985).

Fish, birds and mammals are all susceptible to the brevetoxins. In the mosquito fish (Bambusia affinis) bioassay, the LD50 is reported at 0.011 ug/L (0.005-0.023) while with Japanese madaka (Oryzias latipes) the LC50 was reported to be 0.015-25 ug/ml (Bossart 1998, Forrester 1977, Geraci 1989, O'Shea 1991, Laverty 1993, Trainer 1999, Anderson 1994, Sierra Beltran 1998, Cortes Altamirano 1995, Ellis 1985, ILO 1984, Poli 1988). Fish kills associated with these red tides have been estimated up to 100 tons of fishes per day during an active red tide. The fish are killed apparently through muscle incoordination and paralysis, convulsions, and death by respiratory failure. In the toadfish model, Kennedy et al (1992) found that radiolabeled PbTx 3

was rapidly distributed within 1 hour of intravenous administration (40.2% muscle, 18.5% intestine and 12.4% liver); after 96 hours, levels in the liver remained constant but those in bile, kidney and skin increased, with a variety of metabolites detected. Birds die acutely with neurologic and hematologic effects.

With respect to mammals, the mouse LD50 is 0.170 mg/kg body weight (0.15-0.27) intraperitoneally, 0.094 mg/kg body weight intravenously and 0.520 mg/kg body weight orally (Baden 1983, Baden 1995, ILO 1984). Franz and LeClaire (1989) reported respiratory failure in less than 30 minutes in guinea pigs exposed intravenously to 0.016 ng/kg PbTx-3. With intravenous administration of PbTx 3 in rats, Poli et al (1990a, 1990b) found that approximately 90% was cleared within 1 minute from the circulation. Furthermore, radiolabeling distributed to the skeletal muscle (70%), liver (19%), and intestine (8%) with little activity found in the heart, kidneys, lungs, spleen, testes, or brain. Elimination over a 24-hour period was primarily through the feces. The parent compound was present in the skeletal muscle, but several metabolites of PbTx 3 excreted in the bile were found in the feces. Cattet and Geraci (1993) orally administered sublethal doses (18.6 ug/kg) of PbTx 3 in rats, and found wide distribution to all organs, with the highest concentrations in the liver up to 8 days after exposure. Ingested PbTx3 was eliminated approximately equally in urine and feces.

To evaluate brevetoxin toxicokinetics from acute exposure up to 7 days, Benson et al (1999) exposed 12-week-old male F344/Crl BR rats to a single exposure of 6.6 ug/kg PbTx 3 via intratracheal instillation. Over 80% of the PbTx 3 was rapidly cleared from the lung and distributed via the blood throughout the body, particularly the skeletal muscle, intestines and liver with low but constant amounts present in blood, brain and fat. Approximately 20% of the toxin was retained in the lung, liver and kidneys for up to 7 days. The majority of the PbTx 3 excretion took place within 48 hours from exposure, with twice as much excreted in the feces compared to the urine. The authors concluded that potential health effects associated with inhaled brevetoxins may extend beyond the reportedly transient respiratory irritation reported by humans exposed to Florida red tide brevetoxin aerosol.

Wells et al (1984) reported increased airway resistance in 6 unanaethestized female Hartley guinea pigs when PbTx was inhaled as an aerosol or applied to the nares as nose drops in comparison with cross over exposure to methacholine with and without pretreatment with atropine. Furthermore, the authors reported that the animals were significantly less responsive to PbTx with pretreatment by atropine or by diphenhydramine, although there were no observable effects on the sneezing, drooling and defecation of the animals with pre-treatment. In the unanaesthestized asthmatic sheep, picogram doses of PbTx 3 can cause a significant and rapid increase in respiratory resistance (200 to 300x baseline); as noted above, this brevetoxin-induced bronchospasm can be effectively blocked by the mast cell stabilizing agent cromolyn and the histamine H1 antagonist chlorpheniramine (Singer 1998). Thus, in the lung, brevetoxin appears to be a potent respiratory toxin involving both cholinergic and histamine-related mechanisms.

Multiple die offs of marine mammals have been reported associated with Florida red tide and brevetoxins (Geraci 1989, O'Shea 1991, Bossart 1998). In 1996, a prolonged Florida red tide in the Gulf of Mexico resulted in the documented deaths of 149 endangered Florida manatees (Bossart 1998, Trainer 1999). The brevetoxin exposure of the manatees appears to have been prolonged inhalation of the red tide toxin aerosol and/or ingestion of contaminated seawater over several weeks. This manatee die-off investigation revealed severe catarrhal rhinitis, pulmonary hemorrhage and edema, and non-suppurative leptomeningitis, as well as possible chronic hemolytic anemia with multi-organ hemosiderosis and evidence of neurotoxicity (particularly

cerebellar) in the dead manatees. Therefore, the respiratory tract, liver, kidneys and brains of the manatees were primary brevetoxin targets, and the brevetoxin exposures and effects were believed to be chronic rather than acute. PbTx 3 and its metabolites were identified by a immunohistochemical stain using a polyclonal primary antibody to brevetoxin to be stored in the lung and other organs in alveolar macrophages, and in the brain within lymphocytes and microglial cells. Immunohistochemical staining with interleukin-1-beta converting enzyme showed positive staining with a cellular trophism similar to the brevetoxin antibody staining, suggesting that brevetoxin may initiate apoptosis and/or release inflammatory mediators that culminate in fatal toxic shock. Additional studies demonstrated that brevetoxin binds to isolated nerve preparations from manatee brain with a similar affinity as that reported for terrestrial mammals (Trainer 1999), as well as causing significant liver damage in in vitro mouse liver studies (Rodriguez Rodriguez 1996).

Humans

The two known forms of red tide toxins-associated clinical entities in humans first characterized in Florida are an acute gastroenteritis with neurologic symptoms following ingestion of contaminated shellfish (i.e. NSP), and an apparently reversible upper respiratory syndrome following the inhalation of the aerosols of the dinoflagellate and their toxins (i.e. aerosolized red tide toxins respiratory irritation) (Asai 1982, Baden 1995, Fleming 1999b, Fleming 1998a, Fleming 1998b, Morris 1991, Music 1973, Fleming 2001, Baden 1982b, Poli 2000, Music 1973).

Neurotoxic Shellfish Poisoning (NSP)

Neurotoxic shellfish poisoning may be viewed clinically as a milder form of paralytic shellfish poisoning (PSP) or ciguatera fish poisoning. In human cases of NSP, the brevetoxin concentrations present in contaminated clams have been reported to be 30-118 Mouse Units (MU)/100 g (78-120 ug/mg). Poli et al (2000) reported on the measurement of brevetoxin in urine from 3 persons who suffered from severe NSP after consuming contaminated shellfish from Florida; the urine brevetoxin levels ranged from 42-117 ng/ml via RIA analysis on admission to the emergency room. As a comparison, in PSP fatal paralysis can occur with as little as 1 mg of saxitoxin while picogram levels of ciguatoxin in Ciguatera fish poisoning have been reported to make adult humans severely ill. The shellfish reported to be associated with NSP when contaminated with brevetoxin include oysters, clams, coquinas, and other filter feeders (Keynes 1979, Baden 1995, ILO 1984, Hughes 1976, ILO 1984, Poli 2000).

NSP typically causes gastrointestinal symptoms of nausea, diarrhea, and abdominal pain, as well as the neurologic symptoms primarily consisting of paresthesias similar to those seen with Ciguatera fish poisoning (including reports of circumoral parathesiae and hot/cold temperature reversal), beginning within minutes to three hours after ingestion. Cerebellar symptoms such as vertigo and incoordination also reportedly occur. In severe cases, bradycardia, headache, dilated pupils, convulsions, and the subsequent need of respiratory support have been reported. Cases of death due to NSP (as opposed to PSP or Ciguatera) are very rare. Symptoms resolve reportedly within a few days of exposure, although no studies have been reported evaluating possible chronic health effects after acute NSP (Morse 1977, Sakamoto 1987, Baden 1995, Fleming 1995, Fleming 2001, Morris 1991, McFarren 1965, Viviani 1992, Hughes 1976, Noble 1990, Martin 1996, Music 1973, Hopkins 1997, ILO 1984, Rheinstein 1993, Dembert 1981).

Morris et al (1991) reported on an outbreak of NSP secondary to a red tide of K. brevis (then known as P. brevis) in October 1987 along the North Carolina Coast. Ultimately, over 48 persons who had eaten reportedly delicious cooked and raw oysters at 20 meals being diagnosed with

NSP. Acutely, 23% of the cases reported gastrointestinal and 39% reported neurologic symptoms. These symptoms were described as having a rapid onset (median incubation of 3 hours), mild, and of short duration (maximum malaise and vertigo up to 72 hours with median duration of 17 hours). Ultimately among the cases, 94% had multiple symptoms, and 71% had more than 1 neurologic symptom. Although there were no deaths or respiratory distress, one woman was admitted to the intensive care due to severe neurologic symptoms. There was a significant increase in the illness attack rate associated with an increase in the number of oysters eaten. Of note, 56% of the cases occurred before the first closure of affected shellfish waters to harvesting in early November; North Carolina had no red tide monitoring program at that time.

Inhalation of Aerosolized brevetoxin

There are very few published reports of human exposure and health effects associated with exposure to aerosolized red tide toxins in humans. The exposure usually occurs on or near beaches with an active red tide bloom. On shore winds and breaking surf result in the release of the toxins into the water and into the onshore aerosol (Pierce 1986, 1989, 1990, 2001, Sakamoto 1987, Music 1973, Backer submitted, Horstman 1991, ILO 1984). After initial reports in Florida and Texas, Woodcock (1948) reported respiratory irritation during a severe red tide on the West coast of Florida in 1947. When seawater containing the red tide organisms was sprayed as an aerosol into the nose and throat of volunteers, coughing and a burning sensation similar to that experienced on the beaches were reported (Woodcock, 1948). Pierce et al (1990, 1989) simulated the red tide toxin aerosol in the laboratory by bubbling air through seawater cultures of lysed K. brevis cells; they recorded toxin enrichment in the aerosol of 5 to 50 times the concentration compared with original concentrations in the seawater. Collection of marine aerosol along the Gulf coast of Florida and the North Carolina Atlantic coast during natural red tide blooms showed that the aerosolized toxins were the same as those in the water and as those resulting from the K. brevis culture experiments (Pierce et al., 1989, 1990).

Inhalation of aerosolized red tide toxins reportedly results in conjunctival irritation, copious catarrhal exudates, rhinorrhea, nonproductive cough, and bronchoconstriction (Music 1973, Asai 1982, Asai 1984, Franz 1989, Eastaugh 1989, Pierce 1986, Temple 1995, Sakamoto 1987, Baden 1982b, Davis 1994, Ahles 1974, Hughes 1976, Tommasi 1983, Hopkins 1997, ILO 1984, Dembert 1981, Cummins 1971). Some people also report other symptoms such as dizziness, tunnel vision and skin rashes. In the normal population, the irritation and bronchoconstriction are usually rapidly reversible by leaving the beach area or entering an air-conditioned area (Steidinger 1984, Baden 1983).

However, asthmatics are apparently particularly susceptible; Asai et al (1982) found that 80% of 15 asthmatic patients exposed to red tide aerosol at the beach complained of asthmatic attacks. Further studies by the same investigators (Watanabe 1988) using human bronchial smooth muscle tissue from 12 non asthmatic persons, all with a smoking history, showed similar results to canine smooth muscle studies: brevetoxins caused contraction with a threshold of 0.1 ug/ml with peak response at 12.0 ug/ml (EC50=1.24 ug/ml); this response was blocked by verapamil, atropine and tetrodotoxin, and it was potentiated by neostigmine. The possibility of susceptibility of asthmatics to the brevetoxins is corroborated by recent investigations with an asthmatic sheep model evaluating the exposure of aerosolized red tide toxins discussed above (Singer 1998). Furthermore, there are anecdotal reports of prolonged pulmonary symptoms even after exposure has ceased, especially in susceptible populations such as the elderly or those with chronic lung disease.

Reportedly, aerosolized red tide toxins respiratory irritation is associated only with significant Florida red tide blooms (including significant fish kills with dead fish on the beaches) within a few feet of the breaking surf of an active bloom. However, exposure to aerosolized red tide toxins can cause respiratory irritation, even in non-asthmatics and without obvious fish kills or high dinoflagellate cell counts in the seawater within a few feet of the seashore (K Steidinger, Florida Department of Environmental Protection, verbal communication). This may be due to the concentration of the brevetoxins in the aerosol of sea spray generated by waves hitting the shore during a red tide (Pierce 1990, Pierce 1989, Music 1973, Cummins 1971). It is not known how far inshore this red tide toxins aerosol will travel, especially given strong offshore winds during a red tide bloom.

Cummins et al (1971) sampled water and bivalves during a red tide along the West Coast of Florida in Sept 1967. In addition to identifying K. brevis (formerly G. breve) in the water samples and showing toxicity in the mouse bioassay with shellfish samples, the investigators reported burning of the eyes and respiratory irritation during the course of sampling. These symptoms increased as the surf zone was approached and were associated with organisms in the water. Of note, the investigators report similar symptoms when they received an inadvertent inhalation exposure from an aerosol of G breve organism cultures being aerated in the laboratory during oyster intoxication studies.

Music (1973) reported on a November 1972 K. brevis (formerly G. breve) red tide on the East coast of Florida, after currents and weather patterns had carried an existing red tide from the usual epicenter of West coast of Florida. This red tide coupled with strong Easterly onshore winds resulted in multiple reports of symptoms to the Palm Beach Health Department; the reports came from people on the beach (swimmers, workers, lifeguards) as well as persons living on or near the beach throughout Palm Beach County. Symptoms reported included acute eye and nose irritation (e.g. profuse watery eyes, copious rhinorrhea with burning of the eyes and nose), non-productive cough, and respiratory distress similar to that seen with the Florida West coast red tide. The symptoms were described as having a sudden onset, ie. occurring as soon as people got near the beach areas or were exposed to the onshore winds in their homes. The symptoms reportedly resolved upon leaving the beach or wind exposure, although less rapidly for those who were exposed for a longer time. Exposure to air-conditioning in homes or cars seemed to improve the symptoms more rapidly. Of note, persons on boats or long piers not exposed to breaking surf with onshore winds did not report any symptoms. All reports of symptoms stopped when the winds changed direction and were no longer onshore.

Hopkins et al (1997) briefly reported on a prolonged Florida red tide with confirmed K. brevis (formerly G. breve) identification along the West Coast of Florida from December 1995 through May 1996. The Lee County Health Department conducted a mailed survey of 1100 residents and long-term visitors in areas adjacent to beaches. There were 416 (39%) responses, with the majority of people responding reporting symptoms (although the authors point out that response to the survey encouraged report from symptomatic persons). The symptoms of eye and respiratory irritation were associated with the amount of time spent at the beach, but more serious conditions (ie. bronchitis, pneumonia, and various neurologic problems) were not. Six persons were hospitalized for illnesses they attributed to red tide exposure (although no definite diagnoses by physicians were reported).

Kirkpatrick et al (submitted) conducted a similar pilot study in 1999 using scientists on K. brevis red tide research cruises as volunteer study subjects. Air and water samples were analyzed for brevetoxins and personal interviews and pulmonary function tests were conducted daily. On one

day of the research cruise when seas and winds were higher that other days and cell counts were up to 8 million cells/L, two scientists reported shortness of breath and/or difficulty in taking a deep breath. At that same time, both had a decrease in pulmonary function. Although the pulmonary function decrease was not clinically significant, it is worth noting since neither scientist had any history of lung disease, both were young (30 years old) and neither were smokers.

In a pilot study of aerosolized red tide, Backer et al (submitted) measured the levels of brevetoxins in air and water samples, and conducted personal interviews and pulmonary function tests on people before and after visiting Florida beaches during Karenia brevis red tide events. One hundred twenty-nine people participated in the study, which was conducted during two separate red tide events in the West and East coasts of Florida. During these episodes, K. brevis and brevetoxins were measured in the seawater, as well as brevetoxins in environmental and personal air sampling. Exposure was categorized into three levels: little or no exposure, moderate exposure, and high exposure. Lower respiratory symptoms (e.g., wheezing) were reported by 8% of unexposed, 11% of moderately exposed, and 28% of highly exposed people. A detectable inflammatory response to the inhaled toxins was observed in over 33% of the people examined after they visited the beach. During the moderate and high exposure study periods, people were exposed to up to 36 ng/m^3 or 80 ng/m^3, respectively, of brevetoxin in the air. If an average adult breathes in about 25 liters of air per minute for light exercise, then the authors estimated that people visiting the beaches during the pilot study were inhaling between 54 and 120 ng brevetoxin each hour, or an inhaled dose of between 0.77 and 1.71 ng/kg (assuming an average weight of 70 kg) each hour. There were no clinically significant changes in pulmonary function test results; however, the study population was small. The authors plan to further investigate the human health impact of inhaled brevetoxins in future epidemiologic studies.

Red tide events in the Gulf of Mexico are usually reported from along the western coast of Florida and can occur nearly annually (Kusek et al., 1999). Red tides along the Texas coast are much less frequent (Villareal et al., 2001). Cheng et al. (submitted) reported a red tide episode in the Gulf of Mexico near Corpus Christi, Texas in October 2000. At Marine Science Institute (MSI) and Texas State Aquarium (TSA) airborne PbTx concentrations between 1.6 to 6.7 ng m^{-3} were reported at along with a few reports of upper respiratory symptoms (throat irritation, nasal irritation, and itchy skin) and no reports of lower respiratory symptoms. Although the number of workers was too small for statistical analysis, the reported symptoms were consistent with no/low exposure at the Marine Science Institute and detectable exposures at the Texas State Aquarium. This suggests that at lower environmental concentrations of about 2 to 7 ng m^{-3}, exposure to PbTx could result in upper respiratory symptoms. This lower level of airborne PbTx concentrations could be detected because of a more sensitive LC/MS technique. The PbTx particle size distribution with the impactor samplers, the first time that particle size of PbTx was reported. The MMAD was between 7 to 9 μm (a range of 3 to 20 μm), a relatively large size for inhaled ambient particles. Fine particles below 2.5 μm were not detected. Inhaled particles of this size would be deposited in the upper respiratory tract (nasal, oral, and pharyngeal area) (ICRP, 1994; Yeh et al., 1996), and subsequent respiratory irritation could result from the presence of the particles themselves or from toxins associated with the particles. Inhaled particles also deposited on the face and exposed skin causing the skin to itch.

It is unknown whether the inhalation of aerosolized brevetoxins can result in other systemic health effects (such as affecting the neurologic or immunologic systems), and in chronic not just acute health effects. The manatee evidence, as well as other laboratory animal studies, suggests

that this possibility should be explored further (Fleming 2001, Fleming 1995, Bossart 1998, Benson 1999).

Diagnosis

In general, NSP is a rare event in the United States. This is due in part to the extensive monitoring of shellfish beds for toxins and organisms in endemic areas, resulting in shellfish bed closure if either is elevated. If shellfish are not available for testing, the diagnosis of Florida red tide toxins-associated human diseases has been based primarily on the recognition of the clinical scenario of persons becoming ill with gastrointestinal and neurologic symptoms after eating shellfish, or with acute respiratory symptoms after inhaling aerosols associated with exposure to Florida red tide toxins.

The primary toxicity testing methods for contaminated shellfish currently is the US Food and Drug Administration (FDA) approved mouse bioassay. Several chemical, pharmacological, and immunological techniques, and the in vitro neuroblastoma cytotoxicity assay are available. In spite of specific strengths, each of these methodologies suffers limitations (Hannah1996). The mouse bioassay in particular has been found to give false positives, and it does not conclusively prove the presence of a particular toxin (Kerr 1999).

Recent promising brevetoxin research includes: HPLC, HPLC-MS, and micellar electrokinetic capillary chromatography/laser induced fluorescence detection methodologies for the identification of the K. brevis toxins, as well as an experimental ELISA test using antibodies to brevetoxin, radioimmunoassay, a cell based assay with tritium labeled PbTx 3 and rat brain synaptosomes, a sodium channel specific neuroblastoma cytotoxicity assay, and a neurophysiologic method using in vitro rate hippocampal slices (Templeton 1988, Melinek 1994, Fairey 1997, Hua 1995, Ishida 1996, Whitney 1997, Poli 1995, Naar in press, Trainer 1991, Hannah 1993, Dickey 1999, Kerr 1999, Poli 1990b, Shea 1997, Garthwaite 1996, Manger 1995, Van Dolah 1994). In particular, the brevetoxin ELISA test (based on goat anti-brevetoxin) is currently being applied experimentally to detect brevetoxin in: contaminated seawater, air, and contaminated shellfish (Naar in press). Although water sampling for both the dinoflagellates and the toxins has been performed for many years, red tide toxins air monitoring is presently experimental. Air monitoring could provide qualitative and quantitative time- and geographic-based data.

Work with Florida manatees (apparently killed due the inhalation of the red tide toxins) has lead to the development of a qualitative immunohistochemical stain for the Florida red tide toxins found within the macrophages and lymphocytes in nasal mucosa, lung and other tissues (Bossart 1998). This staining technique has also been used to look for toxins in the tissues of marine birds exposed to red tide toxins (Jessup 1998, Kreuder 1998). This biomarker could be used as both an indicator of exposure and effect. Based on recent research in a sheep animal model using a modified immunocytochemical technique on the bronchial lavage specimens of animals exposed to aerosolized red tide toxins, this biomarker holds promise as a diagnostic and prognostic tool. Initial work shows that the immunocytochemical staining of throat and nasal swab specimens reflect the bronchial lavage results, thus allowing for a more human-applicable biomarker.

Currently, there are no tests available for measuring the brevetoxins in human fluids, although the work of Poli et al (2000) measuring brevetoxin and its metabolites in urine using HPLC-MS and other methods, as well as the new brevetoxin ELISA of Naar et al (in press) are promising.

Treatment & Prevention

Treatment for shellfish poisoning is supportive (i.e. fluid replacement and respiratory support if necessary). In paralytic shellfish poisoning, emesis may not occur, hence gastric lavage is commonly used. Ciguatera fish poisoning caused by the natural marine toxin, Ciguatoxin, has been shown in a clinical trial to respond to the early administration of intravenous mannitol within 72 hours (Palafox 1988, Fleming 1997, Blythe 2001). Since brevetoxin and ciguatera are very similar structurally, it is possible that intravenous mannitol might be efficacious in treating early NSP (Mattei 1999).

Recent efforts have been directed in experimental animals towards developing specific monoclonal antibodies and antidotes against brevetoxin (Templeton 1989a, Templeton 1989b). Furthermore, Templeton (1989a) and Poli (1990b) indicated that in rats pretreated with an infusion of anti-brevetoxin IgG, nearly all the neurologic symptoms were blocked. Additionally, Purkerson-Parker et al (2000) identified brevetoxin derivatives that actually inhibit brevetoxin activity in electrophysiologic experiments. Initial data suggest that one of these derivatives, B-Naphthoyl-PbTx-3 can inhibit increases in pulmonary resistance in asthmatic sheep caused by aerosols of K. brevis cultures as well as aerosols of pure Pb-Tx-2 and PbTx-3.
In the case of aerosolized red tide toxins respiratory irritation, the use of particle filter masks may prevent or diminish the symptoms, while reportedly retreat to air conditioned environment will provide relief from the airborne irritation (Watanabe 1988, Woodcock 1948, Music 1973, Backer submitted). Brevetoxin-induced bronchospasm in asthmatic sheep and other animal models exposed to aerosolized red tide toxins can be effectively blocked by the mast cell stabilizing agent cromolyn and the histamine H1 antagonist chlorpheniramine, as well as by the muscarinic blocker atropine, the beta 2 agonists, the calcium channel blocker verapamil, and the sodium channel blocker tetrodotoxin (Baden 1982a, Gallagher 1980, Asai 1982, Trainer 1991, Singer 1998, Watanabe 1988). In the future, some of these medications may be used to treat, and if used prophylactically, even to prevent the bronchoconstrictive response. It is possible that these medications may be useful for asthmatics and other susceptible persons exposed to aerosolized red tide toxins in the future.

In the laboratory, C. virginica oysters accumulated K. brevis (formerly known as P. breve) in less than 4 hours in the presence of less than 5000 cells/ml of K. brevis; the oysters will then naturally "detoxify" 60% of the toxins in 36 hours when placed in K. brevis free water. There is substantial variability between species of the potency of depuration, even under laboratory conditions. Canning does not decrease the brevetoxin concentration in bivalves. Commercial bivalves are reportedly safe to eat 1 to 2 months after the termination of single bloom episode (Baden 1983, Viviani 1992, Steidinger 1972). Successful ozone-assisted depuration of red tide contaminated shellfish, both killing the organism and inactivating the toxin, have been reported; depuration with ultraviolet light and chlorination have proven unsuccessful (Baden 1995, Blogoslawski 1975, Fletcher 1998, Roderick 1997).

Of note, Poli (1988) reviewed laboratory procedures for the detoxification of equipment and waste contaminated with brevetoxins PbTx 2 and PbTx3. In particular, laboratory equipment can be safely decontaminated using a dilute 0.1N NaOH solution for at least 10 minutes, and disposable waste can be either soaked in the NaOH solution prior to disposal or burned in an incinerator with a combustion chamber of at least 500^{o}C; steam autoclaving is not a viable method of decontamination. Care should be taken to protect workers from skin, oral and inhalation exposures to brevetoxins.

Monitoring & Surveillance

The most effective way to prevent human health effects from the red tides is to prevent exposure to the toxins and organisms. In the case of NSP, this means monitoring shellfish beds for organisms and toxins, and closing shellfish beds to harvest when specified levels are detected. For the aerosolized red tide respiratory irritation, water and air monitoring could detect high levels in the air, and warning notices could be posted along affected coastal areas for susceptible subpopulations. Surveillance and reporting of red tide disease in humans, other mammals, and animals is important for early warning, prevention and the further understanding of these diseases. In addition, education and outreach programs to healthcare providers, workers involved in the seafood and tourism industries, and the general public are important components of successful monitoring and surveillance programs (Fleming 1995, Backer et al in press,).

Since the mid 1970s, the Florida Department of Agriculture and Consumer Services (DACS) has conducted a monitoring program of shellfish beds in the Gulf of Mexico. Closures are made when the level of K. brevis (formerly P. brevis) exceed 5000 cells/liter near or in harvesting areas. The areas are kept closed until at least 2 weeks after a drop in cell counts below the action level and mouse bioassay results in shellfish below 20 MU (mouse units)/100g (Viviani 1984, Park 1995, Baden 1995). There is no regulatory limit for brevetoxin in the seawater. The regulatory limit for shellfish is 20 MU/100 grams of shellfish meat which is equivalent to 80ug PbTx /100 grams of shellfish meat (Subcommittee 1970, Dickey 1999).

The standardized mouse bioassay is used to test specimens for the presence of neurotoxicity. The bioassay is based on the time until death of mice injected intraperitoneally with crude toxin residues extracted from shellfish. Relative toxicity is expressed in mouse units. One mouse unit (MU) is the amount of crude toxin residue that will on average kill 50% of test mice in 930 minutes. Although any detectable level of toxin per 100 grams of shellfish tissue is considered potentially unsafe for human consumption, in practice a residue toxicity $\geq$ 20 MU was adopted as the guidance level for the prohibition of shellfish harvesting (Morris 1991, Dickey 1999).

These monitoring programs should prevent cases of ingestion NSP related to contaminated shellfish consumption in most of the Florida human population, but not in areas where red tide is not an annual event and/or where monitoring programs do not exist (e.g. North Carolina). Furthermore, such monitoring programs do not prevent the respiratory irritation associated with exposure to aerosolized red tide toxins, although they could serve as early warning devices. In Florida where the red tides are almost a yearly occurrence, beaches are not closed to recreational or occupational activities even during very active near-shore blooms.

There is believed to be significant under reporting of the marine toxin diseases such as NSP. This is due to the public and medical misconception that all food poisoning events are mainly due to microbial contamination; furthermore, many healthcare providers even in endemic areas do not realize that case of marine toxin disease are required to be reported to the public health authorities. Thus in the case of Ciguatera Fish Poisoning, the CDC has estimated that only 2 to 10% of cases are actually reported in the US, even in endemic areas such as South Florida (Sierra-Beltran 1998, Cortes Altamirano 1995, Fleming 1995, Fleming 2001, Ahmed 1993, McKee 2001). In 1999, the Florida Department of Health added NSP to their list of reportable diseases; however, aerosolized red tide toxins respiratory irritation is not a reportable illness.

The Florida Poison Information Center at the University of Miami initiated a toll free 24 hour/day Marine and Freshwater Toxin Hotline (1-888-232-8635) in 1997 to increase the reporting of marine and freshwater related illness, including the marine toxin associated diseases such as NSP

and aerosolized red tide toxin irritation. Any cases of reportable illnesses are passed on by the Poison Information Center to the Florida Department of Health for official reporting purposes. Efforts are ongoing to increase knowledge and reporting of these illnesses by healthcare providers and public health officials. These include a Video Conference on the Human Health Effects of Marine Toxins in Florida in June 1999 with a video and educational materials by the NIEHS Marine and Freshwater Water Biomedical Sciences Center at the University of Miami through funding from Centers for Disease Control and Prevention (CDC), the Florida Department of Health and the Area Health Education Coalition (AHEC) (Fleming 1999b, Fleming 1998c).

Economic Impact

The economic impact of all the harmful algal blooms is difficult to quantify. This is due in part to their unreported and unrecognized costs, including public health, seafood industry and tourism (Anderson 2000, Martin 1976). In the case of K. brevis, there are economic costs associated with the closure of the shellfish beds (as well as possible depressed commerce in shellfish even after the beds are re-opened due to worried public perception), the public health and medical costs of NSP and the aerosolized red tide toxin respiratory irritation response, the impact on tourism and related activities from the presence of active red tides in recreational areas, the impact on marine mammals (including endangered animals) and other animals, and the disposal of literally millions of tons of dead fish on beaches and in canals and rivers. For example, in 1971, St Petersburg (FL) officials estimated that it cost $155,763 to remove 2367 tons of fish from their beaches and canals (Steidinger 1972). With regards to potential fisheries impact, Sierra Beltran (1998) has reported that the shellfish beds are closed to harvest due to active red tide contamination along the Eastern coast of Mexico on average 60 days/year. Of note, the 1987 closure of shellfish beds in North Carolina for an entire season due to K. brevis (formerly known as G. breve) had an estimated cost of $25 million, without taking into account the NSP public health investigation and other intangibles (Tester 1997).

Anderson et al (2000) estimated the annual economic impact for all the harmful algal blooms (including K. brevis red tides) for the US. For 1987-92 in 2000 dollars, the average 15 year capitalized impacts were $449,291,987 with an annual average of $49 million/yr; of these impacts, 45% were attributed to public health costs, 37% to commercial fishery costs and losses, 13% to recreation/tourism, and 4% to monitoring and management. The authors believe that these estimates were highly conservative due to low monitoring, reporting and data collection of harmful algal bloom events and impacts.

Identified Research Areas

Inexpensive, reliable and easily accessible testing for the brevetoxins in multiple media (sea water, air, shellfish, and biological fluids) are essential for the understanding of the human health effects of Florida red tide and its toxins. There are no established biomarkers of exposure and effect for either of the Florida red tide toxins-associated conditions in humans. There is very little information on appropriate treatment and prevention methodologies, particularly of the respiratory irritation illness.

The exact composition, including droplet size, of the red tide brevetoxin aerosol is unknown. It is not known how far inshore this red tide toxins aerosol will travel, especially given strong offshore winds during a red tide bloom. Although water sampling for both the dinoflagellates and the toxins has been performed for many years, red tide toxins air monitoring is presently not widely conducted. Expanded air monitoring could provide qualitative and quantitative time- and geographic-based data.

There is very little published literature or formal epidemiologic studies on the human health effects of the diseases, either ingestion NSP or inhalation aerosolized red tide toxins respiratory irritation. Both NSP and aerosolized red tide toxin respiratory irritation are likely to be under-reported and under-diagnosed. There are no population based statistics for the incidence of NSP or aerosolized red tide toxins respiratory irritation, even in endemic areas. It is unknown whether inhalation of aerosolized brevetoxins can result in other systemic health effects such as neurologic or immunologic, and in chronic effects. The manatee evidence, as well as other laboratory animal studies, suggests that this possibility should be explored further. These effects should be considered particularly in possibly sensitive subpopulations.

Finally, education and outreach programs to healthcare providers, workers involved in the seafood and tourism industries, and the general public are important components of successful monitoring and surveillance programs (Backer et al in press, Fleming 1995, Fleming 1998a, Fleming 1998b, Fleming 1999b, Fleming 2000, Anderson 1993, Steidinger 1999, Backer in press, NRC 1999, Anderson 2000, Ahmed 1993, Pierce 1986, Kin Chung 1991, Smayda 1990, Martin 1998, ILO 1984).

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