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# Review of Florida Red Tide and Human Health Effects

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## Abstract

This paper reviews the literature describing research performed over the past decade on the known and possible exposures and human health effects associated with Florida red tides. These harmful algal blooms are caused by the dinoflagellate, *Karenia brevis*, and similar organisms, all of which produce a suite of natural toxins known as brevetoxins. Florida red tide research has benefited



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from a consistently funded, long term research program, that has allowed an interdisciplinary team of researchers to focus their attention on this specific environmental issue—one that is critically important to Gulf of Mexico and other coastal communities. This long-term interdisciplinary approach has allowed the team to engage the local community, identify measures to protect public health, take emerging technologies into the field, forge advances in natural products chemistry, and develop a valuable pharmaceutical product. The Review includes a brief discussion of the Florida red tide organisms and their toxins, and then focuses on the effects of these toxins on animals and humans, including how these effects predict what we might expect to see in exposed people.

**Keywords**

Florida red tide; red tide; neurotoxic shellfish poisoning; NSP; brevetoxins; harmful algal bloom; HAB; *Karenia brevis*; shellfish poisoning; respiratory irritation; marine toxin diseases; neurotoxic fish poisoning

## 1.0 Introduction

Florida red tides are predominantly associated with the blooms of the toxic dinoflagellate, *Karenia brevis* (*K. brevis*), formerly known as *Gymnodinium breve* and *Ptychodiscus brevis. K. brevis* produces a group of potent natural neurotoxins, the brevetoxins (i.e. PbTx or Ptychodiscus toxins), which can cause illness and mortalities in fish, seabirds, and marine mammals. Humans are susceptible to the effects of brevetoxin exposure, and public health surveillance activities have documented cases of intoxications from eating contaminated seafood and many respiratory complaints from inhaling contaminated aerosols (Kirkpatrick et al., 2004a).

Florida red tide blooms have been documented on the Florida west coast since the 1800s. More recently, Florida red tides have spread as far as the eastern coast of Mexico and have been entrained in the Gulf Loop, the current that brings Gulf waters to the shores of North Carolina. Other brevetoxin-producing dinoflagellate blooms have been identified in diverse geographic locations worldwide, including New Zealand, Australia and Scotland (Baden and Fleming 2007; Hernandez Becerril et al., 2007; Haywood et al., 2004; Kirkpatrick et al., 2004a; Nozawa et al., 2003; Steidinger et al., 1983).

In the 1980s and 1990s, there was increased interest in and research activity on harmful algal blooms (HABs). Much of this interest was driven by media attention on the discovery of several new HAB organisms purportedly associated with animal and human exposures and health impacts (e.g. *Pseudo-nitzschia*, *Pfiesteria*, and the phytoplankton producing the newly discovered toxins, the Azaspiracids) (Abraham and Baden 2006; Backer et al., 2003a; Backer et al., 2005a; Backer and Fleming 2008; Fleming et al., 2001; Fleming et al., 2004; Okamoto and Fleming 2005; Twiner et al., 2008; Zaias et al., 2010). There were also concerted efforts by the HAB research and response community to increase national and international attention on the apparent increase in HABs and the resulting increased risk for human exposure and subsequent adverse health effects (e.g. National HAB plan at http://www.esa.org/HARRNESS/). These activities lead to increased funding and interest in HAB research (e.g. the ecology and oceanography of harmful algal blooms [ECOHAB] http://www.whoi.edu/science/B/redtide/nationplan/ECOHAB/ECOHABhtml.html).

Over the past decade, there has been an intensive interdisciplinary and inter-agency research program focused on the possible exposures and health effects in humans and other animals from the Florida red tide toxins, particularly the aerosolized toxins (Abraham and Baden

2006; Backer et al., 2003a; Backer et al., 2005a; Fleming et al., 2004; Fleming et al., 2005a; Red tide research group 2002; Zaias et al., 2010). The findings of this particular research program are summarized below, with particular emphasis on the implications for human health.

## 2.0 Organisms

In the past decade, through the use of new technologies, it has become clear that *K. brevis* is only one of several different species of the Genus, *Karenia*, found throughout the world's oceans. Blooms in the Gulf of Mexico may contain both *K. brevis* and *K. mikimotoi* (another brevetoxin-producing *Karenia* species) (Haywood et al., 2004). Other research has demonstrated varying brevetoxin production among the *Karenia* species, and even among individual *K. brevis* organisms. There have also been major advances in understanding the genomics of these dinoflagellates, such as the identification of the toxin-producing PKS genes, exploration of the impact of environmental change (e.g. temperature, light/dark cycles, etc) on gene expression, and the appreciation of the apparently unique complexity of the *Karenia* genome (Lidie et al., 2005; Monroe et al., 2008; Rein and Snyder 2006).

Despite what has been learned in the past few decades, there remains ongoing controversy concerning the sources and factors contributing to the bloom behavior of dinoflagellates, including *K. brevis*. The actual life cycle of *K. brevis* is still undefined, especially the location or existence of resting cysts. However, the major controversy has centered on the ability of anthropogenic change to influence *K brevis* bloom dynamics In particular, the relative importance of the role of nutrients (e.g. nitrates, phosphorus, silica, and iron) from coastal rivers, non-point coastal sources, or atmospheric deposition in initiating and/or sustaining *K. brevis* blooms is currently an important research and environmental policy topic (Brand and Compton 2007; Olascoaga et al., 2006; Walsh J et al., 2006).

## 3.0 Toxins

There has been an explosion of research on brevetoxins research over the past decade due to increased scientific and public health interest, and the potential to apply a range of new technologies. The brevetoxins (M.W. ~900) are lipid soluble, cyclic polyethers. In biological systems, they act to open voltage gated sodium (Na+) ion channels in cell membranes, leading to Na+ influx into the cell (Baden and Fleming 2007; LePage et al., 2003; Mattei et al., 2008; Twiner et al., 2007). There are over 10 different brevetoxins isolated in sea water blooms and *K. brevis* cultures in the laboratory, as well as multiple analogs and derivatives from the metabolism of shellfish and other organisms (Baden et al., 2005; Baden and Fleming 2007; Campbell et al., 2004; Michelliza et al., 2004 and 2007; Satake et al., 2008 and 2009). Recently, several laboratories have successfully synthesized brevetoxins *de novo* (Crimmins et al., 2009; Fuwa et al., 2006; Kuranaga et al., 2009). During Florida red tide blooms, the major brevetoxin produced is PbTx-2, along with lesser amounts of PbTx-1, PbTx-3, and other brevetoxin analogs (Cheng et al., 2004; Cheng et al., 2005a; Cheng et al., 2005b; Hardman et al., 2004; Lamberto et al., 2004; Pierce et al., 2003; 2005; 2008).

One of the most exciting discoveries of the last decade has been the identification of brevenal, a brevetoxin antagonist, in both *K. brevis* laboratory culture and in the environment during *K. brevis* blooms. This is apparently the first documented case of a toxin-producing organism also producing its own antagonist. Brevenal is produced by *K. brevis* in significant amounts, particularly during bloom senescence, and it acts at a different receptor site on nerve cells than the brevetoxins. Other brevetoxin analogs with varying degrees of antagonism or brevetoxin-like characteristics have also been identified (Abraham et al., 2003; Abraham et al., 2005a and 2005b; Bourdelais et al., 2002; Bourdelais et al., 2004a and 2004b; Bourdelais et al., 2005; Potera 2007).

From the point of view of human exposure and health, the brevetoxins are tasteless, odorless, and heat and acid stable. Thus, these toxins cannot be easily detected, nor can they be removed by food preparation procedures (Backer et al., 2003a; Backer et al., 2005a; Backer and Fleming 2008; Baden and Fleming 2007). Thus, the normal warning mechanisms (e.g. bad taste) or other protections (e.g. cooking contaminated seafood) are useless, and public health protection must focus on preventing human exposure (i.e. primary prevention).

Over the past decade, again thanks to the application of new technologies, major advances have been made in the detection of brevetoxins in a range of substrates, including seawater, air, seafood, and various animal and human clinical specimens (Dechraoui 2005; Dickey et al., 2004; Flewelling et al., 2005; Naar et al., 2007; Plakas et al., 2008; Poli et al., 2007; Weidner et al., 2004; Woofter et al 2003, 2005a and b, 2007). In particular, the creation, development and application of a new brevetoxin ELISA to all of these substrates, coupled with significant improvements in the detection limits of more traditional toxicologic analyses (e.g. Liquid Chromatography Mass Spectrometry (LCMS)), have allowed researchers and regulators to identify brevetoxins at very low levels in multiple environments and in a range of substrates (Naar et al., 2002 and 2004). This improved detection ability has been particularly important in advancing research to document exposures to brevetoxin-contaminated aerosols generated during Florida red tides and to identify the associated health effects in animals and humans. Specifically, using this highly sensitive ELISA, brevetoxins (particularly PbTx2 and 3, as well as brevenal) have been found in seawater and aerosols during active *K. brevis* blooms, as well as during non bloom periods (although at much lower levels).

In addition to establishing the concentrations of brevetoxins seen during a Florida red tide bloom (ranging from 15–90 $mg/m^3$), the particle size of the brevetoxin aerosol has been characterized. The particles have a geometric mean of approximately 8–9 μ. This is important information in terms of the potential for respiratory effects of brevetoxin aerosols in humans. Particle size needs to be less than 5 μ to enter the lower airway; therefore, with a geometric mean of 8–9 μ, only 10–20% of these particles are small enough to enter the human lung (Cheng et al., 2004; Cheng et al., 2005a; Cheng et al., 2005b; Pierce et al., 2003; 2005; 2008). Using the same air sampling technologies, brevetoxin aerosols have been demonstrated to travel as much as a mile inland from coastal areas during an active Florida red tide, particularly when there are strong onshore winds (Kirkpatrick et al., 2010).

In addition to its application for aerosol analysis, improvements in brevetoxin detection and measurement have lead to the discovery of measurable levels of toxin in fish, both in the internal organs and in the filets that might be eaten by people. This creates the new possibility that there is an additional disease, “brevetoxin fish poisoning” (not just shellfish poisoning) that could effect marine mammals and people as discussed below (Flewelling et al., 2005; Kirkpatrick et al., 2009a; Naar et al., 2007).

## 4.0 Cellular processes

Cellular effects associated with both natural and experimental exposure to brevetoxins have been observed in the immune system of many species, although the mechanisms of action of brevetoxin exposure on immune cells and immune competence are not well understood. The number and variety of mediators, critical checkpoints, and key regulators in the immune system are vast, and brevetoxin may impact any one of these pathways individually or in combination. Full characterization of cellular consequences of brevetoxin exposure is critical to fully understand the impact of recurrent red tide events on human health.

Several potential mechanisms for brevetoxin immunotoxicity have been suggested, including the inhibition of cathepsin active sites (Katunuma et al., 2003; Sudarsanam et al., 1992); apoptosis (Bossart et al., 1998; Sayer et al., 2005; Walsh et al., 2008; Murrell and Gibson, 2009; 2010); the release of inflammatory mediators (Bossart et al., 1998; Murrell and Gibson 2010); effects on cell cycle (Han et al., 2003; Murrell and Gibson, 2009; Sayer et al., 2006; Walsh et al., 2005; 2008); and oxidative stress (Radwan and Ramsdell, 2006; Walsh et al., 2009). Brevetoxin exposure has been shown to have the potential to impair the immune system of many species, including manatee (Bossart et al., 1998; Walsh et al., 2005), cormorant (Kreuder et al., 2002), rat (Benson et al., 1999; 2004a and b; 2005) and loggerhead sea turtle (Walsh et al., 2010). Demonstrated effects resulting from brevetoxin exposure include: reduced phagocytosis (Benson et al., 1999); decreased plaque-forming ability (Benson et al., 1999; 2004a and b); and decreased lymphocyte proliferation (Walsh et al., 2005). Levels of lysozyme were found to be elevated in rescued loggerhead sea turtles (Walsh et al., 2010). *In vitro* experiments have demonstrated possible DNA damage (Murrell and Gibson, 2010; Sayer et al., 2005); chromosomal aberrations (Sayer et al., 2006); and effects on cellular growth (Han et al., 2003; Murrell and Gibson, 2009; Sayer et al., 2006; Walsh et al., 2008). Other immune system effects include mast cell degranulation (Hilderbrand et al., 2010) and histamine release (Abraham et al., 2005), cellular effects which may contribute to observed airway responses following the inhalation of aerosolized brevetoxins. Production of the pro-inflammatory cytokine, IL-6, was increased at both the protein (Hilderbrand et al., 2010) and gene (Murrell and Gibson, 2010) level in response to brevetoxin exposure. Several other cytokine genes with roles in pathogenesis of respiratory diseases were also shown to be increased in Jurkat E6-1 cells in response to *in vitro* brevetoxin exposure (Murrell and Gibson, 2010).

Apoptosis as potential mechanism of brevetoxin immunotoxicity was suggested based on the presence of interleukin-1 converting enzyme in lymphocytes and macrophages in manatee tissues collected during an epizootic (Bossart et al., 1998). DNA damage in human lymphocytes treated with brevetoxins *in vitro* (Sayer et al., 2005) supports apoptotic effects. Apoptosis, as measured by activity of caspase-3, was reported in a cell line (Jurkat E6-1) exposed to PbTx-2 and PbTx-6, but not when exposed to PbTx-3 (Walsh et al., 2008). Murrell and Gibson (2009) also demonstrated apoptosis occurring in brevetoxin-treated Jurkat cells through an increase in caspase 3/7 activity and activation of poly (ADP-ribose) polymerase (PARP), processes which were toxin-congener dependent, again with PbTx-3 failing to induce apoptosis. Several genes involved in apoptotic processes were affected by *in vitro* brevetoxin exposure in Jurkat cells (Murrell and Gibson, 2010).

Several studies have indicated that oxidative stress may play a role in the cellular response to brevetoxins. Glutathione depletion, an indication of oxidative stress, resulted in a U-937 human monocyte cell line treated with PbTx-2 (Walsh et al., 2009). Observations of DNA strand breaks (Sayer et al., 2005) and chromosomal aberrations (Sayer et al., 2006) are also consistent with oxidative stress. Brevetoxins have been shown to proceed through cytochrome P450 metabolic pathways, which may lead to oxidative damage. Evidence for cytochrome P450 involvement includes the metabolism of PbTx-2 by rat hepatocytes (Radwan and Ramsdell, 2006) and the U-937 human monocyte cell line (Walsh et al., 2009), and following treatment with cDNA-expressed rat cytochrome P450 enzymes (Radwan et al., 2005). The systemic administration of PbTx-2 to rats (Radwan et al., 2005) also demonstrated brevetoxin metabolism through cytochrome P450 pathways. Such metabolic processes can generate nucleophilic intermediates with the potential to bind DNA, and may have led to the brevetoxin-nucleic acid adducts detected in rat lung cells following both *in vitro* and *in vivo* exposure (Radwan and Ramsdell, 2008). Leighfield et al. (2009), however, reported that neither PbTx-2 nor the epoxide (PbTx-6) showed mutagenic potential. Some

genes related to DNA damage, however, were increased in expression in Jurkat cells exposed to brevetoxin (PbTx-2) (Murrell and Gibson, 2010).

## 5.0 Animals

Significant die-offs of marine mammals, seabirds, and other animals throughout the 1990s and early 2000s enhanced awareness of the impacts of Florida red tides, and led to substantial increases in the resources available to support relevant interdisciplinary research (Kirkpatrick et al., 2004; Kreuder et al., 2002; Van Dolah et al., 2003; Zaias et al., 2010). In particular, the deaths of a significant population of the highly endangered Florida manatee during the prolonged 1996 Florida red tide focused attention on the potential health impacts for both animals and humans, particularly those associated with inhaling aerosolized toxins (Bossart et al., 2002; 2003a; 2003b). Another important finding demonstrating the impacts of brevetoxins on animals involved a major dolphin die-off in the early 2000s. Although not temporally associated with an active Florida red tide bloom, the cause of death was exposure to brevetoxins via the food web. Fish found in the dolphins' stomachs tested positive for brevetoxins, particularly in the organs but also in the muscle. This episode raised the possibility of "brevetoxin fish poisoning" in humans and other animals who consumed whole fish contaminated with brevetoxins (Flewelling et al., 2005; Kirkpatrick et al., 2009a; Naar et al., 2007).

Recent laboratory studies in animals have been particularly important in exploring exposure and toxicity mechanisms, validating brevetoxin exposure, and demonstrating biological plausibility and possible mechanisms of action for the health effects reported in human studies (described below). Short and long term exposures of rodents (rats and mice) to aerosols containing brevetoxin have not demonstrated the same level of toxicity as seen in humans and other animal models. However, rodent studies have shown that aerosolized exposure to brevetoxins can lead to rapid systemic distribution, particularly to the neurologic system, implying potential adverse neurologic health impacts with respiratory exposure to aerosols (Benson et al., 2004a and 2004b; Benson et al., 2005a; Tibbetts et al., 2006). For example, exposing mice to aerosols containing brevetoxins (and exposing fish to water containing brevetoxins) caused changes in vestibular and auditory nerve function (Benson et al., 2005b; Lu and Tomchik 2002). Long term exposures of rodents to aerosolized brevetoxins have demonstrated immune dysfunction, including delay of viral clearance and possible enhancement of the pathogenicity of influenza A (J Benson, Lovelace Respiratory Research Institute, personal communication). Rodent studies have also been important in demonstrating that brevetoxins delivered in aerosols are not teratogenic in multi-generational exposure studies (Benson et al., 2006).

The sheep model of asthma has served as an important tool for the exploration of possible health effects from aerosolized brevetoxin exposures. The highlight of this model is that the sheep respond to brevetoxin exposures at levels similar to those experienced by humans at the beach during a Florida red tide bloom (Abraham and Baden 2006; Abraham et al., 2003; Abraham et al., 2004; Abraham et al., 2005a and b; Abraham et al., 2009; Zaias et al., in press). This model has demonstrated that both asthmatic and non asthmatic sheep react with significantly decreased respiratory function and experience dose-dependent airway hypersensitivity after exposure to very small concentrations of aerosolized brevetoxins (~10 pg/ml of PbTx-2 or PbTx-3, the two main toxins found in the air during a *K. brevis* bloom). In the asthmatic sheep, these effects are larger and last longer, particularly when there has been exacerbation of the asthma prior to the brevetoxin exposure. Chronic exposures in sheep demonstrate reduced function of alveolar macrophages, suggesting immune dysfunction (Zaias et al in press). This same model system has been important in the exploration of the pathogenesis and binding of many different types of brevetoxins and their

analogs, including the new antagonist brevenal, since it allows for precise exposure delivery and effect measurement.

## 6.0 Humans

Humans can be exposed to brevetoxins through food, water, and air (Backer et al., 2003a; Backer et al., 2005a; Backer and Fleming 2008; Fleming et al., 2001; Fleming et al., 2002; Okamoto and Fleming 2005). Until recently, the health effects associated with exposure to Florida red tide have been driven primarily by anecdote and case report, as well as the evidence described above from wild marine mammal illnesses and deaths. It is only in the past decade that interdisciplinary epidemiologic research has been applied to the exposures and health effects of Florida red tide and its toxins.

### 6.1. Consumption of contaminated seafood

The traditional illness associated with exposure to Florida red tide and its toxins through the consumption of contaminated shellfish is neurotoxic shellfish poisoning (NSP). The assumption has been that this is a relatively rare disease due to the stringent monitoring and timely closure of toxin-contaminated shellfish beds in the Gulf of Mexico. However, a recent comprehensive Review by Watkins et al., (2009) found that, this illness is likely to be misdiagnosed, and is probably more common than previously thought, particularly among visitors and subpopulations not informed of shellfish bed closures or shellfish harvesting bans. Based on a review of emergency room cases in Florida, it is clear that NSP can be a severe acute disease with emergency room and intensive care required during the first hours, and, in severe cases days, to prevent respiratory failure (Abraham A et al., 2008; Watkins et al., 2009). Even with a severe acute illness, victims are usually discharged from the hospital within days; there is almost nothing known about the subchronic or chronic sequelae of an acute NSP episode. Furthermore, nothing is known about the possible health effects of long term very low level exposures from eating shellfish with low levels of contamination over a long period of time.

With regards to the possible new illness of “brevetoxin fish poisoning,” it is not known if there are human cases of illness associated with eating brevetoxin-contaminated finfish. Nevertheless, evaluation of emergency room admissions for gastrointestinal illnesses during an active Florida red tide and again when there was not an active bloom demonstrated significantly increased gastrointestinal illness emergency room admissions during the active Florida red tide period (Flewelling et al., 2005; Kirkpatrick et al., 2009a; Naar et al., 2007; Perez Linares et al., 2009).

### 6.2 Inhalation exposure

The major advances in the past decade in defining the nature and extent of human health effects from exposure to Florida red tide and its toxins have been in the area of aerosol exposures (Backer et al., 2003b; Backer et al., 2005b; CDC 2008; Fleming et al., 2005a and [b]; Fleming et al., 2009; Kirkpatrick et al., 2002; Kirkpatrick et al., 2004a; Kirkpatrick et al., 2006; Kirkpatrick et al., 2009a; Kirkpatrick et al., 2009b; Kirkpatrick et al., 2010; Milian et al., 2007; Quirino et al., 2004; Steensma 2007). An early study demonstrated that (similar to the studies in the sheep model) all persons, regardless of their underlying respiratory function, can be affected by exposure to aerosols generated during Florida red tides. Complaints included respiratory symptoms which appeared to move from the upper to the lower respiratory track with increasing exposure levels of the aerosolized brevetoxins (Backer et al., 2003b). Subsequent studies in a group of very healthy non-asthmatic lifeguards found significantly increased self-reports of respiratory symptoms after completing an 8 hour work shift during an active Florida red tide confirmed by finding

brevetoxin in the water and in aerosols. There was no increase in symptoms after completing a work shift in the absence of a Florida red tide. Measurements in these lifeguards did not demonstrate a significant decrease in their pulmonary function associated with exposure to aerosolized brevetoxins during an active Florida red tide nor during a non exposure period (Backer et al., 2005b).

While the results in the lifeguards suggested that the effects from aerosolized Florida red tide were acute and of minor significance in a very healthy cohort, there are other groups of people for whom these aerosols might pose an important health risk. Asthmatics aged 12 and older had significant increases in self-reported respiratory symptoms and significant decreases in respiratory function measured by spirometry after only 1 hour of acute exposure to aerosolized brevetoxins during an active Florida red tide. The changes in symptoms and lung function were not present when the participants went to the beach when there was no active Florida red tide (Cheng et al., 2004; Cheng et al., 2005a; Cheng et al., 2005b; Fleming et al., 2005a; Fleming et al., 2007b; Milian et al., 2007; Pierce et al., 2003; 2005; 2008;). In addition, there was a dose response relationship to the symptoms (but not the pulmonary function changes) during the 1 hour of brevetoxin exposure (Fleming 2009). The subgroups that appeared to react most significantly in terms of both symptoms and pulmonary function changes to the 1 hour brevetoxin exposure were those reporting recent use of asthma medications (suggestive of less controlled asthma), and those who lived over 1 mile inland from the coastal regions (possibly relatively unexposed prior to the study beach exposure) (Fleming et al., 2005b; Fleming et al., 2007b; Fleming et al., 2009; Kirkpatrick et al., 2010; Milian et al., 2007).

As seen in the sheep asthma model, when the asthmatic study participants were followed up over a 5 day time period, their symptoms persisted for 3–4 days after the acute 1 hour beach exposure (Kirkpatrick et al., 2009b). Even more importantly, their pulmonary function decreased even further the day after the 1 hour beach exposure and did not recover for the subsequent 4 more days of follow up. Again, the less controlled asthmatics and those who live inland seemed to experience the greatest changes in symptoms and lung function.

Another way to assess the public health impact from an environmental exposure is to examine contacts with the local health care systems. Kirkpatrick et al. (2006) evaluated emergency room admissions during an active Florida red tide period and compared them with admissions during a non active period. The authors found an increase in emergency room admissions for acute and subchronic respiratory health effects (e.g. asthma, bronchitis, and pneumonia) during active Florida red tides, particularly for coastal residents. Another study compared calls to the Poison Information Center with and without reported Florida red tide exposure. The results suggested that callers experienced prolonged respiratory symptoms, and increased use of medication and doctor visits, among those who were exposed to the Florida red tide aerosols (Quirino et al., 2004).

Taken together, these data suggest that at least in asthmatics (and possibly in others with underlying respiratory illness), exposure to aerosolized Florida red tide toxins leads to acute, subacute, and possibly more chronic illness (Kirkpatrick et al., 2006; Kirkpatrick et al., 2009b; Zaias et al., 2010). However, initial evaluation of longitudinal data in the cohort of asthmatic residents who were exposed almost annually to *K. brevis* blooms did not identify any particular subgroup of asthmatics at increased risk, nor does there appear to be any longitudinal health effect over years of intermittent exposure. Despite potential intermittent brevetoxin environmental exposures, continued intermittent exposure to aerosolized Florida red tide toxins over several years follow up did not appear to cause major respiratory changes in the asthmatic study group,; however, these results need to be explored further to be confirmed (J. Bean, the CincinnatiChildrens Hospital, personal communication ).

## 7.0 Treatment and Prevention

The sheep model of asthma discussed above has demonstrated that commonly used asthma medications (e.g. beta agonists, cromolyn, and steroids), as well as antihistamines and brevenal, can prevent the respiratory effects of subsequent aerosolized brevetoxin exposure. In addition, the beta agonists and brevenal can reverse or treat these effects if given after the brevetoxin exposure (Abraham and Baden 2006; Abraham et al., 2003; Abraham et al., 2004; Abraham et al., 2005a and b; Abraham et al., 2009; Zaias et al., in press). The sheep model is now being used to explore the mechanisms of the cellular response to brevetoxin exposure in the lung, including the possibility that there are additional brevetoxin receptors in addition to those associated with sodium channels. Finally, aside from the effects of Florida red tide aerosols, experiments with brevenal in the sheep model have identified a potentially powerful new pharmacokinetic activity. Specifically, administration of brevenal substantially increased the mucociliary clearance in the lung. Furthermore, the similarities between the response to brevenal and sodium channel blockers in mucus clearance, suggest that brevenal might be a possible candidate to treat other diseases with impaired mucus clearance (such as chronic obstructive lung disease (COPD) or cystic fibrosis) (Clarke et al., 2008; Sabeter et al., 2008; Sabeter et al., 2009; Potera 2007; Raloff 2005).

While there is still much more to learn, we can develop some preliminary public health messages about exposure to Florida red tides. For example, during an active Florida red tide, particularly if the bloom is close to the coast and with a strong onshore wind, asthmatics and others with underlying respiratory diseases should consider staying inland (at least 1–2 miles from the coast) or indoors with the windows shut and air conditioning on (Fleming et al., 2005a; Kirkpatrick et al., 2010). Other research research by Cheng et al., (Y-S Cheng, Lovelace Respiratory Research Institute, personal communication) has demonstrated that inhalation of brevetoxiin-contaminated particles from Florida red tide aerosols can be decreased by up to 45% by using a paper surgical mask. However, it is not known for how long this protective effect lasts, nor is it known if this is a sufficient decrease in exposure to the aerosolized brevetoxins to protect asthmatics and other susceptible persons with compromised lung function.

## 8.0 Economics

There has been considerable interest in quantifying the economic impacts of HABs in general in the US since the work of Hoagland and Anderson which estimated these impacts based on public health, commercial fisheries, recreation and tourism, and monitoring and management effects (Anderson et al., 2000; Hoagland et al, 2002). Since then, as part of a cost-of-illness study, Hoagland et al., (2009) created a model to explore the relationship between *K. brevis* blooms and respiratory illness visits to hospital emergency rooms while controlling for environmental factors, disease, and other factors. The model included data on emergency room visits for respiratory complaints, *K. brevis* cell densities, and measures of pollen, pollutants, community illness (influenza), and intra-annual population changes. *K. brevis* cell counts lagged by 1 week from measurement (as well as low air temperatures, influenza outbreaks, high pollen counts, and tourist visits) were predictive of the number of respiratory-specific emergency room diagnoses. The authors estimated that capitalized estimated marginal costs-of-illness for emergency room respiratory illnesses associated with *K. brevis* blooms in Sarasota County (FL) ranged from $0.5 to $4 million, depending upon bloom severity. Of note, this study did not capture the entire cost of interacting with other components of the medical care system (such as visits to the pharmacy, primary care physicians or specialists, or hospitalizations).

Nierenberg et al., (2010) evaluated lifeguard attendance data during an active Florida red tide bloom. Absenteeism results in significant direct and indirect increased costs to organizations; absenteeism associated with the lifeguards and Florida red tide was significantly increased during an active bloom with costs estimated of $3,000/bloom. The capitalized costs of lifeguard absenteeism were estimated to be up to $100,000 at Sarasota County (Florida) beaches alone. The costs could not be estimated for presenteeism, that is, the cost of people coming to work when they are ill. However, lifeguards reported not only that they experienced adverse health effects from exposure to Florida red tide, but also that they believed their attentiveness and abilities to take preventative actions decreased when they worked during a bloom. The authors noted that this presenteeism could affect beach safety by hampering the abilities of lifeguards to identify and respond to emergency situations.

## 9.0 Monitoring, surveillance, outreach & education

Over the decade, there has been an explosion of outreach and education on Florida red tide, using diverse mechanisms and targeted at a range of populations. Kuhar et al., (2009) investigated the public perception and consequent reactions to Florida red tides among persons living and visiting coastal areas regularly affected by the HABs. Using questionnaire surveys and semi-structured interviews, the researchers explored various perceptions of the risk surrounding red tides along two beaches on the west coast of Florida. Among other findings, the results indicated that coastal residents and tourists may not have efficiently delivered and up-to-date information about Florida red tides and their impacts because of inconsistent public outreach. Nierenberg et al., (in press) further pursued these issues assessing the public knowledge about Florida red tide. Again gaps in public knowledge regarding Florida red tides were identified, even among coastal residents; and preferred information sources for obtaining information on Florida red tide were also identified. Specifically, the biology of Florida red tide blooms, what is and is not safe to ingest (commercial versus recreationally caught), swimming in, and Florida red tide associated human mortalities were found to be inconsistently and incorrectly responded to by both tourists and residents of coastal Florida counties. The informational sources preferred by 80% of tourists and by 53% of residents was the Internet; these participants also looked to Mote Marine Laboratory, the local science organization, the majority of the time (66%), while toll free numbers were rarely (14%) used by tourists.

The Beach Conditions Reporting System (http://coolgate.mote.org/beachconditions/; tel: 1–941-BEACHES) has been set up to collect and report real time data from life guards and beach managers on a range of beach-related issues (including respiratory irritation and dead fish) to the public. The information is accessible through phone or internet. Initiated in Sarasota County (FL), the Beach Conditions Reporting System has now spread throughout the western coast of Florida, with plans to extend this reporting system throughout the Gulf of Mexico (Kirkpatrick et al., 2004b; Kirkpatrick et al., 2008; Nierenberg et al., 2009). The Florida Poison Information Center has created and formally evaluated a 24/7 toll free number (tel: 888 232 8635) on aquatic toxins which allows the caller to access information on a range of aquatic toxin issues including Florida red tide in English and Spanish, as well as speak directly with a trained Florida Poison Information Specialist (Fleming et al., 2007b).

Monitoring information for the Florida red tide organism has become more available through the Florida Fish and Wildlife Commission (http://research.myfwc.com/features/view_article.asp?id=9670), and through the NOAA Gulf of Mexico HAB Bulletin (http://tidesandcurrents.noaa.gov/hab/bulletins.html). The FWC monitoring data are collected by a volunteer network, and report *K. brevis* cell counts

throughout Florida marine waters biweekly. The NOAA HAB Bulletin uses these monitoring data, the Beach Conditions Reporting Data, and satellite remote sensing data incorporated into a wind and current model to identify and predict the location of Florida red tide blooms throughout the Florida coast. Of note, ongoing work by other researchers is also leading to increasingly accurate detection and predictions of Florida red tide blooms. These efforts include creating and making operational an optical phytoplankton discriminator (OPD) also known as the "BreveBuster." The BreveBuster has been installed on a variety of different platforms including fixed buoys and in the payload of autonomous underwater vehicles (AUVs). The Slocum glider (Web Research, Falmouth, MA) AUVs are buoyancy-driven through the water column, and use the OPD to identify blooms. The AUVs surface periodically to send back real-time data via satellite). Other efforts include detecting of *K. brevis* by off-shore portable buoys (again with transmission of real time data by satellite), and improvements in the algorithms used to detect *K. brevis* blooms using remote sensing data (Carvahlo et al., 2010; G Kirkpatrick et al., 2000; Stumpf et al., 2009; Wynne et al., 2005; J Walsh 2006).

The Centers for Disease Control and Prevention (CDC), in collaboration with a range of State Departments of Public Health, has created a unique surveillance system that captures health effects and exposure information for humans and animals, as well as information characterizing the blooms themselves; the system is called the Harmful Algal Bloom-related Illness Surveillance System **(**HABISS) (http://www.cdc.gov/hab/surveillance.htm). This system incorporates data from the National Poison Data System, public health reports, and media reports, as well as environmental monitoring data. Major objectives of this system are to establish baselines for the incidence of the harmful algal bloom-related illnesses (including for Florida red tide), and to identify new occurrences of HABs that cause human and animal exposures and health effects.

Finally, community groups (e.g. Solutions to Avoid Red Tide [START] http://www.start1.com/), health educators, public health managers, and researchers have developed targeted materials to educate various groups about exposure to and health effects from Florida red tide toxins, including: coastal residents and tourists, healthcare providers, and beach managers. The Florida Department of Health has established a fulltime position called the Aquatic Toxins Coordinator. In addition to coordinating surveillance and outreach about HABs, including Florida red tide, the Coordinator has established a model HAB response plan that can be adapted and adopted for all of the Florida County Departments of Health (http://www.myfloridaeh.com/medicine/aquatic/index.html). The Florida Department of Health in conjunction with START, Mote Marine Laboratory, the University of Miami Oceans and Human Health Center, and the Florida Poison Information Center have also created a range of educational materials including: annotated Power Points® presentations and video for healthcare providers and beach managers, (http://www.med.miami.edu/poisoncontrol/x57.xml and http://www.mote.org/niehsredtidestudy/) for tourists and residents. In addition, they have created the START Florida Red Tide Card and traveling Florida Red Tide Exhibit, and Florida red tide beach signage (Figure 1).

## 10.0 Conclusions

This Review of recent developments in Florida red tide research has focused on the potential exposures and subsequent health effects in humans and animals. It has necessarily left out additional exciting basic science and ecology research which is also important and relevant. Nevertheless, the lessons to be learned from this Review include not only the establishment of new and potential exposures and health effects from Florida red tides and their toxins, but also a clear message that the application of new technologies, additional resources, and the

focus of truly interdisciplinary research efforts can lead to remarkable new discoveries and insights in harmful algal bloom research, as well as expanded resources for effected communities in knowledge, outreach and education. Without these interdisciplinary efforts and resources, brevenal would not have been discovered, and a new and important natural product which could treat chronic obstructive pulmonary disease (COPD) and cystic fibrosis, deadly human illnesses, would never have been developed (Fleming et al., 2005a). Furthermore, the issue of actue and subacute respiratory effects after exposure to aerosolized Florida red tide toxin exposure was considered to be anecdotal until formal interdisciplinary epidemiologic research in collaboration with effected coastal residents demonstrated measurable respiratory effects, particularly among asthmatics (Fleming et al., 2007a). One can only imagine the new and important discoveries that can be made by the HAB research community with the application of resources and interdisciplinary research activities in the future.

## Abbreviations

| | |
|---|---|
| **PbTx** | Brevetoxin |
| **cm** | Centimeter |
| **COPD** | chronic obstructive pulmonary disease |
| **ELISA** | Enzyme linked immunosorbent assay |
| **HAB** | Harmful algal bloom |
| **HABISS** | Harmful Algal Bloom-related Illness Surveillance System |
| ***K. brevis*** | *Karenia brevis* |
| **km** | Kilometer |
| **LCMS** | Liquid chromatography mass spectroscopy |
| **mg/m$^3$** | milligram per meter cubed |
| **ug/L** | Microgram per liter |
| **ng/m$^3$** | nanogram per meter cubed |
| **NSP** | Nurotoxic shellfish poisoning |
| **OPD** | Optical phytoplankton discriminator |

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**Figure 1.**

Florida Red Tide Beach Signage (Florida Dept of Health, START, Mote Marine, University of Miami Oceans & Human Health Center, Florida Poison Information Center, and Ms Wendy Stephan MPH)