

# Neurotoxicology of Red Tide Poisoning

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## Editorial

Red Tide poisoning is a result of toxins released from marine dinoflagellates (various algae) and received its name from the discolored (reddish) water created by an algal bloom. It appears this event has occurred for centuries in many locations even before the occurrence of pollution, agricultural run-off and current observations of global warming. There were reports of the Red Tide in Florida during the 1800's [1, 2]. However, historical reports indicate that the Red Tide occurred throughout history with an observation noted as early as 1528 in the Gulf of Mexico; although, the first "verifiable" event was in 1648 [2, 3]. The Red Tide occurs throughout tropical waters of the world [4]. In the United States the predominant region is Florida, mostly in the Gulf of Mexico; but events have been noted in the Atlantic and Pacific Oceans. Periodically, there have also been occurrences off the Texas coast [2]. Other locations of notable interest where events occur include Scotland and the South Pacific (e.g. Australia), indicating harmful algal events can occur in northern locations and are likely experiencing an expanding geography due to global warming. There is an increasing frequency of Red Tide phenomena throughout the world with temperature and pollution being indicated as the contributing factors [2].

The most common dinoflagellate responsible for the Red Tide is *Karenia brevis*; although, there are a number of other species of algae (e.g. *Karenia papillonacea*, *Chattonella* species, *Fibrocapsa japonica*) having been reported to produce toxins associated with this event [4-6]. These toxins generated by the marine dinoflagellates are brevetoxins (PbTx's), with two primary structural forms (backbone A and B) [4]. Fundamentally, these toxins result in three different types of events (a) fish kills (harm to wildlife), (b) toxicity from ingestion of an organism accumulating the toxin and (c) inhalation toxicity [2, 4]. For man, Red Tide events are due to harmful algal blooms (HAB) that result from high numbers of a species of algae producing a toxin that usually accumulates in another organism (filter feeders), which is frequently shellfish. It has been estimated that 60,000 human toxicity cases occur a year worldwide with a mortality rate of about 0.15% for PbTx [7]. Generally, toxins from these dinoflagellates function as either neurotoxins or hemolytic agents [6, 8]. There have been reports of this alga also producing immune-toxicity, cardiotoxic and anti-cholinesterase phosphorus-containing agents [8, 9]. Brevetoxins have been implicated in harmful effects to various marine organisms (e.g. fish, dolphins, manatees) as well as wide-spread inhalation toxicity to humans near the seashore [10-12].

Brevetoxins are tasteless, lipid soluble, and both heat and acid stable that cause (depolarization) opening of sodium voltage

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gated ion channels. These toxins have a molecular weight of about 900 [8]. Due to their lipid solubility, brevetoxins can cross the blood-brain barrier, are easily absorbed into the body, and exhibit wide spread distribution with primary metabolism in the liver. These characteristics suggest a one-compartment model. Excretion occurs through bile and to minor extent urine [4]. Disruption of sodium channels causes an inward flow of sodium ions and is the primary cause for neurotoxic shellfish poisoning (NSP). Disruption of sodium channels cause dysfunction of the respiratory and cardiac system due to spontaneous firing (uncontrolled sodium influx) [8]. There may also be inhibition of calcium related pathways in neurons resulting in disruption of calcium homeostasis [13]. For respiratory effects, there appears to be involvement of mast cells (degranulation) which can result in the release of histamine causing bronchoconstriction. These findings are supported by animal studies (e.g. sheep, guinea pigs) where increased airway resistance has been observed yet could be blocked by cromolyn and a histamine H1 antagonist [6, 8]. This, in part, explains respiratory symptoms associated with exposure to this alga. As for many toxins, brevetoxin metabolites

may have greater potency than the parent product with likely biotransformation occurring through the P450 system [8]. Brevetoxins are difficult to detect in the laboratory and cannot be removed from food products.

Over 10 different brevetoxins have been isolated along with an antagonist, brevenal [14, 15]. Brevenal may be the first antagonist produced by an organism directed toward its own toxin. It has been reported that the concentration of brevetoxin in water during a Red Tide event is 5-10 ug/L with particles of toxin being 6.7  $\mu\text{m}$  (mass median aerodynamic diameter) [16]. Respiratory symptoms have been reported for airborne brevetoxins in the range of 3-4  $\text{ng}/\text{m}^3$ ; although, much higher concentrations have been observed (21-39  $\text{mg}/\text{m}^3$ ) [15-17]. However, even when there was no Red Tide event occurring, airborne levels in the range of 1 to 49  $\text{ng}/\text{m}^3$  have been recorded, with some reporting respiratory symptoms [15]. Since *K. brevis* is an unarmored dinoflagellate wave action can fracture the organism releasing toxins. This results in sea spray, droplets and salt particles containing toxins, especially during blooms [16, 17].

Human exposure to brevetoxin occurs either through inhalation or ingestion of contaminated shellfish (molluscs) which results in NSF [1, 4, 17]. Characteristics of NSF include gastrointestinal issues, diarrhea, nausea, abdominal distress loss of motor control, ataxia, paresthesia, vertigo, and muscle pain [4, 6, 8]. Symptoms occur in about 3 h; although a range of 15 min to 18 h have been reported [4]. In severe cases, seizures, convulsions, tachycardia and partial paralysis have been observed [4]. In general, symptoms are usually mild and either not reported or misdiagnosed. A NSF event can last a few days from consumption of contaminated sources (e.g. clams, mussels, coquinas or other types of filter feeders) [8]. In most cases multiple symptoms are reported.

The first report of an association with respiratory disease and the

Red Tide was made in 1917. However, there are other algae that can cause similar symptoms (*Trichodesmium*), but are generally not observed in the Gulf of Mexico [2]. Commonly inhalation can result in rapid occurrence of chest tightening, bronchoconstriction, congestion, eye and respiratory irritation, but usually wains when leaving the seashore area [8, 18].

There is a report of respiratory effects occurring from the Red Tide by personnel conducting dredging of a marine channel in Florida [19]. Around this time period a fish kill was observed along with a high level of *K. brevis* ( $\geq 1,000,000$  cells/L). A study by Mendoza et al. [20] reported brevetoxin exists in sediment and these levels may increase after blooms occur. From this information, it is possible that sediment and sand could be a potential source of brevetoxins with exposure occurring from contact along with aerosolization of particles. This investigation supports another occupational concern involving Lifeguards where a decreased respiratory function (upper airway) was observed in those exposed to aerosolized brevetoxins [21]. In a study of asthmatics, decreased airway function was observed after exposure to *K. brevis* [22]. A case study [23] indicated those with chronic pulmonary problems may be at an increased risk from exposure to brevetoxins resulting in significant changes in spirometry. Such reports indicate these toxins, and possibly others from HAB, may have stronger immunological consequences than indicated in the literature. These studies together indicate that recreational beachgoers may experience respiratory problems when exposed to aerosols containing brevetoxin or *K. brevis* [8]. During Red Tide events there has been a report of increased rates of pneumonia among coastal residents [24]. Reports of this nature suggest Red Tide events, and toxins associated with them, may have a much greater health effect on local populations than previously considered. This makes brevetoxin not only an important issue related to food poisoning but an environmental and occupational hazard as well.

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