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TOXICOLOGICAL ASSESSMENT OF CYANOBACTERIAL TOXINS

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ABSTRACT
Input of phosphorous and nitrogen into the lakes from the domestic and agriculture sector accelerates the process of eutrophication. The process of eutrophication results in luxuriant growth of standing crop as a consequence of increased input of mineral nutrients. In eutrophied water bodies excessive growth of cyanobacteria occurs and the health risk effects, generated by cyanobacterial toxins in drinking water, are now established. Cyanobacteria produce various types of cyanotoxins such as hepatotoxins, neurotoxins, dermatotoxins, endotoxins, embryotoxins and peptide toxins. Some algae produce an organic compound which reacts with chlorine to form organohalides which is carcinogenic and other potent toxins which are responsible for numerous health related problems. Changes in cyanobacterial community due to environmental factors and toxicity in enhancing the mortality of starved zooplankton and animals are also documented. The protection of health of general population and productivity of lake waters from the adverse effects of cyanotoxin needs immediate attention.

INTRODUCTION

Cyanobacteria are now recognized as a serious water quality problem with regard to both drinking water supply and recreational water use. The deterioration of our water resources through poor land and catchments management, water pollution and water allocation practices, is now better understood and acknowledged. Algal blooms are often a symptom of the resulting changes in water quality of lakes. The conditions which favour the growth of cyanobacteria and lead to blooms are nutrient enrichment (largely phosphorus but also nitrogen), warm temperatures, and calm stable water conditions such as those occurring in slow-flowing rivers and thermally stratified lakes. These conditions are often caused by human actions and activities, but can often be equally associated with natural climatic cycles (Burch and Humpage, 2005). Cyanobacteria are a common and natural component of most water ecosystems. Mass development of cyanobacteria closely correlates with eutrophication of water. The development of cyanobacterial water blooms in lakes decreases water quality from view point of water management, hygiene and fishery.

Cyanobacteria can produce and incidentally release into their environment substances having a biological activity such as enzymes, vitamins, toxins, extracellular polysaccharides, attractants, amino acids and other organic acids, antibiotics and hormones. Carmichael, (1992) divided the cyanotoxins according to methods of detection into cytotoxins and biotoxins. The biotoxins may be classified according to their biological activities as neurotoxins, hepatotoxins, cytotoxins, genotoxins, immunotoxins and embryotoxins. Cyanobacteria, popularly known as blue green algae, are well known to produce a variety of biotoxins, which are toxic to aquatic biota such as fish and also to wild life and human (Jochimsen *et al.,* 1998). The biotoxins can reach the human through drinking water and food chain contaminants. Toxic cyanobacteria found in eutrophic municipal and residential water supplies are an increasing environmental hazard in several parts of world. The toxins produced by cyanobacteria include alkaloid neurotoxins and peptide hepatotoxic viz. microcystins and nodularins and are water soluble and temperature stable. Since these organisms occurs in both in recreational and drinking water lakes and rivers, and are known to be strong liver tumor promoters, they present a health hazard to a human populations (Gopal, 2007).

Environmental influences on cyanobacterial growth and toxicity

Pelechata *et al*. (2006) studied the water samples of the Lubuskie lakes (Mid Western Poland) recorded 73 taxa of cyanoprokaryota and found that water blooms were caused by *Planktothrix agardhii*, *Anabaena flos-aquae*, and *Pseudonabaena limnetica*. The genus *Anabaena* represented the highest number of species. TN/TP ratio plays an important role in cyanobacterial dominance. Smith, (1983) reported that bloom forming cyanobacteria tended to dominate in lakes where the TN/TP ratio was less than 29. Ke *et al.,* (2008) observed that cyanobacteria were mainly promoted by increased temperature and decreased concentrations of nitrogen compounds in lake Taihu (China). Xie *et al.,* (2003) indicated that low TN/TP is not a cause but rather a result of *Microcystis* blooms, which may indirectly enhance the release of phosphorous from sediment. Smith, (1983) reported that total N: P ratio (TN:TP) of 29:1 differentiates between lakes with cyanobacteria dominance (TN:TP < 29:1) and lakes without such dominance (TN: TP > 29:1). It is generally agreed

upon that the N:P ratio is an important determinant of the species composition of phytoplankton assemblages. Forsberg and Ryding, (1980) was found in Swedish waste receiving lake at N:P ratio below 10:1, nitrogen is found to limit algal growth, whereas for ratios above 17:1, phosphorous is the most growth-limiting nutrient. In the range between 10:1 and 17:1, one or both of these elements limits the growth of algae. Flett *et al.,* (1980) showed that N_2 fixing cyanoprokaryotes such as *Anabaena* or *Aphanizomennon* dominated in lakes with N:P ratio less than 10:1.

Parikh *et al*. (2006) collected water samples from Vatva industrial areas in Gujarat were found to contain varied composition of cyanobacterial species. Twelve species from 7 genera viz. *Chroococcus*, *Gloeothece*, *Gloeocapsa*, *Dermocarpa*, *Oscillatoria*, *Phormidium* and *Nostoc* were observed. Ankleshwar industrial estate recorded only 9 cyanobacterial species from 6 genera (*Chroococcus*, *Synechocystis*, *Oscillatoria*, *Phormidium*, *Lyngbya* and *Spirulina*). Atul industrial estate is comparatively richer with 19 species recorded from 10 genera belonging to 4 families. Mishra *et al*. (2009) observed that Chlorophyll-a concentration remained scattered through out the study period showing the exceptionally high concentration during monsoon. Lehman, (1981) have shown that the ratios of chl-a/chl-b vary significantly with changes in species composition, while chl-a/carotenoid ratio also serves as an indicator of phytoplankton standing crop. The average transparency value during rainy and post rainy seasons were 134.4 cm and 139.7 cm, high transparency values were also indicative of low primary productivity (Prakasam and Joseph, 2000). It is important to mention here that high pH is partly the result of high density of cyanobacteria, which further enhances their dominance in Steilacoom lake, Washington (Jacoby *et al.,* 2000). Shapiro, (1997) pointed out that high pH or low concentration of free CO_2 during July to December; in the lake water were not the factors stimulating growth of cyanobacteria. Gupta *et al*. (2006) reported in lake Nainital Uttaranchal, India that the high pH, low concentration of CO_2, high concentration of dissolves oxygen, NH_4-N and NO_3-N, and low concentrations of PO_4-P, Fe and Zn favours growth of cyanobacterial community.

Effect of light and temperature on cyanobacterial growth

The major factor influencing *Cylindrospermopsis raciborskii* populations seems to be temperature, while it can survive perennially in tropical areas (Briand *et al.,* 2004). It seems to be limited to warm summer months in temperate regions (Saker *et al.,* 2003). *C. raciborskii* tends to favour surface water temperatures over 25ºC (Saker and Griffiths, 2001; McGregor and Fabbro, 2000). In cultures, the optimum temperature seems to be 30ºC with a range of sub-optimum temperatures from 25-35ºC (Briand *et al.,* 2004; Shafik *et al.,* 2001). A study showed that there is an exponential correlation between algal growth rate and light intensity. The saturating and semi-saturating light values for *Cryptomonas* sp. cells are 150 and 47 *i* mol photons m^{-2} s^{-1}, respectively. More uptakes of Fe, P, and other trace elements such as Zn, Mn, Co, and Mo are observed in the low light cultures, although the algal growth rates are slow. The growth rate at 10 *i* mol photons m^{-2} s^{-1} is only 10% of that at 150 *i* mol photons m^{-2} s^{-1}, whereas Fe and P uptake increases by 150 and 100%, respectively. The above results of Weng *et al*. (2009) suggested potential implications of differentiation in absorption of iron and phosphorus at different light intensities for the occurrence of harmful algal blooms.

According to Carmichael *et al.,* (1990) toxicity from cyanobacteria has been reported since the late 19th century, mostly from poisonings in freshwater environments. Animals are more prone to algal poisonings because they are not deterred by foul taste, odours, or surface scums. Human exposure usually occurs through direct contact or accidental uptake via swelling or aspiring cells. The toxins may bioaccumulate in fresh water crustaceans, and in shellfish also (Saker *et al.,* 2004). Codd *et al*. (1999) reported several cases of lethal poisoning of human, livestock, wild life and fishes and that have been correlated with exposure to water contaminated with cyanobacteria. Toxic cyanobacteria are also known to affect profoundly both zooplankton community structure (Christoffersen, 1996a) and secondary production (Christoffersen, 1996b). However, cyanobacteria are poorly utilized as food by zooplankton because of endotoxins, and other inhibitors (Jakobi *et al.,* 1996).

Agrawal *et al.,* (2001) observed that the production of protease inhibitors by cyanobacteria is a factor responsible for feeding inhibition and mortality in zooplankton. In San Francisco Bay Estuary in California Lehman *et al.,* (2005) found that microcystins from the bloom entered the food web and were present in both total zooplankton and clam tissue. Initial laboratory feeding tests suggested the cyanobacteria were not consumed by the adult copepod *Eurytemora affinis,* an important fishery food source in the estuary. *M. aeruginosa* blooms impact recreation through direct contact and ingestion that can cause skin and eye irritation, hay fever symptoms, dizziness, fatigue and stomach upset (Carmichael, 1995). Magalhaes *et al*. (2003) reported in Sepetiba Bay in Brazil that the sport fishing is an important economic resource and could be impacted because of the health risk associated with ingestion of concentrated microcystins in animal tissue caused by bioaccumulation. If mucilaginous algae fail to avoid ingestion, they may yet resist digestion during the period of their passage through the consumer's gut (Porter, 1976).

Cyanobaterial toxins

Microcystins

Microcystins (Fig. 1) in water are cyclic heptapeptide (Contain seven peptide-linked amino acids) with the general structure of cyclo-(D-alanine[1]-X[2]-D-MeAsp[3]-Z[4]-Adda[5]-D-glutamate[6]-Mdha[7]) in which X and Z are variable L amino acids, D-MeAsp is D-erythro-*â*-Methylaspartic acid, and Mdha is N-methyldehydroalanine. The amino acid Adda, (2S,3S,8S,9S)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid, is the most unusual structure in this group of cyanobacterial cyclic peptide toxin (Sivonen and Jones, 1999). Annila *et al*. (1996) found that the microcystin toxicity in mammalian is mediated through their strong binding to key cellular enzymes called protein phosphatase. In solution, microcystins adopt a chemical shape that is similar, especially in the Adda-glutamate part of the cyanotoxin molecule. Chen *et al*. (2009) reported that the hepatotoxic microcystin are most common cyatotoxins in eutrophic fresh water. In 1996,

human intoxications by microcystins caused death of 76 patients at Caruaru dialysis center in Brazil. Falconer and Humpage, (2005) observed that cyanobacterial toxins families that have been internationally assessed for health risk by the WHO are the microcystins which caused acute liver injury and are active tumor promoters. The provisional guideline level of microcystin-LR for drinking water of 1 μg/L. Wilson *et al*. (2005) observed ninety-one percent of the 53 genetically unique *M. aeroginosa* clones contained the microcystin toxin gene (mcyA) most clones being distantly related to clone collected from lakes directly attached to lake Michigan (a Laurentian Great lake) and culture collection stains collected from Canada, Scotland and S. Africa. Matsunaga *et al*. (1999) reported that a bloom of *M. aeruginosa* was evident in September of that year and some 20 ducks died at the site; Oo-ike pond, in Japan 1995. Necropsy of one of the affected ducks showed a liver that was necrotic and severely jaundices. Skulberg *et al*. (1993) studied more than 40 species belong to *Nostoc* genus but only four toxigenic species *Nostoc linkia, Nostoc paludosum, Nostoc rivulare* and *Nostoc zetteresteditii*, were reported. Freshwater and terrestrial *Nostoc* may produce cytotoxins and other bioactive compounds (Trimurtulu *et al.,* 1995; Todorova and Juttner, 1996). The toxicity of several microcystin variants determined by Rinehart *et al*. (1994) by intraperitoneal (i.p.) mice bioassay ranged from 50 to >1,200 *ì* g kg^{-1} body weight. The survival time was estimated to be from 2-5 hr, and the calculated i.p. LD_{50} in mice ranged from 15 to 125 mg kg^{-1} body weight, liver damage with extensive haemorrhage necrosis and sinusoid capillary destruction, which showed the hepatotoxicity (Oudra *et al.,* 2009). Rodger *et al.,* (1994) described that the histopathological changes of brown trout (*Salmo trutta*) associated with the death of water blooms of *Anabaena flos-aquae*. The changes in liver were characterized by confluent necrosis showing cellular degeneration and loss of obvious cell boundaries. In lake Pamvotis (Greece) Kagalou *et al.,* (2008) observed that the accumulation of microcystins in fish tissue of *C. gibelio*. Even though the target organ for microcystins is the liver, microcystins were found also in the rest of *C. gibelio* tissues in the following order: intestine> kidney> brain>gonads> muscle. Muscle tissue contained concentrations of microcystins that correspond to 0.096 *ì* g/kg/day well above the recommended limit for human consumption (0.04 *ì* g/kg/day). According to Northcott *et al*. (1991) the cyanobacteria are regular components of the cyprinid diet and it is known to feed on non-toxic strains of *M. aeruginosa* in field conditions. Beveridge *et al*. (1993) showed suppression in filtration rate and growth of two species, *H. molitrix* and *O. niloticus*, in the presence of toxic *M. aeruginosa*. Picanco *et al*. (2004) studied the intravenous exposure to microcystins and can represent a risk to the lungs in addition to the known targets, *i.e.,* liver and kidney. Thus, whenever human health depends on the quality of water for direct consumption and recreational or medical use, such as dialysis treatment, the increase of cyanobacterial blooms producing microcystins in the water supplies ought to be carefully considered. Cyanobacterial hepatotoxin which target the liver due to specific binding organic anion transport system in hepatocyte cell membranes, have been implicated in the deaths of birds, wild animals, agricultural livestock and fish, and have been responsible for human illness and death, reported from India, China, Australia and Brazil (Kaebernick and Neilan, 2001). Microcystin-LR has been characterized from planktonic *Anabaena, Microcystis*, *Oscillatoria, Nostoc* and *AnabaenopsisI* species, and from terrestrial *Hapalosiphon* genera.

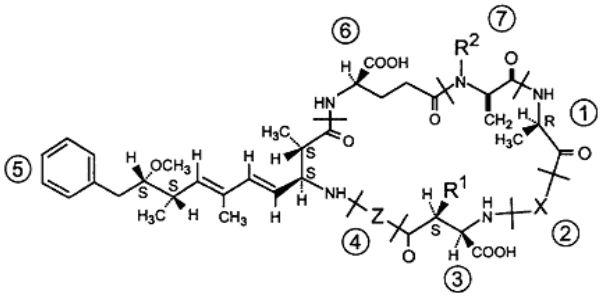

Figure 1: Chemical structures of Microcystins (Briand *et al.,* 2003) (X and Z are variable amino acids, R = H or CH3)

Nodularin

The toxin produced by *Nodularia spumigena* is a pentapeptide nodularin, cyclo-(D-MeAsp-L-arginine-Adda-D-glutamate-Mdhb). D-MeAsp is D-erythro-*â*-methylaspartic acid, Mdhb is 2(methylamino)-2-dehydrobutyric acid and Adda is (2S,3S,8S,9S)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid, an amino acid is found in cyanobacterial toxins (Rinehart *et al.,* 1988; Sivonen *et al.,* 1989). Nodularin is produced nonribosomally by the nodularin synthetase enzyme complex, which is encoded by the 48-kb nodularinsynthetase genes *ndaA* to *ndaI* (Moffitt and Neilan**,** 2004). (Mazur and Plinski, 2003) noticed that *N. spumigena* forms extensive blooms in summer in Baltic Sea. A high concentrations toxin in recreational waters of the Gulf of Gdansk constitutes a health risk in bathing areas. Benthic species *N. spumigena* may produce toxins causing severe dermatitis among swimmers. Fujiki *et al*. (1990) reported that the inflammatory activity of Nodularin (Fig. 2) causes aplysiatoxins and debromoaplysiatoxin which are tumor promoters and protein kinase C activators. Koskenniemi *et al.,* (2007) developed a specific quantitative real time PCR method for the quantification of hepatotoxic nodularin from *Nodularia*. Specific PCR primers were designed for subunit F of the nodularin synthetase gene (*ndaF*), which encodes the *ndaF* subunit of the nodularin synthetase gene complex needed for nodularin production.

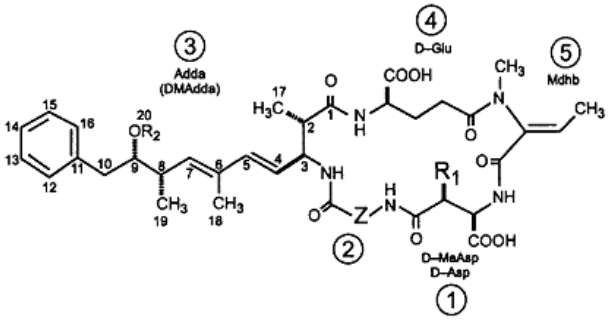

Figure 2: Chemical structures of Nodularins (Briand *et al.,* 2003) (X and Z are variable amino acids, R = H or CH3)

Table 1: Cyanobacterial toxins and general features (Metting and Pyne, 1986; Chorus and Bartram, 1999; Falconer *et al.,* 1999; Chorus, 2000)

Cyanobacterium	Toxin(s)	Structure	Primary target organ in mammals	Mechanism of action
Microcystis aeruginosa, Oscillatoria, Planktothrix Anabaena, Nostoc	Microcystin	Cyclic peptide	Liver	Inhibition of protein phosphatase, tumorpromoting activity and liver hemorrhage
	Microcystis-type-c	Peptide	Liver	
	2-Microcystin-like-toxins, Microcystin-like	Peptides, Peptide	Liver	
Nodularia spumigena	Nodularin	Peptides	Liver	Inhibition of protein synthesis
Cylindrospermopsisraciborskii	Cylindrospermopsins	Alkaloids	Liver	Inhibition of protein synthesis, affecting liver, kidney and lungs
Aphanizomenon flos-aquae, Planktothrix Fasciculation, Anabaena flos-aquae	Aphantoxins	Alkaloids		Decreased movement, abdominal breathing, respiratory failureBlocking post synaptic depolarizeAction
	Neosaxitoxin	Alkaloids	Nerve axons	
	Saxitoxin	Alkaloids	Nerve axons	
	Anatoxin-a	Alkaloids	Nerve synapse	
	Anatoxin-b	Alkaloids	Nerve synapse	
	Anatoxin-c	Alkaloids	Nerve synapse	
Schizothrix calcicola,	Aplysiatoxins	Alkyl phenols	Skin	Protein kinase C.
Lyngbya gracilis L .majuscule,	Debromoaplysiatoxin	Alkyl phenols	Skin, gastrointestinal tract	Activators, inflammatory
Oscillatoria nigroviridis,	Debromoaplysiatoxin	Alkyl phenols	Skin, gastrointestinal tract	activity
Nostoc muscorum,				
Calothrix crustacean,				
S. muscorum	Lygbyatoxin	?	Skin, gastrointestinal tract	
	Aplysiatoxin	Alkyl phenols	Skin	
All	Lipopolysaccharides (LPS)	Alkaloids	Potential irritant: affect any exposed tissue	Potential irritant, Allergen

Cylindrospermopsin

The toxin is a stable tricyclic alkaloid containing a guanido group linked at C7 to hydroxymethyl uracil at the hydroxyl bridge; there are two possible epimers, cylindrospermopsin and 7-epicylindrospermopsin both occur naturally and are equal by toxic (Banker *et al.,* 2001). Cylindrospermopsin is toxic because negatively charged sulphate group and positively charged guanido group, the molecule is a zwitterion and water soluble. The structural formula has been verified by total synthesis (White and Hansen, 2005). Cylindrospermopsin (Fig. 3) is an alkaloid toxin that has been isolated from three species of cyanobacteria *C. raciborskii* (Ohtani *et al.,* 1992), *Aphanizomenon ovalisporum* and *Anabaena bergii* (Stuken *et al.,* 2009). Griffiths and Saker, (2003) reported that cylindrospermopsin is produced by *Anabaena bergii, Aphanizomenon ovalisporum, Raphidiopsis, Umezakia natans,* and *C. raciborskii*. *C. raciborskii* is able to produce a wide range of toxin such as cylindrospermopsin in Senegal lake Guiers, West Africa (Berger *et al.,* 2006). *C. raciborskii* is able to produce a wide range of toxin such as cylindrospermopsin in Australia (Saker and Griffiths, 2000), in U.S.A (Carmichael, 2002), and in Asia (Chonudomkul *et al.,* 2004). Mikolaj *et al.* (2009) studied that the concentration of cylindrospermopsin in shallow, eutrophic lake of Western Poland were in the range of 0.16-1.8 μg/L, and involved in triggering illness of human and animals. Cylindrospermopsin potently inhibits protein synthesis (Terao *et al.,* 1994; Froscio *et al.,* 2003). Falconer *et al.* (1999) studied the cyanobacterium which is highly toxic through both oral consumption and injection of cylindrospermopsin and results into kidney damage. Chorus *et al.* (2000) reported that the clinical symptoms of poisoning of cylindrospermopsin are kidney and liver failure and damage to the spleen, heart, intestine and thymus. *C. raciborskii* may produce unknown toxins in addition to the characterized hepatotoxin cylindrospermopsin (Hawkins *et al.,* 1997). The hepatotoxin cylindrospermopsin, a sulfated-guanidinium alkaloid with substituted dioxypyrimidine (Uracil) moiety and Reisner *et al.,* (2004) suggested that the uracil moiety is crucial for the toxicity and that such toxicity could partly stem from competitive binding of the toxin to a catalytic site(s) involved in the synthesis of pyrimidine nucleotides. According to Mankiewicz *et al.,* (2003) cylindrospermopsin is more dangerous because clinical symptoms may become manifest several days after exposure. In the case of cattle death in Australia in 2001, histopathology showed hepatocyte degeneration and necrosis, nephrosis and multifocal cardiomyopathy. Farm water samples, rumen contents, liver, kidney and muscle were analyzed by HPLC tandem mass spectrometry for cylindrospermopsin, which was found in all samples except muscle. Shaw *et al.* (2004) reported that water and rumen samples contained cylindrospermopsin concentrations in excess of 1 mg/L. Norris *et al.* (2002) suggested that activation of cylindrospermopsin by cytochrome P_{450} is of primary importance in mechanism of action. The nucleotide structure of cylindrospermopsin and the presence of potentially reactive guanidine and sulphate groups suggested that the toxin may exert its effect through an interaction with DNA or RNA covalent

binding of cylindrospermopsin or its metabolites to DNA has been reported in treated mice (Shaw *et al.,* 2000).

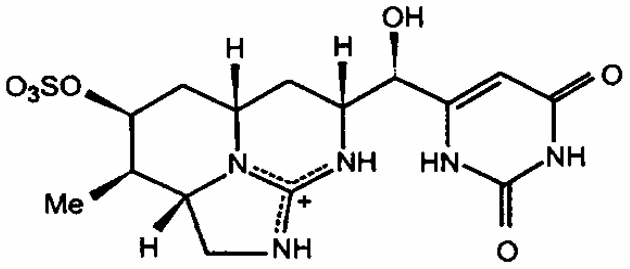

Figure 3: Cylindrospermopsin http://www. cyanobacteriaplatform. com/Material/ Cylindrospermopsin.gif

Neurotoxins

Chorus and Bartram, (1999) have described that the four groups of cyanobacterial neurotoxins: anatoxin-a, anatoxin-a(s), Saxitoxin (Fig. 4) and neosaxitoxin. Anatoxin-a have been reported by Gugger *et al.,* (2005) in French waters, and causative organism identified as *Phormidium* species responsible for neurotoxic signs in 37 dogs (with 26 deaths) in 2002 and 2003 in the South France ponds. Puschner *et al.* (2008) have been reported that anatoxin-a, is a potent neurotoxin. Ingestion of water contaminated with the toxin results in acute neurological signs and death. Of all samples of *A. circinalis* analyzed from the Murray-Darling basin, none contained anatoxin-a, and Velzeboer *et al.* (2000) concluded that symptoms of neurotoxicity precluded the presence of anatoxin-a(s). The neurotoxin including the C-toxins and gonyautoxins involved in paralytic shellfish poisoning (PSP) and consequently classified as PSPs. These toxins, which inhibit, the enzyme acetylcholinesterase the biomolecular reaction occurs with formation of enzyme anatoxin-a(s) complex, which results in phosphorylation of the enzyme. The toxins produced by *Dinoflagellate* species, *Alexandrium* spp, *Gymnodinium catenatum*, *Pyrodinium bahamense* as toxic "red tide" events (Carmichael, 1994; Singh *et al.*, 1999). In fresh water reservoir in southern Brazil Yunes *et al.* (2003) studied that the bloom of *Cylindrospermopsis raciborskii* and *Anabaena spiroids* were identified and able to produce neurotoxic compound known as anatoxin-a(s). According to Katircioglu *et al.,* (2004) anatoxin-a ($C_{10}H_{15}NO$) (Mw = 165) and anatoxin-a(s) ($C.H.N_4O_4P$) inhibit transmissions at the neuromuscular junction by molecular mimicry of the neurotransmitter acetylcholine and inhibition of acetylcholinesterase activity respectively. Oshima, (1995) observed that the PPTs (Paralytic Shellfish Toxins) are basically constituted of a tetrahydropurine, with more than 26 structures. They can be classified in three groups according to the net charge; at neutral pH: (a) N-sulfocarbamoyl-11-hydroxysulphate toxins (C-toxins) with a net charge of 0, (b) gonyautoxins (GTXs), with net charge of + 1, and (c) saxitoxin (STXs) group with net charge of + 2. PPTs are neurotoxins that block the sodium voltage-gated channels of excitable cells impending neuronal transmission (Strichartz, 1984). According to Kao, (1993) the neurotoxic saxitoxins or paralytic shellfish poisons (PSPs) are one of a number of groups of toxins produced by *dinoflagellates* in the marine environment. Shellfish feeding on toxic *dinoflagellates* can themselves become toxic and hazardous if consumed, even causing human illness and mortality. Poisoning incidents usually coincide with the sudden proliferation of these organisms to produce visible blooms, the so-called 'red tides' (Anderson, 1994). Saxitoxins have now also been found to be responsible for neurotoxicity in three cyanobacterial species *Aphanizomenon flos-aquae* (Ferreira *et al.,* 2001), *Lyngbya wollei* (Carmichael *et al.,* 1997) and *Cylindrospermopsis raciborskii* (Lagos *et al.,* 1999). According to Kaas and Henriksen, (2000) saxitoxins in Danish lakes appear to be produced by *Anabaena lemmermannii*. Llewellyn *et al.* (2001) studied that saxitoxin given in high doses to human and animals, it shatter the normal signaling between nerve and muscle and can caused death by respiratory paralysis. Duy *et al.* (2000) found that the effects of neosaxitoxins or saxitoxins can lead to death by respiratory arrest. Banack *et al.* (2007) found that the *Nostoc* may produced neurotoxic non-protein amino acid *â*-Methylamino-L-alanine (BMAA), which can accumulate in increasing level within food chain and at low concentrations causes the death of motor neurons or trigger motor neuron disease.

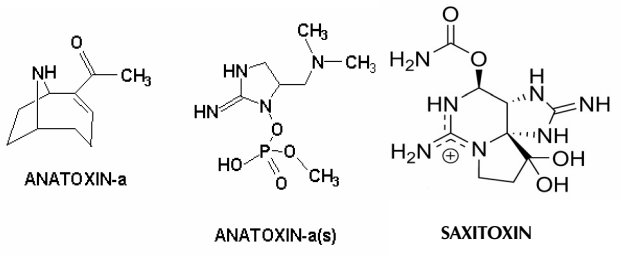

Figure 4: Neurotoxins http://www.asanltr.com/newsletter/02-2/articles/ http://upload.wikimedia.org/wikipedia/commons/9/95/ Saxitoxin.png

Effects on Enzyme and Protein Synthesis

In a study conducted by Masten and Carson, (2000) it was found that cylindospermopsin severely depleted glutathione (GSH) *in vivo* in mouse bioassays. A dose and time dependent inhibition of GSH synthesis was observed *in vitro* in rat hepatocyte incubated with cylindospermopsin. In all cases, the decrease in GSH preceded signs of toxicity in the cells as determined by lactate dehydrogenase release. There was also a significant decrease in hepatic P_{450} of mice dosed with cylindospermopsin when compare to controls. Cylindospermopsin completely inhibited globin synthesis in a rabbit reticulocyte cell-free *in vitro* system. According to Chorus and Bartram, (1999) cyanotoxins contains three broad groups of chemical structure: cyclic peptides, alkaloids and lipopolysaccharides (LPS). In (Table 1) there are specific toxic substances within these broad groups that have been identified to different genera of cyanobacteria, together with their primary target organs and mechanism of action in humans and animals.

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