*NOU J. Sc. & Tech.* Vol. 3 & 4 (I) : 62-73, 2015

# Phycotoxin- a threat to aquatic life and human health

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## Abstract

Throughout the world observations of several algal species producing toxins are being reported with increasing frequency. Often, these events are accompanied by severe impacts to aquatic life, local economies, and public health. Their presence and persistence represent a significant and expanding threat to aquatic life and human health. Some of these toxins have direct and deleterious effects on local plants and animals; others have indirect affects on organisms by changing local environmental conditions. Symptoms of exposure to these toxins include gastrointestinal, neurological, cardiovascular, and hepatological symptoms. The algae that produce these toxins, and the specific symptoms they cause, are summarized here. A significant proportion of algae and cyanobacteria produce such potent toxins. If water containing high concentrations of toxic algae and cyanobacteria or their toxins is ingested (in drinking water or accidentally during recreation), they pose potential threat to human health. In discussing the problems arising from phycotoxins a fatalistic attitude is commonly adopted in which it is stated that the toxins will always be with us and that the simplest and most successful course would be to learn how to manage around the toxins.

**Key words:** Algae, Cyanobacteria, Metabolites, Phycotoxin, Toxin

## Introduction

Algae are considered an important biological organisms. They are the source of oxygen and the first ring of the food chains in aquatic systems. Algae range from small, single-celled organisms to multi-cellular organisms, some with fairly complex and differentiated form. Like plants, algae require primarily three components to grow: sunlight, carbon-dioxide and water. Algae are small photosynthetic organisms found in almost every environment on Earth, even in desert sand. Most people are familiar with aquatic algae, those found in rivers, lakes and streams. Algae are an important source of food for many organisms and also produce oxygen. Under the right conditions, such as high nutrients and sunlight, algae can grow rapidly and "bloom". Algal blooms often accumulate on the surface of water bodies, giving the water a green, brown, or red appearance. They are a vital part of the aquatic ecosystem providing food and shelter to other organisms. They play a crucial role in the ability of an aquatic ecosystem to absorb nutrients and heavy metals [1]. Algae are a large and diverse group of organisms from which a wide range of secondary metabolites have been isolated. Marine and freshwater algae are recognised to produce a diverse array of toxic bioactive metabolites.A number of these compounds possess biological activity such as toxicity, antibacterial, antifungal, antiviral, and antitumor and activities [2].

Algal toxins are organic molecules pro-duced by a variety of algae in marine, brackish and freshwater as well as on wet soils [3]. These toxic metabolites are globally widespread, and humans and other animals can be exposed to them through both direct routes, including contamination of drinking water and recreational exposure, and indirect routes, including accumulation of these toxins by (and consequent contamination of) various species of fish, shellfish and other animals used as food. According to the produced effects, the species involved in outbreaks of toxic algal blooms can be distinguished in three main groups [4]:

• 1st group:-Species that cause water colouration only, resulting in a decrease of the water transparency, and which may exceptionally grow causing some episodes of fish and invertebrate mortality, related to oxygen consumption during their decomposition [4]. Species of dinoflagellates and diatoms belong to this group

• 2nd group:-Species which produce powerful toxins that accumulate along the trophic web and can cause effects in upper consumers (animals and humans); dinoflagellates belonging to Alexandrium, Gymnodinium, Dinophysis, Prorocentrum and diatoms belonging to the genus Pseudo-nitzschia are included in this group [4].

• 3rd group:-Species that are not toxic to humans but are noxious to fish and invertebrates (*i.e. Gyrodinium aureolum*, *Chaetoceros convolutus*, *Nodularia spumigena*, *Chattonella spp*). In addition, some toxic species spread their toxins through the production of aerosols reaching the coasts (i.e. *Gymnodinium breve* and *Ostreopsis spp.*) [4].

The literature on toxic algal blooms and red tides, documents a global increase in the frequency, magnitude, and geographic extent of these events over the last two decades. It also appears likely that toxic algal species have spread within regions over spatial scales of hundreds of kilometers, moving with major water currents and storms, [5-8]. Freshwater toxins are different from their marine counterparts in two respects. First, cyanobacteria, rather than dinoflagellates, almost exclusively synthesize freshwater harmful algal bloom toxins [9-11]. Second, the chemical structures of the freshwater toxins are more diverse and include alkaloids, phosphate esters, macrolides, chlorinated diaryllactones, and penta- and heptapeptides[10]. Toxin producing plankton (TPP) release toxic chemicals in the water and reduce the grazing pressure of zooplankton. As a result TPP may act as biological control for the termination of planktonic blooms [12-13]. A wide variety of toxins produced by five phyla of algae: Chlorophycophyta (green algae), Cyanophycophyta (bluegreen algae [cyanobactena]), Chrysophycophyta (diatoms, yellow-green and golden algae), Pyrrhophycophyta (dinoflagellates) and Rhodophycophyta (red algae). The types of molecules involved are diverse, going from simple ammonia to complicated polypeptides and polysaccharides. The cyanobacterial toxins are broadly classified as either neurotoxic, hepatotoxic, or dermatotoxic [10]. Interestingly, cyanobacteria synthesize saxitoxins, the primary agent of PSP in freshwater [9] whereas dinoflagellates and bacteria synthesize these toxins in marine systems.

The production of algal toxins is nor-mally associated with algal blooms, or the rapid growth and exception-ally dense accumulation of algae. The term Harmful Algal Bloom (HABs, commonly called "red tides") is used to describe a proliferation of al-gae, or phytoplankton. A harmful algal bloom is a bloom of certain types of algal species that produce toxins as it blooms or dies. The fate and behaviour of these toxins in the marine environment is not well known but they will undergo microbial biodegradation when released into the environment. Some dinoflagellate species of toxic algae form cysts that can accumulate in the sediment and act as an inoculum for a new population when conditions favour germination of the cysts. The conceptual model below (fig.1) illustrates routings through which toxins impact many different tropic compartments (the coloured boxes are hotlinks). Low oxygen levels in bottom water caused by non-toxic algae may also have adverse effects on the ecosystem.

In many cases the toxins can be transported through the food web to humans, to other organisms of the community often through contaminated fish & shellfish (fig.2). The toxins have impact on humans in different ways leading to mild symptoms or even death. Algal toxins can give rise to a number of different poisoning syndromes like

- NSP - neurotoxic shellfish poisoning;
- PSP - paralytic shellfish poisoning;
- ASP - amnesic shellfish poisoning;
- DSP - diarrhoetic shellfish poisoning

Cyanobacteria (blue-green-algae) are known to produce various toxins. Cyanobacteria live in terrestrial, fresh, brackish, or marine water [14]. Some of

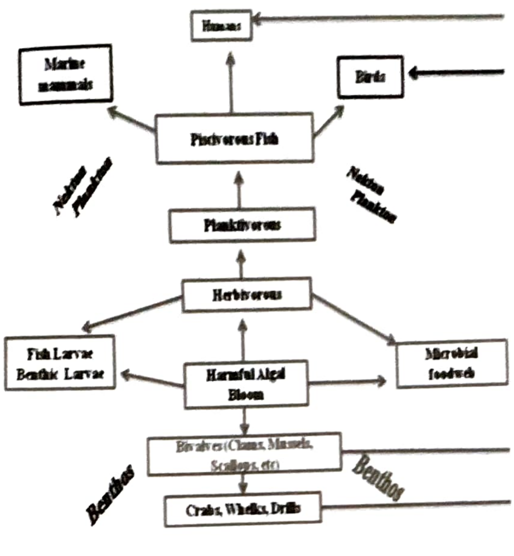


Figure 1: Routing of algal toxins at different tropic levels

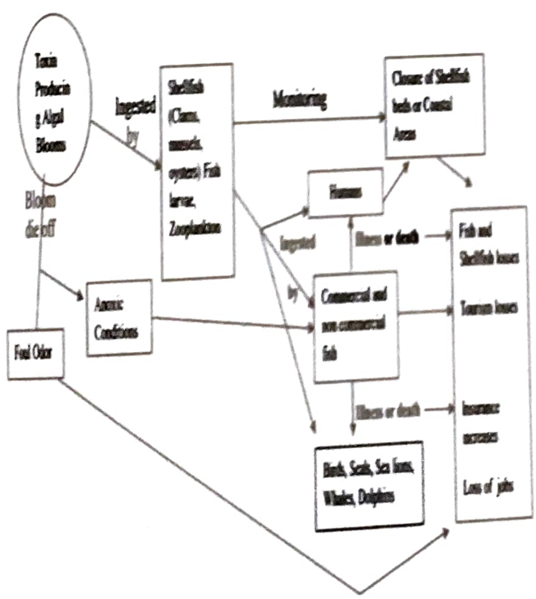


Figure 2: Effect of algal toxins on different communities

the toxins they produce can be highly toxic, others can cause severe taste and odor problems in drinking water supplies. Cyanobacterial toxins can make drinking water and recreational use of water unsafe. Animals die each year as a result of cyanotoxins, and though human death is not common, many people experience symptoms indicative of cyanotoxin exposure. Very little is known about the long-term side effects of the ingestion of cyanotoxins, although there is a guideline set by WHO for safe concentrations, these minimal concentrations could have an effect over time[15].

Many secondary metabolites are potent toxins, causing health problems for animals and humans when the producer organisms occur in masses in water bodies. The toxins produced by cyanobacteria (cyanotoxins) are grouped into two categories (cytotoxins and biotoxins) on the basis of the bioassay methods used to screen them [16].

Cyanotoxins are of three chemical types: peptides (cyclic and linear), alkaloids, and lipopolysaccharides [17]. Cyanotoxins implicated in human illness include microcystin, cylindrospermopsin, anatoxin, saxitoxin, and â-methylamino alanine (BMAA)[18]. Members of the cyanobacterial genera *Microcystis*, *Oscillatoria* and *Anabaena* produce cyclic peptides, denoted microcystins, which are potent hepatotoxins. These substances are responsible for the death of fish, birds, wild animals and agricultural livestock in many countries where freshwaters contain toxic cyanobacterial blooms, and the adverse effects of these toxins on human health have been recognized [19-20].

Cyanobacterial toxins can be clas-sified several ways. They may be classified according to their chemical structures as cyclic peptides (mi-crocystin and nodularin), alkaloids (anatoxin-a, anatoxin-a(s), saxitoxin, cylindros permopsin, aplysiatoxins, lyngbyatoxin-a) and lipopolysaccha-rides [21]. However, cyanotoxins are more commonly discussed in terms of their toxicity to animals while there are several dermatotoxins (e.g., lyng-byatoxin and aplysiatoxins), which are produced primarily by benthic cyanobacteria, and are mostly either neurotoxins or hepatotoxins [21].

Table 1 : General features of the cyanotoxins

| Toxin group | Primary target organ in mammals | Cyanobacterial genera producing toxins | References |
|---|---|---|---|
| **CYCLIC PEPTIDES** | | | |
| Microcystins | Liver | *Microcystis, Anabaena, Planktothrix (Oscillatoria), Nostoc, Hapalosiphon Anabaenopsis* | 17,22 |
| Nodularin | Liver | *Nodularia* | 22 |
| ***ALKALOIDS*** | | | |
| Anatoxin-a | Nerve synapse | *Anabaena, Planktothrix (Oscillatoria), Aphanizomenon* | 23 |
| Anatoxin-a(S) | Nerve synapse | *Anabaena* | 23 |
| Aplysiatoxins | Skin | *Lyngbya, Schizothrix, Planktothrix (Oscillatoria)* | 22,24 |
| Cylindrospermop sins | Liver | *Cylindrospermopsis, Aphanizomenon, Umezakia* | 22,23 |
| Lyngbyatoxin-a | Skin, gastro-intestinal tract | *Lyngbya* | 22,24 |
| Saxitoxins | Nerve axons | *Anabaena, Aphanizomenon, Lyngbya, Cylindrospermopsis* | 23 |
| *Lipopolysacchari des* (LPS) | Potential irritant; affects any exposed tissue | All the above | 23- 24 |

**Neurotoxins:** - Neurotoxins are or-ganic molecules that can attack the nervous systems of vertebrates and invertebrates. Three primary types of neurotoxins have been identified: 1) anatoxin-a, an alkaloid, inhibits transmissions at the neuromuscular junction by molecular mimicry of the neurotransmitter acetylcholine (blocks post-synaptic depolarization); 2) anatoxin-a(s) blocks acetylcholin-esterase (similar to organophosphate pesticides); 3) saxitoxins are carbamate alkaloids that act like carbamate pesti-cides by blocking sodium channels. Neurotoxins are produced by several genera of cyanobacteria including *Anabaena*, *Aphanizomenon*, *Microcystis*, *Planktothrix*, *Raphidiopsis*, *Arthrospira*, *Cylindrospermum*, *Phormidium* and *Oscillatoria*. Neurotoxins produced by *Anabaena spp*, *Oscillatoria spp*, and *Aphanizomenon flosaquae* blooms have been responsible for animal poison-ings around the world [16, 25]. Neurotoxins usually have acute effects in vertebrates, with rapid pa-ralysis of the peripheral skeletal and respiratory muscles. Other symptoms include loss of co-ordination, twitch-ing, irregular gill movement, tremors, altered swimming, and convulsions before death by respiratory arrest.

**Hepatotoxins:** - Hepatotoxins are produced by many genera of cy-anobacteria and have been impli-cated in the deaths of fish, birds, wild animals, livestock and humans around the world[25,16]. The cyclic hep-tapeptides, or microcystins, inhibit eukaryotic protein phosphatases type 1 and type 2A, resulting in excessive phosphorylation of cytoskeletal ele-ments and ultimately leading to liver failure [26]. These toxins target the liver by binding the organic anion transport system in hepato-cyte cell membranes.

Microcystins are the largest group of cyanotoxins, with more than 70 structural variants [27]. Microcystin is the only cyanotoxin for which the biosynthetic pathway and gene cluster have been identified [28]. Microcys-tins are produced in freshwater by species of *Microcystis*, *Anabaena* and *Planktothrix*. Symptoms of poisoning in fish include flared gills because of difficulty breathing and weakness or inability to swim. Channel catfish, *Ictalurus punctatus*, can become intox-icated at 50 to 75 ìg microcystin/L water [29]. All fish may be killed within 24 hours of exposure and liver was found to be target organ as evidenced from severe lesions in the tissues [29].

One potent hepatotoxin, cylindrosper-mopsin, is produced by *Cylindrosper-mopsis raciborskii*, a relatively small cyanobacterium. Cylindrospermopsin is an alkaloid that suppresses glu-tathione and protein synthesis. *C. raciborskii* has been in the South and Southeast for decades and is becom-ing more widespread. Mammals (such as humans) are relatively sensitive to cylindrospermopsin and may be affected when they eat fish that have been exposed to the toxin. A study reporting the bioaccumulation of cylindrospermopsin in muscle tis-sue of the red claw crayfish (*Cherax quadricarinatus*) and visceral tissues of rainbow trout (*Oncorhynchus mykiss*) shows that exposure could occur from farm-raised freshwater aquatic foods. Fish are generally more tolerant of algal toxins than mammals and tend to accumulate them over time [30]. Although toxin cylindrpspermopsin from *C. raciborskii* has not yet been a problem in aquaculture, it could become a problem in the future.

## Effect of environment on algal toxin production

Environmental parameters such as high light intensity, changes in temperature, nutrients and trace metals played a vital role on algal toxins production. The effects of environmental factors on toxin production are much studied and widely disputed [31, 21]. Blooms in the same body of water can be toxic or non-toxic from one year to the next. A different strain composition (i.e., toxic versus non-toxic), which can-not be distinguished microscopically if belonging to the same species, is a common explanation for this oc-currence. However, some species are known to produce high or low levels of toxicity under different laboratory conditions. The stimulus for toxin production in such species is not known. Environmental parameters such as light intensity, temperature, nutrients and trace metals have been mimicked under laboratory conditions and their effect on cyanotoxin pro-duction investigated. Studies on light intensity are not definitive, but it is known that intense light increases the cellular uptake of iron, which may be responsible for more toxin production. However, low concentrations of iron lead to higher microcystin concentra-tions [27]. Nutrients such as nitrogen and phosphorus are essential for cyanobacterial growth. Phosphorus is usually the limiting fac-tor in ponds, so small increases in this nutrient may influence toxin produc-tion simply as a result of increasing algal growth. Generally, decreased amounts of microcystin (produced by *Anabaena*, *Microcystis* and *Oscillatoria*) and anatoxin-a (produced by *Aphani-zomenon*)

Table-2: Known algal species producing toxins, their symptoms and course of the disease.

| Types of poisoning | Toxins | Toxin Producing Algae | Symptoms | Course of Disease |
|---|---|---|---|---|
| Ciguatera Fish Poisoning (CFP) | Ciguatoxin, Scaritoxin, Maitotoxin, Okadaic acid | *Gamberdiscus toxicus* (Dinoflagellate) | **Gastrointestinal**: diarrhea, vomiting, abdominal pain **Neurological**: headache, reversal of hot and cold sensations, vertigo, muscular weakness, numbness **Cardiovascular**: irregular heart rhythm, lowered blood pressure | No antidote, Self-limiting, symptoms, subside within several days, Initial signs of poisoning occur within six hours after ingestion. |
| Paralytic Shellfish Poisoning (PSP) | Saxitoxins (>20) | *Alexandrium* | **Neurological**: respiratory paralysis, tingling, burning, numbness, drowsiness, incoherent speech, rash | No antidote, life threatening, Onset of symptoms is rapid (within 1 or 2 hours), With medical support, the victim usually recovers within 12 hours. |
| Diarrheic Shellfish Poisoning (DSP) | Vessotoxin, Dinophysis toxins, Pectenotoxi, Okadaic acid | *Dinophysis sp.,* | **Gastrointestinal**: nausea, vomiting, diarrhea, abdominal pain, chills, headache, fever | No antidote, recovery normally occurs within three days, Onset is rapid, occurs,one-half to two hours after ingestion |
| Amnesic Shellfish Poisoning (ASP) | Domoic acid | *Pseudo-nitzschia.* (Diatom) | **Gastrointestinal**: nausea, vomiting, abdominal cramps, diarrhea **Neurological**: dizziness, headache, seizures, disorientation, short-term memory loss, respiratory difficulty, coma | No antidote, gastrointestinal symptoms begins within 24 hours of ingestion, and neurological symptoms occur within 48 hours |
| Neurotoxic Shellfish Poisoning (NSP) | Brevetoxins | *Gymnodinium Breve* (dinoflagellate) | Gastrointestinal: diarrhea, vomiting Neurological: tingling and numbness of lips, tongue, and throat, muscle aches, dizziness, reversal of hot and cold sensations | No antidote recovery normallyoccurs within hours to several days of onset with few after effects, Onset is rapid, occurring within minutes to a few hours after ingestion. |
| Cyanobacterial Poisoning | Microcystins, Anatoxins | *Anabaena sp., Aphanizomenon sp., Microcystis sp.* | **Neurological**: derangement, staggering, tremors **Hepatological**: induce liver failure, abdominal pain | No antidote, it is not known which dosages trigger certain responses. Death may occur due to liver failure. |

have been reported under the lowest phosphorus concentrations tested [32].

**Causes of algal toxin production**

Algal toxins are emerging contaminants of public health significance. One of the most significant problems regarding algal blooms is the harmful effect due to different types of toxins produced by some phytoplankton species (e.g. dinoflagellates) on fish, invertebrates and humans. Climate change may also be considered as a possible reason for HABs increase [33]. Some dinoflagellates and cyanobacteria produce toxins that can affect domestic animals and humans. Cyanobacterial toxins can make drinking water and recreational use of water unsafe. Animals die each year as a result of cyanotoxins, and though human death is not common, many people experience symptoms indicative of cyanotoxin exposure. Some of these toxins such as domoic acid, saxitoxin (paralytic shellfish poisoning or PSP toxin), brevetoxin, and cyanobacterial toxins (including anatoxins, microcystins, and nodularins) have been suspected, but they have rarely been documented, as the cause of bird mortality. Marine algal toxins such as domoic acid, saxitoxin, and brevetoxin that bioaccumulate or are magnified in the food chain by fish and shellfish, and anatoxins from freshwater cyanobacteria, affect the nervous system. The effects of some harmful algae are not related to toxin production but rather are related to depleted dissolved oxygen concentrations in water due to their proliferation, death, and decay, or night respiration. Other harmful effects include occlusion of sunlight by large numbers of algae and physical damage to the gills of fish caused by the structure of some algal species. All of these effects can lead to mortality of aquatic organisms such aquatic plants, fishes and birds and it may produce an environment conducive to botulism [34].

**Detection of algal toxins**

Algal toxins produced by marine and freshwater microalgae present a significant analytical challenge because of their complex structures and frequent occurrence as mixtures of structural congeners, which differ in toxic potencies and are present at varying proportions in contaminated samples [35]. Rapid, sensitive in vitro detection methods specific for each class of algal toxins have been developed over the past decade, including immunoassays, enzyme inhibition assays, receptor assays, and cell assays. Immunoassays (especially ELISA) have proven to be rapid, sensitive, accurate, and cost-effective. ELISAs have previously been described and widely applied to the detection of pesticides and other environmental contaminants in various sample. Other immunoassay formats utilizing immunochromatography are often simple devices, where a test sample is analyzed for the presence of certain analytes. For example, a specified volume of the sample is added to a tube containing a pre-dispensed antibody-gold conjugate and allowed to react. The solution is then contacted with one end of a test strip containing discrete reactive zones. As the sample is wicked up the test strip, the analyte in the sample continues to reacts with the antibody. As the reaction mixture flows up the strip, any reaction between the antigens and the analyte, if present, may be observed by the appearance or absence of colour in the discrete zones.

**Control of toxin production**

Because it is difficult to identify algal toxins as the cause of mortalities, there has been little opportunity to consider control measures. Currently, there is much interest in algal toxins and their threat to human, water and food supplies. Identification of the conditions that trigger harmful algal blooms may aid in developing strategies to prevent red tides or freshwater cyanobacterial blooms and associated mortality. Controlling nutrient loading through reduced fertilizer use, improved animal waste control, and improved sewage treatment may reduce the number, or likely locations, of toxic algal blooms.

**Conclusion**

Algal toxins are responsible for extensive die-offs of fish and shellfish, as well as mortality in seabirds, humans, livestock and other animals depending on aquatic food web. Lots of information are available concerning acute intoxications, while little is known about environmental health effects of chronic exposure to low levels of algal toxins. Although algal blooms historically have been considered a natural phenomenon, the frequency of occurrence of harmful algae appears to have increased in recent years. Careful monitoring and early detection of potentially toxic algal blooms could allow time to initiate actions to prevent or reduce mortality.

**References**

[1Cannell, R. J. (1993). Algae as a source of biologically active products. ***Journal of Pesticide Science***, 39:147-153.

[2]Chekroun, K. B. and Baghour, M.,(2013). The role of algae in phytoremediation of heavy metals: A review. ***Journal of Materials and Environmental Scince***, 4 (6):873-880.

[3]Falconer, I. R. (1993). Algal toxins in seafood and drinking water. San Diego: ***Academic Press.*** pp. 224.

[4]Bruno, M. (2000). Toxic algae in sea and freshwater: health impact and control strategies. *ISTISAN Reports* 00/ 31, Istituto Superiore di Sanità, Rome ,pp 1–94.

[5]John, U., Medlin, L. K. and Groben, R.( 2005). Development of specific r-RNA probes to distinguish between geographic clades of the *Alexandrium tamarense* species complex. ***Journal of Plankton Research***, 27:199-204.

[6]Kim, S. (1999). Food Poisoning: Fish and Shellfish. In: *Poisoning and Drug Overdose. 3rd ed. Olson K, ed. Stamford:* **Appleton and Lange**, pp-175-176.

[7]Klopper, S., Scharek, R. and Gerdts, G (2003). Diarrhetic shellfish toxicity in relation to the abundance of *Dinophysis spp*. Ehrenberg 1839 in the German Bight near Helgoland, ***Marine Ecology-Progress Series***, 259:93-102.

[8] Leikin, J and Paloucek, F. (1998). Ciguatera Food Poisoning. In: ***Poisoning and Toxicology Compendium***. *Cleveland:* Lexi-Comp Inc.pp- 783.

[9] Carmichael, W. W. (1992). Cyanobacteria secondary metabolites

the cyanotoxins. ***Journal of Applied Bacteriology***, 72: 445-459.

[10]Carmichael, W. 'W., Mahmood, N. A. M. and Hyde, E. G. (1990). Natural toxins from cyanobacteria (blue-green algae). In Marine toxins: Origin, structure, and molecular pharmacology. ***Journal of the American Chemical Society Symposium Series***, 418:87-106.

[11]Carmichael, W. W. and Faieoner, I. R. (1993). Diseases related to freshwater blue-green algal toxins and control measures, Zn 1. R. Falconer red. 1, ***Algal toxins in seafood and drinking water Academic***, pp 187-209.

[12]Chattopadhyay, J., Sarkar, R. and Abdllaoui, A. E. (2002a). A delay differential equation model on harmful algal blooms in the presence of toxic substances. *IMA Journal of Mathematics* ***Applied in Medicine and Biolology***, 19:137–161.

[13]Chattopadhyay, J., Sarkar, R. and Mandal, S. (2002b). Toxinproducing plankton may act as a biological control for planktonic blooms – field study and mathematical modelling. ***Journal of Theoritical Biology***, 215:333–344.

[14]Mankiewic, J., Tarczynska, M., Walter, Z., Zalewski. M. (2003). Natural toxins from cyanobacteria. ***Acta Biologica Cracoviensia Series Botanica***, 45: 9 - 20.

[15]World Health Organization (WHO). Guidelines for drinkingwater quality. 2nd ed. Addendum to Vol. 2. **Geneva**: *WHO*; 1998.

[16]Carmichael, W.W. (1997). The cy-anotoxins, In J.A. Callow (ed.), ***Advances in Botanical Research***, Vol. 27. London: Academic Press. pp 211-256.

[17]Sivonen, K. and Jones, G. (1999). Cy-anobacterial toxins. *In*: I. Chorus and J. Bartram (eds.) Toxic Cy-anobacteria in Water: *a Guide to their Public Health Consequences, Monitoring and Management. Lon-don: Spon*. pp 41-111.

[18]Sivonen K., Jones G. (1999). Cyanobacterial toxins. In: Chorus I., Bartram J. (eds) Toxic Cya nobacteria in Water: *a Guide to Public Health Significance, Monitoring and Manage ment. London: F & FN Spon*, pp 41–111.

[19]Mackintosh, C., Beattie, K. A., Klumpp, S., Cohen, P. and Codd, G.A. (1990). Cyanobacterial microcystin-LR is a potent and specific inhibitor of protein phosphatases 1 and 2A from both mammals and higher plants. *FEBS Letters*, 264: 187-192.

[20]Matsushima, R. N., Nishiwaki, S., Ohta, T., Yoshizawa, S., Suganuma, M., Harada, K. I., Watanabe, M. F. and Fujiki, H. (1991). Structure function relationships of microcystins, liver tumor promoters, in interaction with protein phosphatase. ***Japanese Journal of Cancer Research***, 82: 993-996.

[21]Codd, G.A., Lindsay, J., Young, F.M., Morrison, L.F. and Metcalf, J.S. (2005). Harmful cyanobacteria: from mass mortalities to manage-ment measures, In J. Huisman, H.C.P. Matthijs and P.M. Visser (eds.), ***Harmful Cyanobacteria. Springer***, Dordrecht, The Nether-lands. pp. 1-23.

[22]Li, R. H., Carmichael, W. W., Brittain, S., Eaglesham, G. K., Shaw, G. R., Liu, Y. D., Watanabe, M. M., (2001). First report of the cyanotoxins cylindrospermopsin and deoxycylindrospermopsin from Raphidiopsis curvata (cyanobacteria). ***Journal of Phycology***, 37:1121-1126.

[23]Cox, P. A., Banack, S. A. and Murch, S. J. (2003). Biomagnification of cyanobacterial neurotoxins and neurodegenerative disease among the Chamorro people of Guam. ***Proceedings of the National Academy of Sciences***, 100(23):13380-13383.

[24]Wacklin, P., Hoffmann, L. and Komárek, J. (2009). Nomenclatural validation of the genetically revised cyanobacterial genus Dolichospermum (Ralfs ex Bornet et Flahault) *comb. nova*. ***Fottea***, 9(1):59–64.

[25]Briand, J. F., Jacquet, S., Bernard, C. and Humbert, J. F. ( 2003). Health hazards for terrestrial vertebrates from toxic cyanobacteria in sur-face water ecosystems. *Veterinary* ***Reserach***, 34:361-377

[26]Codd, G. A., Morrison, L. F. and Metcalf, J.S. (2005). Cyanobacterial tox-ins: risk management for health protection. ***Toxicology and Applied Pharmacology***, 203:264-272.

[27]Huisman, J., Matthijs, H. C. P. and Visser, P. M. (eds). (2005). ***Harmful Cyanobacteria***. *Berlin, Germany: Springer*

[28]Malbrouk, C. and Kestemont, P. (2006). Effects of microcystins on fish. ***Environmental Toxicology and Wa-ter Quality***, 25:72-86.

[29]Zimba, P.V., Khoo, L., Gaunt, P.S., Brittain, S. and Carmichael, W.W. (2001). Confirmation of catfish, *Ictalurus puntatus* (Rafinesque), mortality from *Microcystis* toxins. ***Journal of Fish Diseases***, 24:41-47.

[30]Carson B. (2000).Cylindrospermop-sin – Review of Toxicological Literature. National Institute of Environmental Health Sciences: ***Research Triangle Park***, NC. pp.49.

[31]Codd, G.A. (2000). Cyanobacterial toxins, the perception of water quality, and prioritization of eutrophication control. ***Ecological Engineering***, 16:51-60.

[32]Watanabe, M. F., Harada, K., Carmichael, W.W. and Fujiki, H. (1995). Toxic Microcystis. **Boca Raton**: *CRC Press*. pp.272.

[33]Pal, A., He, Y.L., Jekel, M., Reinhard, M. and Gin, K.Y.H. (2014) Emerging contaminants of public health significance as water quality indicator compounds in the urban water cycle. ***Environment International***, 71: 46-62.

[34]Anderson, D.M., Cembella, A.D., Hallegraeff, G.M. (2012). Progress in Understanding Harmful Algal Blooms: Paradigm Shifts and New Technologies for Research, Monitoring, and Management. ***Annual Review Marine Science***, 4:143-176.

[35]Hallegraeff, G.M.( 2010). Ocean climate change, phytoplankton communýty responses, and harmful algal blooms: a formidable predictive challenge. ***Journal of Phycology***, 46:220-235.