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**Review**

# A novel cyanobacterial toxin (BMAA) with potential neurodegenerative effects

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**Abstract** The non-protein amino acid β-N-methyl-amino-L-alanine (BMAA) is a neurotoxin that was recently found to be produced by most cyanobacteria. The neurotoxin was discovered in 1967 in the seeds of the cycad *Cycas micronesica*, but this BMAA may originate from the symbiotic cyanobacterium *Nostoc*, which inhabits the roots of cycads. BMAA is thought to be the cause of the deadly neurodegenerative disease amyotrophic lateral sclerosis/parkinsonism dementia complex (ALS/PDC), common among the Chamorro people of Guam. It was demonstrated that the Chamorros, in all probability, have been exposed to high levels of BMAA through dietary consumption of flying foxes which fed mainly on cycads seeds. BMAA production may be a common conserved evolutionary feature among cyanobacteria and due to their wide global distribution, the toxin may be a common concern and potentially involved in provoking degenerative diseases worldwide. BMAA may likewise be bioaccumulated in other cyanobacterial based food webs within ecosystems outside Guam, and it is proposed that such webs may exist in the Baltic Sea, with its massive occurrence of cyanobacteria (blooms).

**Key words:** β-N-methyl-amino-L-alanine (BMAA), cyanobacteria, Baltic Sea, amyotrophic lateral sclerosis/parkinsonism dementia complex (ALS/PDC), symbiosis.

Cyanobacteria (blue-green algae) are ancient prokaryotic organisms, which arose approximately 3.5 billion years ago (Schopf 1996; Whitton and Potts 2000). They revolutionized life on earth by introducing the chlorophyll-a based photosynthesis, which also brought about oxygenation of the atmosphere (Des Marais et al. 1992). By forming an endosymbiosis with a eukaryotic progenitor, which resulted in the evolution of chloroplasts, they also gave rise to all algae and plants (Miyagishima 2005). These events have shaped our present day atmosphere and biosphere. Cyanobacteria are among the most common prokaryotic groups on Earth. They have a cosmopolitan distribution and are found in most ecosystems, ranging from hot deserts to cold arctic regions (Waleron et al. 2007), and from tropical oceans (Berman-Frank et al. 2001; Capone et al. 1997; Karl et al. 2002), to brackish waters (Gallon et al. 2002; Jonasson 2006) and terrestrial environments (Dodds et al. 1995; Ward and Castenholz 2000; Vincent 2000).

Cyanobacteria are known for their capacity to establish long-lived symbioses with a range of plants and marine organisms (Bergman et al. 2007; Rai et al. 2002; Vessey et al. 2005). The oldest are the symbioses with fungi, to form lichens that evolved at least 400 billion years ago in coastal habitats (Paszkowski 2006). Such cyanolichens (*Peltigera* spp. *Nephroma* spp. *Stereocaulon* spp. etc) are common in most boreal forests and mountain areas. Cyanobacteria also live in association with common boreal mosses (e.g. with *Pleurozium*) and they form symbiosis with liverworts and hornworts (Read et al. 2000), with one genus of ferns (*Azolla*), with gymnosperms such as cycads and with one angiosperm, *Gunnera* spp.

The production of bioactive compounds such as toxins is a well-known feature among cyanobacteria and has for long and in many cases been connected with adverse or lethal health effects (van Apeldoorn et al. 2007). The first report of fatalities resulting from cyanobacterial poisoning was from a lake in Australia in 1878 (George 1878). Since then, instances of human poisoning/death from cyanobacteria have repeatedly been reported. The main toxinogenic cyanobacteria considered as a potential health risk so far occur in aquatic environments, where they under certain conditions form massive surface scums or 'blooms'. The most studied cyanobacterial toxins are the hepatotoxins, produced by members of the genera *Microcystis* (Carmichael et al. 1988) and *Nodularia* (Sivonen et al. 1989) and neurotoxins produced by genera such as *Anabaena* and *Aphanizomenon*. Several of these toxin producing cyanobacteria regularly bloom in the brackish water of

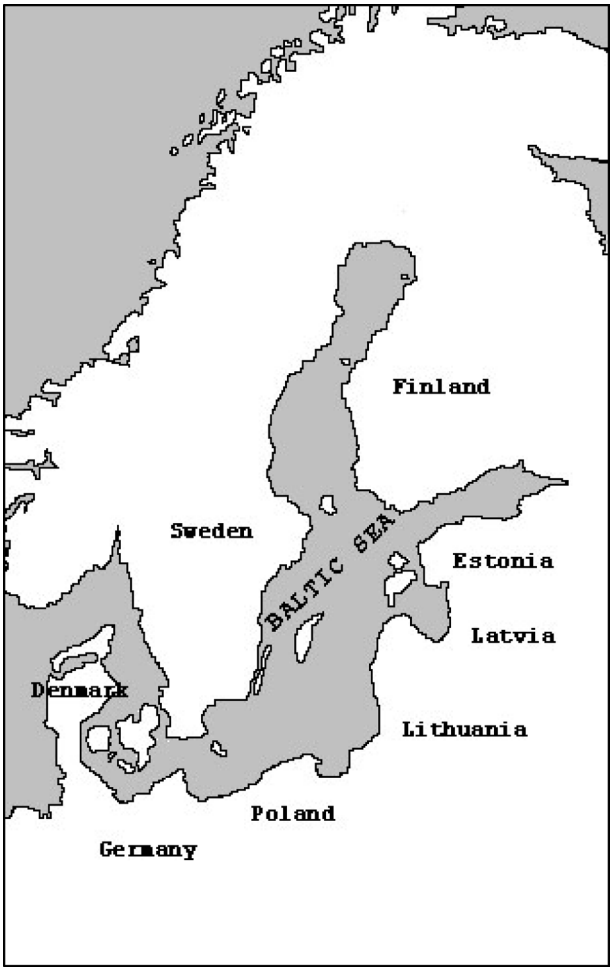


Figure 1. Map of the Baltic Sea.

the Baltic Sea, located in northern Europe (Figure 1) (Gugger et al. 2002; Mahmood and Carmichael, 1986).

### *The Guam hypothesis*

The non-protein amino acid $\beta$-N-methyl-amino-L-alanine (BMAA) is a neurotoxin that was recently discovered to be produced by cyanobacteria (Cox et al. 2005). However, BMAA was found already in 1967 in the seeds of the cycad (Gymnosperm) *Cycas micronesica* (Vega and Bell 1967). At the time, the discovery was thought to be the key to the deadly neurodegenerative disease amyotrophic lateral sclerosis/parkinsonism dementia complex (ALS/PDC), which was common amongst the native Chamorro people of Guam compared to ALS/PDC incidence elsewhere (Kurland and Mulder 1954). BMAA has been shown to be a neurotoxin that effects the motor neurons at lower concentrations than those causing general neurodegeneration. Recent reports have shown that BMAA concentrations as low as 10–30 $\mu$M BMAA can cause selective death of motor neurons (Lobner et al. 2007; Rao et al. 2006). The selective damage to motor neurons caused by purified BMAA was reproduced by crude cycad extracts. ALS/PDC does not only cause loss of motor neurons function, but also exhibits the same features of neurofibrillary tangles, as those found in Alzheimer's disease (Rao et al. 2006).

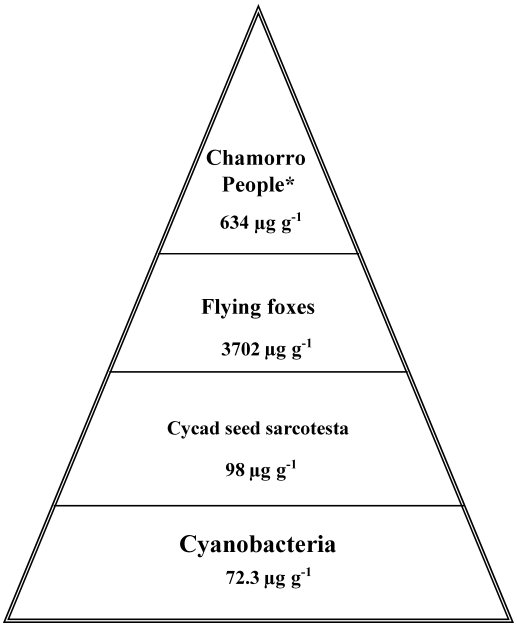


Figure 2. Schematic illustration of the biomagnification of the neurotoxin BMAA (both free and protein bound) through the Guam ecosystem, from cyanobacteria in the roots of cycads, via flying foxes to man (Murch et al. 2004a). * Guam's population is estimated to 152,000 people with about 47% belonging to the Chamorros.

BMAA has been detected in biopsies of diseased Chamorroan people suffering from ALS/PDC, as well as in biopsies from Canadian patients diseased in progressive neurodegenerative disease. No BMAA was found in the comparison group who died of causes unrelated to neurodegeneration (Cox et al. 2003; Murch et al. 2004b). First it was hypothesized that the Chamorro people were exposed to a naturally occurring toxin through their consumption of traditional tortillas made of cycad seed flour (Banack and Cox 2003; Banack et al. 2006; Brownson et al. 2002). However, it was later shown that the exposure came indirectly from cycads via consumption of flying foxes (*Pteropus mariannus mariannus*), a prized food of the indigenous Chamorro people. The flying foxes feed on cycad seeds and was shown to have a tissue concentration of BMAA more than 400 times that of cycad seeds (Murch et al. 2004a). A biomagnification of BMAA from the cycad seeds to flying foxes and to man could explain the exposure of the Chamorroan people to extremely high levels of BMAA (Figure 2).

Cox and Banack (2003) later showed that BMAA is produced by the cyanobacteria *Nostoc*, which is living in symbiosis with cycads. The *Nostoc* filaments colonize the roots of cycads, and as they are able to fix atmospheric nitrogen, they support the plant with all nitrogen needed for growth (Bergman et al. 2007; Vessey

et al. 2005). A still unresolved question is therefore whether the cycads are able to synthesize BMAA or whether all cycad derived BMAA actually originates from the symbiotic cyanobacterium. As only a few cycads have been analysed for BMAA so far, and all natural cycad populations are colonized by *Nostoc*, additional investigations are needed.

The biomagnification of BMAA through the Guam ecosystem fits a classical triangle of increasing concentrations of toxic compounds up the food chain (Figure 2). This is similar to that of lipophilic compounds such as DDT, PCBs, and other industrial toxins/pollutants (Mariussen and Fonnum 2006). However, since BMAA is not lipophilic but water soluble, its biomagnification pathway must differ from that of the lipophilic agents. It has been hypothesized that BMAA associates with proteins and/or is compartmentalized within the cell, and that this fraction functions as an endogenous neurotoxic 'reservoir' from which BMAA slowly with protein turnover, is released over time. This increases the potential health risk even for organisms exposed to lower doses of BMAA and would explain its non-acute mode of toxic action (Murch et al. 2004a).

BMAA may occur in both free and protein-bound form and it has been shown that the ratio between the protein-bound and free BMAA is present in a ratio between 60:1 and 120:1 (Ince and Codd 2005). The function of BMAA in cyanobacteria and in the cycads is still unknown. However it has been hypothesized by Cox et al. 2003 that BMAA in cycads may function as a chemical deterrent to herbivory. Recently it was documented that BMAA is produced by cyanobacteria not only in the *Nostoc*-cycad symbioses, but also in other plant symbioses (Cox et al. 2005). And perhaps even more importantly, BMAA was found to be biosynthesized in the majority of the free-living cyanobacteria tested (Cox et al. 2005). This finding suggests that the BMAA toxin can, like cyanobacteria, have a global distribution and therefore the occurrence of BMAA may be a widespread phenomenon.

### *The Baltic Sea and BMAA*

Since cyanobacteria are globally widespread and harbour many different habitats, the biomagnification of cyanobacterial BMAA may not be unique to Guam. BMAA might likewise be transferred in food-webs of ecosystems outside Guam, and potentially be biomagnified through other food chains. It is therefore of key-importance to examine whether BMAA is produced in natural environments outside tropical areas. The Baltic Sea may exhibit a similar classical cyanobacterial based biomagnification triangle as the Guam ecosystem (Figure 3). This semi-enclosed sea is one of the world's largest brackish water bodies, and could serve as a model system for studies on the occurrence of BMAA and its fate in a temperate environment.

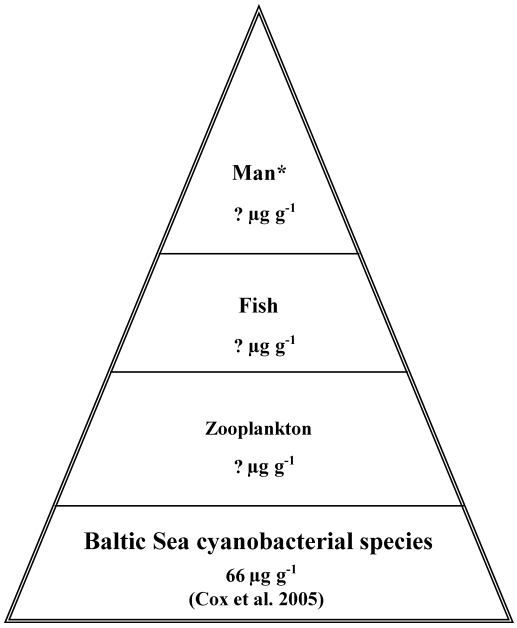


Figure 3. A proposed biomagnification scenario of BMAA through the Baltic Sea ecosystem. * Man in the figure represents the 16 million people living along the shores of the Baltic Sea and which are dependent on its services.

Massive accumulations of surface 'blooms' of the nitrogen-fixing cyanobacterial genera *Nodularia*, *Aphanizomenon*, *Nostoc*, and *Anabaena*, are typical phenomena during July-August in the Baltic Sea (Figure 1). These cyanobacteria are independent of a combined nitrogen source as they are able to fixate atmospheric nitrogen (Degerholm et al. 2006; Gallon et al. 2002). The dense summer blooms of cyanobacteria are a nuisance for fishing industries and holiday makers that may be exposed to toxic compounds produced by some of these cyanobacteria. The Baltic Sea has always been an important resource to people living along its shores and affects sixteen million people living in nine countries surrounding it (Boesch et al. 2005).

The availability of dissolved P is an important factor determining the spatial and temporal distribution of nitrogen-fixing cyanobacteria in the Baltic Sea (Karlson et al. 2007). Even though waste water treatment has greatly improved in countries surrounding the Baltic Sea during the last decades, there is still today no significant reduction in average phosphate availability and cyanobacterial blooms of the Baltic Sea have increased due to other anthropogenic activities causing nitrogen and phosphate run-offs from e.g. surrounding farming areas (Jonasson, 2006; Karlson et al. 2007). Such circumstances may increase the production and spread of cyanobacteria that potentially produce the well-known toxins and BMAA and negatively affect all organisms exposed to and dependent on Baltic Sea services. For

instance, in the Baltic Sea cyanobacteria constitute a food source for zooplankton, which in turn are eaten by fish and later by seal and man. Many coastal areas and lakes that are used for fish or shellfish farming harbour other potentially BMAA producing cyanobacteria.

Thousands of birds (primarily gulls) showing symptoms of nervous disturbances and mass die-offs have also been noted in coastal areas of Sweden in 2000–2004 (National veterinary institute 2004). The reason for this has still not yet been established, but cyanobacterial toxins like BMAA may be involved.

Cyanobacterial blooms are not restricted to lakes and the Baltic Sea, but similar mass-occurrences are a circum-global phenomena proven to occur in warmer surface waters of all oceans. For instance, the larger planktonic cyanobacterium *Trichodesmium* spp. dominate nutrient poor tropical and subtropical surface waters together with small unicellular genera such as *Prochlorochoccus* and *Synechococcus* (Capone et al. 1997; Karl et al. 2002). It was recently shown that BMAA is produced by *Trichodesmium* and there are reasons to believe that this is also the case in the extremely common unicellular genera mentioned (Cox et al. 2005).

Until now, only a few cycads have been analysed for BMAA production. As a complimentary organism the water fern *Azolla*, which forms symbiosis with cyanobacteria, should be included. This fern is commonly used as a fertilizer in rice fields worldwide (Bergman et al. 1993). Due to the high nutrient composition of *Azolla* it is frequently utilized as an efficient and effective feed for livestock by several farmers in Asia (Kamalasanana Pillai et al. 2002). So far, little or no research regarding this potential route of BMAA bioaccumulation has been done. However, since BMAA is a potentially hazardous compound, identifying and excluding all sources of BMAA is of immense importance.

As cyanobacteria have a cosmopolitan distribution, there are possibly other areas where BMAA may occur and bioaccumulate. For instance, annual or even permanent blooms of cyanobacteria have become increasingly common in drinking water reservoirs (Metcalf et al. 2008). There are a number of events where humans have been poisoned by cyanobacterial toxins. The most well characterized case was the poisoning of renal dialysis patients in a clinic in Caruaru, Brazil, in 1996 (Falconer and Humpage 2005). The occurrence of cyanobacteria and their toxins in water bodies for production of drinking water poses a technical challenge for water management (Codd et al. 2005; Falconer and Humpage 2005).

Several methods are available for identification of toxin-producing cyanobacteria, and for removal of their toxins during drinking water treatment (Codd et al. 2005; Hitzfeld et al. 2000). Unfortunately, there are no efficient methods for BMAA detection in drinking water; however such research is currently in progress.

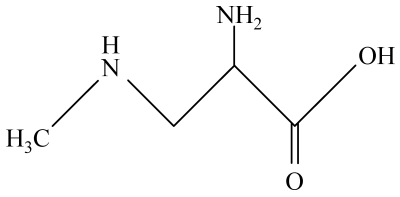


Figure 4. The structure of BMAA. BMAA is a hydrophilic amino acid with a molecular weight of 118.13 Da and two nitrogen functional groups. It has a relatively high chemical stability.

As BMAA (Figure 4) is a small (118.13 Da), hydrophilic molecule with no chromophores, its detection has caused analytical challenges. In order to detect with either fluorescence or by UV-VIS BMAA needs to be derivatized. There are several reagents available for pre-column derivatization (Cohen and Michaud 1993; Sarwar and Botting 1993; Strydom and Cohen 1994), however due to its stability and rapid reaction rate, carbamate 6-aminoquinolyl-N-hydrosuccinimidyl (AQC) has shown to be a suitable derivatizing agent for BMAA. AQC reacts both with primary and secondary amines and yield fluorescent derivates. (Banack and Cox 2003; Banack et al. 2006; Cox et al. 2005; Murch et al. 2004a).

To rule out any contributions of other interfering molecules, all analytical methods must be supported with additional data obtained with a complimentary detection technique e.g. with liquid chromatographic masspectrometry (LC-MS) (Banack et al. 2007; Cox et al. 2003; Cox et al. 2005; Murch et al. 2004a; Murch et al. 2004b).

### *Concluding remarks*

So far, the only documented biomagnification of BMAA is in the Guam ecosystem, where it also has been shown to negatively affect mankind by causing severe neurodegeneration. Besides in cycads, BMAA is also produced by numerous symbiotic and free-living cyanobacteria, including the main bloom-forming cyanobacterial species in the Baltic Sea. It is therefore possible that BMAA biomagnification scenarios may be present not only in tropical, but also in temperate regions where cyanobacteria dominate or act as important primary producers on which other heterotrophic organisms feed. Extensive research is therefore now ongoing to examine the BMAA occurrence and potential biomagnification outside of Guam. The theory that BMAA causes neurodegeneration in humans is not undisputed, although it is apparent that BMAA is produced by most cyanobacteria and that it is neurotoxic (Buenz and Howe 2007; Cox et al. 2005; Papapetropoulos 2007).

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