



## Fact Sheet

# Update on BMAA

In 2003, the hypothesis was raised that a causal link existed between exposure to the non-protein amino acid BMAA (beta-amino-L-alanine - produced by some species of cyanobacteria) and a number of human neurodegenerative diseases including Alzheimer's Disease, ALS (amyotrophic lateral sclerosis; also known as motor neurone disease or MND), and Parkinson's Disease (1). This theory evolved from a chain of evidence dating back to the 1950s when research was undertaken into the possible environmental causes for elevated frequencies of ALS and Parkinson's Disease among the indigenous people on the Pacific island of Guam. Studies of the traditional diet led to a search for neurotoxic compounds in native trees of the Cycad family, resulting in the identification of BMAA in 1967. BMAA is an amino acid that is not normally found in proteins. A number of such non-protein amino acids have been identified in plants, and have been hypothesised to play a role in defences against grazing by herbivores and/or to act as signalling compounds in plant metabolism.

BMAA in flour made from the seed of cycad trees on the island was initially postulated as the causative agent of neurological diseases in Guam, but this theory was abandoned when animal studies failed to demonstrate neurotoxic effects except at exposures hugely in excess of possible human consumption levels. In addition, there was no recognised mechanism by which a water-soluble compound such as BMAA could accumulate in the body, and therefore chronic accumulation of BMAA to reach toxic levels did not appear to be feasible.

Decades later, researchers at the Institute of Ethnobotany in Hawaii reported that BMAA could bioaccumulate in the Guam food chain, leading to high levels of human exposure through traditional consumption of flying foxes (large bats) which feed on cycad seeds (2). It was suggested that BMAA could be erroneously incorporated into protein, forming a persistent endogenous reservoir from which BMAA could be released during protein metabolism, and thus providing a mechanism to explain chronic effects. This hypothesis was supported by small studies demonstrating detection

of BMAA in the brains of people who had died from neurological diseases, but not in those who had died from non-neurological causes.

It was also reported that BMAA was synthesised by *Nostoc* cyanobacteria living in a symbiotic association with cycad roots, rather than being produced directly by the trees. A subsequent survey of cyanobacterial strains from several countries showed the presence of BMAA in a wide range of free-living and symbiotic cyanobacteria, including some species which occur in freshwater bodies used as drinking water sources (3). Cyanobacteria are a major component of both freshwater and marine food chains, so this finding opened the possibility that BMAA exposure through food and water might be widespread in human populations, rather than being confined to the few locations where Cycads are currently found. The resultant media publicity largely accepted this preliminary hypothesis as established fact and speculated that exposure to BMAA in drinking or recreational water could be a major cause of neurological diseases in the community.

Since 2003, more than 200 papers on BMAA have been published but definitive evidence of the involvement of BMAA in human neurological disease has not yet been demonstrated. A substantial proportion of the publications have not contributed any new data, but have simply reiterated the hypothesis and in some cases extended the scope of conjecture. There have been a number of studies on the toxicological effects of BMAA *in vitro* and *in vivo*. A range of adverse effects on neurological and other cell types have been reported, but in the absence of information on dietary BMAA intake, absorption via the digestive system and resultant concentrations in body tissues, it is not possible to determine how relevant these effects are to actual human exposure levels. Despite the postulated importance of bioaccumulation of BMAA through the food chain to reach levels high enough to cause toxic effects in the Guam scenario, there have been few reports of testing for BMAA in fish, shellfish or crustaceans, which might be expected to form a major route of human exposure to this substance.

Epidemiological evidence has been sought by re-examining past studies of apparent geographic clusters of ALS in an effort to establish links with exposure to cyanobacterial blooms or consumption of fish, but the lack of systematic records limits the quality of such retrospective analyses, and no conclusions could be drawn.

In addition, there has been controversy in the literature about the reliability of different BMAA assay methods, and a direct comparison of three detection methods indicated that use of highly selective assay methods produced BMAA estimates 10 to 100-fold lower than the more commonly used but less selective techniques (4). Similarly, a commercially marketed ELISA kit for water testing was also found to produce overestimates of BMAA and false positive results. A recent review concluded there is serious doubt as to whether BMAA was identified correctly in some studies because of poor analytical methods, or because inadequate reporting of analyses made it impossible to verify the results (5). This has thrown doubt on the results of surveys showing BMAA production to be common among cyanobacteria, and there have been conflicting reports from groups using different assay methods on BMAA occurrence in human brain tissues. Advancement of the science on this issue will require development and use of selective, inter-laboratory validated methods and detailed reporting of the analytical work to ensure that results are accepted as reliable.

A new epidemiological study conducted by the French National Research Agency is investigating possible links between ALS and BMAA (6). The project is focusing on ten counties in three regions of France and will include all ALS cases diagnosed between 1 January 2003 and 31 December 2011. The study will collect information on exposures and behaviours from both ALS cases and healthy controls, examine clinical samples for the presence of BMAA, and sample for cyanobacteria and test their BMAA content. BMAA analysis will be conducted using liquid chromatography (LC) coupled to tandem mass spectrometry (LC-MS/MS), which is recognised as a specific and accurate analytical methodology. Exposures to other suspected occupational and environmental risks factors for neurological disease will also be assessed. The three year study, which began in early 2012, should provide high quality data to either confirm or refute the involvement of BMAA in development of ALS.

In addition, an extensive study of BMAA metabolism is currently being undertaken by the US National Toxicology Program (NTP). This study, performed in rats and mice of both genders, is evaluating the fate of radioactively labelled BMAA administered by single and multiple oral doses, and by intravenous injection. The study will assess the disposition of BMAA in various body tissues, seek to identify metabolites of BMAA and track elimination via urine, faeces and exhaled breath. The effect of fasting and other dietary variations will be examined to test the hypothesis that BMAA may be released during protein catabolism. Other proposed work includes an examination of the biological activity of BMAA,

including interactions with known neurotoxicants, and measuring BMAA levels in dietary supplements derived from cyanobacteria to assess levels of public exposure. This study will definitively establish whether BMAA is incorporated into proteins and the outcomes will determine whether further testing is undertaken by the NTP.

The study of risk factors for neurological diseases is difficult because of the long time frames involved, and there is increasing evidence that subtle neurological changes may occur years or even decades before disease symptoms become apparent. Risks from exposures to BMAA or other postulated environmental toxins (e.g. pesticides, heavy metals) may relate to cumulative exposure over many years or exposure at critical time periods for the neurological system (perhaps even *in utero*). The picture is further complicated by the possible role of variations in genetic susceptibility in the population, and the potential for interactions between different environmental factors.

At present the evidence on BMAA is not sufficient to conclude whether this compound is a contributing factor to human neurological disease. There is also uncertainty about how common BMAA production is among cyanobacterial species, and insufficient information to characterise current human exposure levels and determine the relative importance of drinking water, recreational water, food or other sources. Research studies currently underway should help to resolve some of the major uncertainties that currently limit understanding of the significance of BMAA to human health.

## References

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