



# $\beta$ -Methylamino-l-alanine (BMAA): Knowns and unknowns!



More than 60 years have passed since the world became aware of an unusually high proliferation of neurodegenerative disease within a small tribe in Guam. Known as *lytico-bodig* to the native Chamorro people (combining the terms for paralysis and dementia), this complex of diseases shared similarities with other fatal but little understood motor neuron diseases, like amyotrophic lateral sclerosis (ALS) and Parkinson's disease (PD). The notable increase in patient deaths prompted action from the research community, with specialists from diverse backgrounds – water engineers, biochemists, nutritionists, neuroscientists and neurologists – working to discover the root cause. Today, many years later, the origins of the outbreak remain poorly understood.

Over the last 40 years, a number of studies have implicated  $\beta$ -Methylamino-l-alanine (BMAA), a toxin produced by water-dwelling cyanobacteria and other microorganisms, as an environmental risk in the development of neurodegenerative disease (Cox, 2020). Notably there is a lack of scientific consensus that causality has been established. Cyanobacterial blooms are becoming increasingly common and pose a threat to modern water supply systems, as they can lead to the generation of cyanotoxins and potentially BMAA with hypothesized adverse health effects (Buratti *et al.*, 2017). It is thus important to understand not only how they may be removed from the water supply (Nisol *et al.*, 2019), but also how these toxins affect public health. Could BMAA turn out to be a factor in the development of neurodegenerative disease? Is the reality more complicated? Or could this compound have no link to disease?

## What is BMAA?

$\beta$ -Methylamino-l-alanine, or BMAA, is a non-protein amino acid reportedly produced by a diversity of cyanobacteria, as well as by some other microorganisms such as certain diatoms and dinoflagellates (Bishop and Murch 2019). Although generally found in water, cyanobacteria have also been found in a range of other ecosystems, including in soil in deserts and tropical rainforests (Popova and Koksharova, 2016; Buratti *et al.*, 2017). The toxins produced by cyanobacteria, also referred to as cyanotoxins include some of the most poisonous substances found in nature, and they have been responsible for the death of wild and farm animals and also human illness (Buratti *et al.*, 2017).

Although the lethality of cyanobacteria has been known of for more than a century, the idea that BMAA may have caused *lytico-bodig* (now referred to as the ALS-PD complex of Guam) only began to gain traction in the 1980s (Spencer *et al.*, 1987). At the time, BMAA was discovered in the seeds of *Cycas micronesica*, a plant native to the region (Popova and Koksharova, 2016). This discovery sparked a surge of interest in the decades-old mystery, with a flood of studies (Fig.1) emerging to test the hypothesis that BMAA has a chronic role in the development of ALS-PD, as well as other degenerative disorders.



## Key points:

- $\beta$ -Methylamino-l-alanine (BMAA) has been suggested to be a cause of neurodegenerative diseases including amyotrophic lateral sclerosis (ALS) and Parkinson's disease (PD).
- The lack of a standard method for detecting BMAA has led to many conflicting research findings; the recent review of analytical methods for the detection and quantification of BMAA (Bishop and Murch 2020) should be consulted prior to selecting or developing analytical methods.
- A thorough understanding of the requirements for robust detection and quantification of BMAA is essential when evaluating the literature and interpreting unpublished data.
- It is difficult to measure BMAA and isolate it from other compounds, which makes studying its impact on human health more challenging.
- While the presence of BMAA has been linked to neurodegenerative disease, there is still a lack of clear evidence for this compound's contribution to human neurological disease and causality at this time.

## Future directions:

- Safe levels of BMAA and/or cyanotoxins in water systems and food supplies should be determined.
- Research should be conducted to determine the causality and interaction effects of cyanotoxins and genetic factors in the development of neurodegenerative disease.



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## Complications of measuring BMAA

As it turns out, BMAA is notoriously difficult to detect and quantify. Several techniques have been developed to detect the compound in food and the environment, although each one possesses its own limitations and none are particularly consistent (Faassen *et al.*, 2012, Bishop and Murch 2020). The absence of reliable detection methods has led to many conflicting research studies, and has complicated efforts to compare findings across different studies (Faassen, 2014). Although most of these disagreements stem from the use of different detection methods across studies (Fig.2), some variation may be caused by the involvement of different cyanobacteria in each study, as the amount of BMAA produced by certain species can be greater than others (Faassen, 2014).

One challenging aspect of BMAA measurement is that the toxin does not normally appear in isolation, often coexisting with several other compounds present in the environment. The presence of chemical isomers of BMAA increases the likelihood of false positives (Banack and Murch, 2018). As a result, detection methods with low sensitivity and selectivity may therefore fail to detect an accurate amount of BMAA or even its presence (Popova and Koksharova, 2016).

## Presence in the environment and food supply

The renewed interest in BMAA and its discovery in Guam's food chain led many research groups to search for the toxin in other communities (Popova and Koksharova, 2016). Most studies found variable amounts of BMAA in widespread geographical locations such as the United States, Australia, South Africa, China, and many countries throughout Europe. The most common route for BMAA to enter the human body is through seafood consumption, however it can accumulate and spread throughout the whole food chain by what is referred to as *biomagnification* (Cox *et al.*, 2003). For example, once BMAA is released into a lake, it can be consumed by successively larger animals in the food chain – from microscopic phytoplankton to larger zooplankton, shrimp and krill, small and large fish – before potentially being consumed by a human. Further efforts are needed to identify other potential sources of exposure.

## Effect on humans

Our understanding of how BMAA affects human health is limited by the lack of a reliable detection method. While some postmortem studies found clear evidence of BMAA in brain specimens of patients who had passed away from neurodegenerative disease in Guam, Canada and the United States (Banack *et al.*, 2010), other groups failed to replicate these results (Montine *et al.*, 2005). These studies show that the issues with detection are not only limited to quantifying the amount in the environment or food, but also to detection of the compound in human tissue samples. The presence of BMAA in cerebral spinal fluid has been shown in a relatively small number of subjects ante mortem, which demonstrates that BMAA can find its way into the brain and possibly act either as a neurotoxin or augment the effect of other compounds (Berntzon *et al.*, 2015). It is of course not out of the question that genetic factors may also affect the accumulation rate of BMAA in the brain, which in turn could affect the likelihood and severity of neurodegeneration (Bradley and Mash, 2009). Despite lack of evidence that BMAA contributes to human neurological disease, limited exposure is advised (Banack and Murch, 2018).

## Possible mechanisms

Many studies have been conducted to show the effects of BMAA and to discover the pathways through which it may cause harm in the body. In fact, most studies in the field are focused on this matter as well as the effects of BMAA on the nervous system (Fig.1). These studies employed in vitro and in vivo models to determine how the molecule affects the internal organs, the behaviour of the subject, the pathways through which these changes take place and ultimately, how these pathways may be disrupted (Karamyan and Speth, 2008). These studies propose several mechanisms through which BMAA can induce the death of motor neurons and induce ALS-like symptoms, including the activation of glutamate receptors resulting in the overstimulation and death of motor neurons (Popova and Koksharova, 2016). It has also been suggested that BMAA can potentiate the effects of other neurotoxins such as methyl mercury (Rush *et al.*, 2012). Most of these studies investigated the effects of acute administration of the toxin in large amounts, across a variety of species. Attempts to replicate these findings in chronic studies with smaller amounts administered over longer periods of time yielded conflicting results (Karamyan and Speth, 2008).

## Summary

It is unfortunate that despite the resources and intellectual efforts devoted to this topic, the effects of BMAA on public health continue to be heavily debated (Duncan, 1992; Chernoff *et al.*, 2021). Some authors who weighed the evidence up closely conclude that “the key question that needs to be answered first is whether the proposed toxic effects of BMAA can be confirmed in health-relevant dose ranges” (Chernoff *et al.*, 2021). While there is little doubt that environmental factors play a role in the development of some neurodegenerative disorders, reviewed literature (Fig.1) indicates that the lack of standard detection methods for BMAA makes it difficult to determine the causality of each factor at play. If we can solve this problem, we may get closer to understanding the potential public health risk, or lack thereof, from BMAA.

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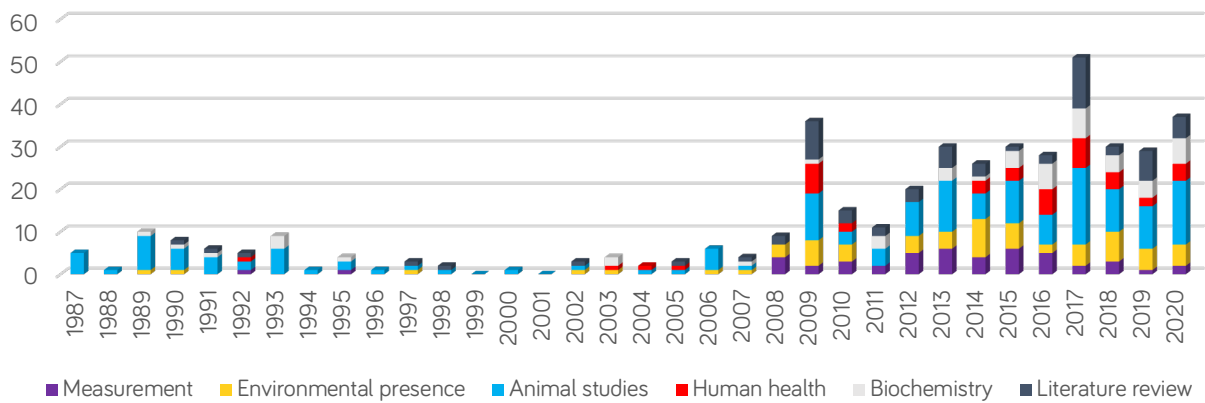


Figure 1: A PubMed search of the BMAA term reveals 430 articles dating back from 1987 to the present day, with the rate of articles increasing by the year 2009. While the number of animal studies investigating the physiological effects of the toxin remains steady (light blue), there is a recent surge of interest in detection methodology (purple).

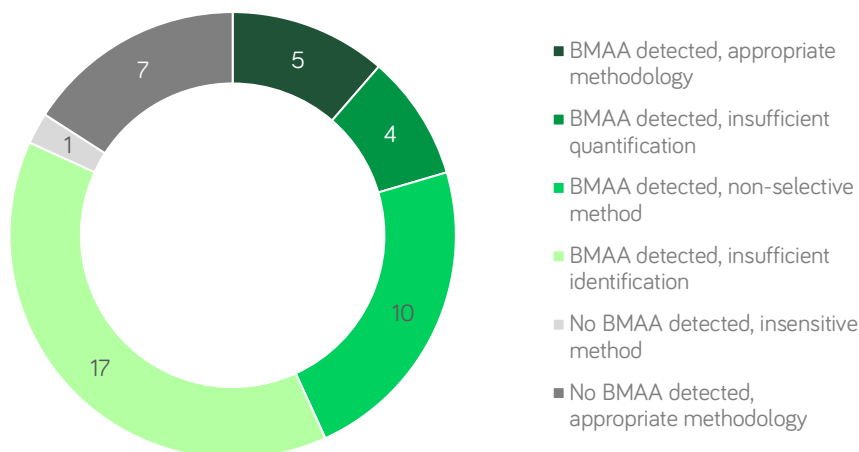


Figure 2: BMAA detection across different studies. Green shading indicates studies that detected BMAA, while shades of grey indicate negative findings. Studies represented by the top three sections (16/44; darker colors) reported a more comprehensive detection methodology (Faassen, 2014).