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A systematic review on analytical methods of the neurotoxin β-N-methylamino-L-alanine (BMAA), and its causative microalgae and distribution in the environment

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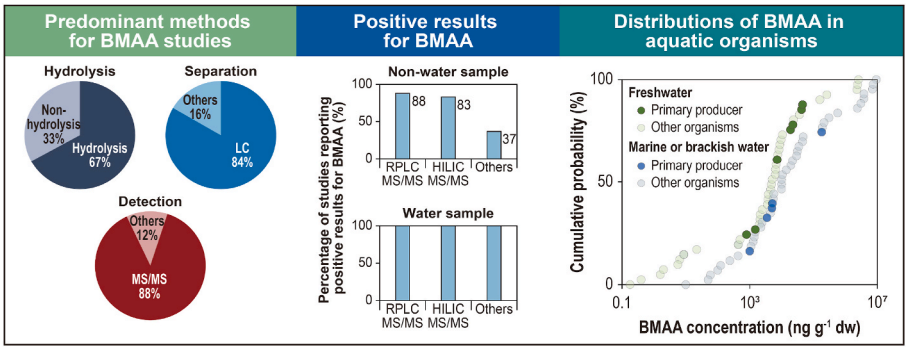
HIGHLIGHTS

- LC-MS/MS was the predominant method for BMAA analysis between 2019 and 2024.
- Hydrolysis is essential for extracting and quantifying BMAA in various matrices.
- RPLC-MS/MS yielded the highest percentage of BMAA-positive results.
- BMAA is widely distributed in both freshwater and marine ecosystems globally.

GRAPHICAL ABSTRACT



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ABSTRACT

β-N-Methylamino-L-alanine (BMAA), a neurotoxin produced by various microalgal groups, is associated with neurodegenerative diseases and is considered a major environmental factor potentially linked to sporadic amyotrophic lateral sclerosis. This study systematically reviews the analytical methods used to study BMAA in publications from 2019 to the present. It also investigates the causative microalgae of BMAA and its geographical distributions in aquatic ecosystems based on studies conducted since 2003. A comprehensive search using the Web of Science database revealed that hydrolysis for extraction (67%), followed by quantification using LC-MS/MS (LC: 84%; MS/MS: 88%), is the most commonly employed method in BMAA analysis. Among analytical methods, RPLC-MS/MS had the highest percentage (88%) of BMAA-positive results and included a high number of quality control (QC) assessments. Various genera of cyanobacteria and diatoms have been reported to produce BMAA. The widespread geographical distribution of BMAA across diverse ecosystems highlights significant environmental and public health concerns. Notably, BMAA accumulation and biomagnification are likely more potent in marine or brackish water ecosystems than in freshwater ecosystems, potentially amplifying its ecological impacts. Future research should prioritize advanced, sensitive methods, particularly LC-MS/MS with as many QC assessments as possible, and should expand investigations to identify novel microalgal producers and

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previously uncharted geographical areas, with a special focus on marine or brackish water ecosystems. This effort will enhance our understanding of the environmental distribution and impacts of BMAA.

1. Introduction

Biotoxins, substances of biological origin produced by various organisms, present significant ecological and health challenges. Microalgae such as cyanobacteria, diatoms, and dinoflagellates are particularly notable for their capacity to produce diverse biotoxins (Chorus et al., 2000; Cox et al., 2005; Hasle, 2002; Jiang et al., 2014a; Paerl and Otten, 2013). Their ability to produce biotoxins, coupled with their increased seasonal proliferation due to global climate change and escalated nutrient influx, poses significant risks that negatively affect ecosystems, wildlife, and human health (Berdalet et al., 2016; Griffith and Gobler, 2020; Tester et al., 2020). Algal biotoxins are responsible for various symptoms and can be categorized into cytotoxins, dermatoxins, hepatotoxins, and neurotoxins based on their harmful effects. For example, cytotoxins such as cylindrospermopsin induce cell damage (Gutiérrez-Praena et al., 2012; Straser et al., 2013), while dermatoxins like aplysiatoxins and lyngbyatoxins irritate or damage the skin (Rzymski and Poniedzialek, 2012). Hepatotoxins, including microcystin and nodularin, target the liver, leading to damage or dysfunction (Chen et al., 2013; Shi et al., 2021). Neurotoxins, such as anatoxin, β-N-methylamino-L-alanine (BMAA), domoic acid (DA), saxitoxin, and 2,4-diaminobutyric acid (DAB), impair the nervous system, resulting in neurotoxicity (Costa et al., 2010; Li et al., 2024; Metcalf et al., 2021b).

BMAA, a non-proteinogenic amino acid, has been implicated in neurotoxic effects through mechanisms such as excitotoxicity, protein misincorporation, and oxidative stress (Cox et al., 2016; Dunlop et al., 2013; Li et al., 2024; Liu et al., 2009; Lobner et al., 2007; Rao et al., 2006; Van Onselen and Downing, 2018). It is associated with neurodegenerative diseases such as amyotrophic lateral sclerosis-parkinsonism dementia complex (ALS-PDC) and Alzheimer's disease (AD) (Cox et al., 2003; Pablo et al., 2009). Additionally, numerous studies have demonstrated the adverse effects of BMAA not only in mammals, including humans and monkeys (Cox et al., 2003, 2016; Pablo et al., 2009), but also in marine animals (Fu et al., 2022; Li et al., 2020), microalgae (Downing et al., 2012; Kim et al., 2022, 2024b; Li et al., 2023), and plants (Brenner et al., 2000; Contardo-Jara et al., 2013; Samardzic et al., 2021). A recent study identified 83 environmental factors potentially linked to sporadic ALS (SALS), with BMAA ranked as the most significant (Newell et al., 2022). Formaldehyde, ranked second, along with heavy metals such as manganese, mercury, and zinc, was also noted for its significant association with SALS, emphasizing the importance of investigating environmental determinants in the etiology of neurodegenerative diseases (Newell et al., 2022).

BMAA was first isolated from the cycad tree *Cycas circinalis* in the 1960s (Vega and Bell, 1967). This discovery was prompted by the unusually high incidence of ALS-PDC among the indigenous population of Guam, the Chamorro people (Kurland and Mulder, 1954; Nunn, 2017; Zimmerman, 1945). Although initial interest in BMAA was evident, the hypothesis linking BMAA and ALS-PDC was controversial due to the high concentration of BMAA required to elicit toxicity (Duncan et al., 1988, 1990; Perry et al., 1989). In 2003, the bioaccumulation and biomagnification of BMAA were demonstrated in the Chamorro food chain, from cyanobacteria and cycads to flying foxes and humans, suggesting dietary consumption as a potential cause of ALS-PDC in Guam (Cox et al., 2003). Since then, various cyanobacteria and diatoms have been identified as BMAA producers at the genus, species, and strain levels (Cox et al., 2005; Jiang et al., 2014a). Bioaccumulation of BMAA has been reported in diverse organisms across many countries (Brand et al., 2010; Jiang et al., 2014b; Jonasson et al., 2010; Masseret et al., 2013; Wang et al., 2021; Wu et al., 2019). Furthermore, biomagnification of BMAA in aquatic ecosystems was observed in the Baltic Sea, Thai Lake, China, and Jiaozhou Bay, China, highlighting the widespread occurrence of this environmental neurotoxin (Jonasson et al., 2010; Wang et al., 2021; Wu et al., 2019).

The analysis of BMAA has significantly evolved over time, with methodologies becoming more sensitive and precise. Initially, BMAA detection employed paper chromatography and electrophoresis, known as iontophoresis (Cohen, 2012; Vega and Bell, 1967). As research advanced, methods incorporated technologies like gas chromatography-mass spectrometry (GC-MS) and reverse-phase liquid chromatography (RPLC) with derivatizing agents such as 9-fluorenylmethylchloroformate (FMOC) (Cohen, 2012; Duncan et al., 1988; Kisby et al., 1988). These advancements improved analytical sensitivity and specificity, allowing more reliable detection of BMAA in complex biological and environmental samples. Despite these developments, challenges persisted due to the low concentrations of BMAA and the complexity of the matrices (Cohen, 2012). Until the beginning of 2019, the most recognized and widely used method for BMAA analysis was liquid chromatography-tandem mass spectrometry (LC-MS/MS) (Bishop and Murch, 2020; Faassen, 2014). This technique offers superior sensitivity and specificity, enabling accurate detection of BMAA across various samples.

Numerous studies on BMAA have examined its toxicity, associated diseases, analytical methods, causative microorganisms, and environmental distribution. This review is organized into four main sections: 1) trends and the main topics of BMAA study, 2) analytical methods of BMAA, 3) causative microalgae of BMAA, and 4) geographic distributions of BMAA across diverse ecosystems. In the section "analytical methods of BMAA", we conducted a systematic review to summarize the methods employed between 2003 and early 2019 (Bishop and Murch, 2020). For the period from 2019 to 2024, we performed our own review. Each section is thoroughly examined to provide a comprehensive understanding of BMAA and to identify emerging trends. Finally, future directions are proposed based on the current understanding and limitations of BMAA research.

2. The trends and main topics of BMAA study

2.1. Data collection and research trend analysis

The discovery of BMAA as an environmental neurotoxin, its biomagnification in the food web of Guam, and its identification in cyanobacteria as the initial producer have sparked significant interest in BMAA research (Cox et al., 2003, 2005). From 2003 to 2024, a total of 459 research articles and 7311 citations, excluding self-citations, have been recorded in the Web of Science™ (WoS) database (https://www.webofscience.com), as searched on March 30, 2024, using the terms 'β-N-methylamino-L-alanine' or 'BMAA'. Articles published in 2024 were included in those in 2023 for counting (Fig. 1a). Irrelevant fields, such as telecommunications and arts and humanities, were excluded. The number of published articles and citations increased until 2018 (Fig. 1a). Subsequently, a decline in article publications was observed until 2021, while citation numbers fluctuated through 2024. This review of published papers revealed that the USA is the leading country in BMAA research from 2003 to the present (Fig. 1b). The involvement of the USA in publications constituted 27%, followed by Sweden (9%), Canada (6%), China (6%), Australia (5%), and South Africa (5%). Countries that published fewer than 30 articles from 2003 to 2024 were grouped under "others", constituting 42%.

2.2. Bibliometric network analysis and main topics

Keywords from 459 research articles were identified through a network analysis using VOS viewer software (Version 1.6.19, Leiden University, Leiden, The Netherlands) (Van Eck and Waltman, 2010). The analysis type was set to occurrence, and full counting was chosen as the counting method to visualize bibliometric network graphics and display frequently mentioned words. The minimum number of occurrences for a keyword was set to nine. Out of 2279 keywords, 93 met this criterion and were clustered into four groups. The ten most prominent keywords in each cluster were selected based on standard weighting scores (Stephan et al., 2017). The top keywords in Clusters 1, 2, 3, and 4, related to "harmful algae and algal biotoxins", "BMAA and related mechanisms and diseases", "First finding of BMAA as a neurotoxin in Guam", "BMAA and analytical method", were highlighted in red, green, blue and yellow, respectively (Fig. 1c and Table 1). The colors of the nodes indicate different clusters, the size of nodes reflects the frequency of keyword occurrences, and the thickness of lines connecting nodes shows the closeness between words (Fig. 1c).

The top 10 keywords in Cluster 1, "harmful algae and algal biotoxins", were BMAA, methylamino-L-alanine, cyanobacteria, cyanotoxins, toxins, toxicity, blooms, DAB, neurotoxins, and microcystins (Fig. 1c and Table 1). Cyanobacteria and diatoms have been continuously reported as BMAA producers (Baptista et al., 2011; Błaszczyk et al., 2021; Cox et al., 2005; Fan et al., 2015; Jiang et al., 2014a; Lage et al., 2016a; Li et al., 2010; Réveillon et al., 2014, 2015; Violi et al., 2019b; Wang et al., 2021). One study suggested dinoflagellate as a possible BMAA producer (Lage et al., 2014), although this result has not been further supported. DAB, a structural isomer of BMAA, causes neurotoxicity similar to BMAA (Schneider et al., 2020; Spasic et al., 2018; Weiss et al., 1989). Bacteria, cyanobacteria, and diatoms are known to produce DAB (Catch et al., 1948; Jiang et al., 2014a; Violi et al., 2019a, 2019b; Wang et al., 2021). Microcystins are hepatotoxins produced by freshwater cyanobacteria (Codd, 1995; Sivonen and Jones, 1999). Additionally, okadaic acid, dinophysistoxins, yessotoxins, pectenotoxins, brevetoxins, and azaspiracids are biotoxins produced by various harmful algae (Daugbjerg et al., 2000; Paz et al., 2007; Pizarro et al., 2008). More detailed information on BMAA producers is provided in "4. Causative microalgae of BMAA".

Cluster 2, "BMAA and related mechanisms and diseases", includes keywords such as ALS, beta-N-methylamino-L-alanine, neurotoxin, oxidative stress, exposure, disease, neurodegeneration, neurotoxicity, acid, and amino-acids. The neurotoxicity of BMAA and its related diseases were comprehensively summarized in a recent review article (Li et al., 2024). Keywords for Cluster 3, related to "First finding of BMAA as a neurotoxin in Guam", include amyotrophic lateral sclerosis, Guam, flying foxes, cyanobacterial neurotoxins, Chamorro people, parkinsonism-dementia, biomagnification, ALS-PDC, amyotrophic lateral sclerosis, and cycad neurotoxins. The history of BMAA was thoroughly described by Nunn (2017). Thus, the Clusters 2 and 3 will not be covered in the present review.

Cluster 4, "BMAA and analytical method", includes neurodegenerative disease, amino-acid, cyanobacterial neurotoxin, neurotoxic amino-acid, 2,4-diaminobutyric acid, neurotoxin BMAA, mass-spectrometry, tandem mass-spectrometry, beta-N-methylamino-L-alanine, and quantification. We used a published paper to summarize extraction and analytical methods employed between 2003 and early 2019 (Bishop and Murch, 2020) and reviewed the methods used from 2019 to 2024.

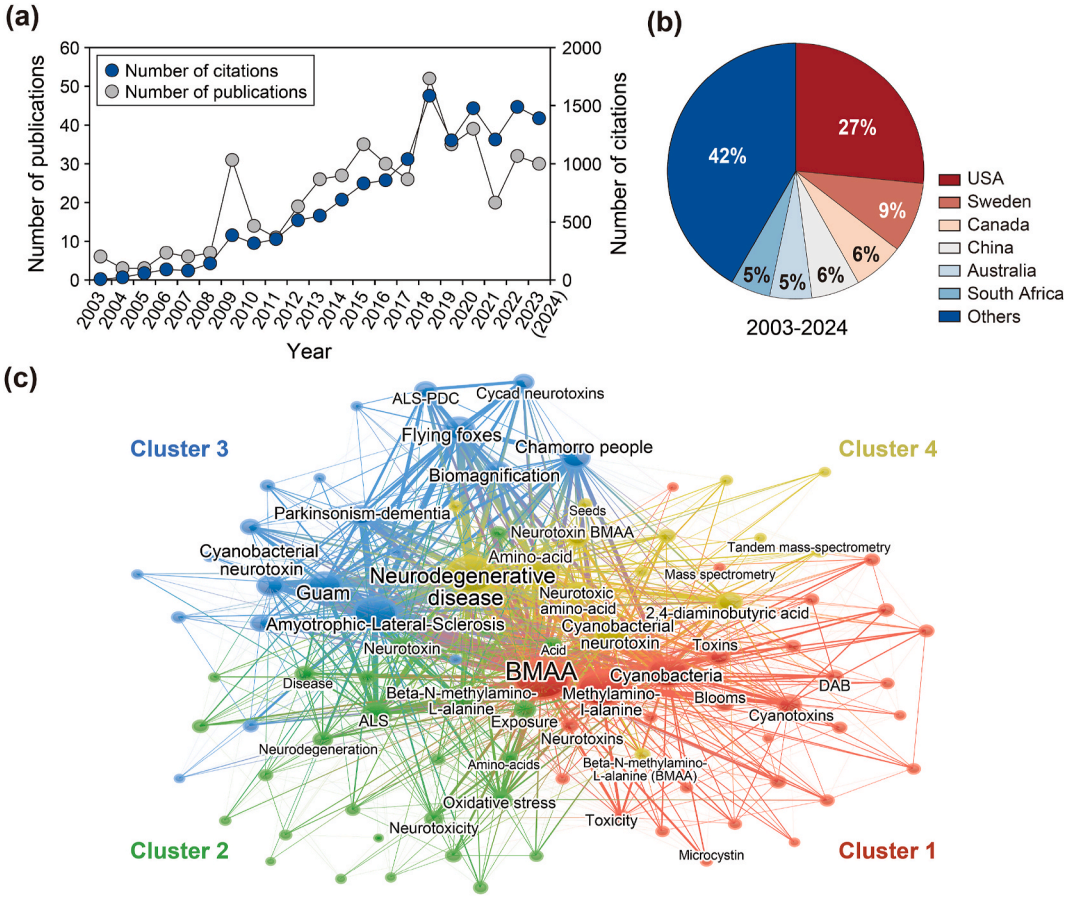

Fig. 1. (a) The number of publications and citations searched for the term 'β-N-methylamino-L-alanine' or 'BMAA', **(b)** the proportion of countries involved in the publications, and **(c)** the bibliometric network analysis from reviewed articles (2003–2024) using VOS viewer.

Table 1
The top 10 keywords relevant to BMAA in each of the four clusters produced by keywords network analysis.

Top	Cluster 1	Cluster 2	Cluster 3	Cluster 4
1	BMAA	ALS	Amyotrophic-lateral-sclerosis	Neurodegenerative disease
2	Methylamino-l-alanine	Beta-N-methylamino-l-alanine	Guam	Amino-acid
3	Cyanobacteria	Neurotoxin	Flying foxes	Cyanobacterial neurotoxin
4	Cyanotoxins	Oxidative stress	Cyanobacterial neurotoxins	Neurotoxic amino-acid
5	Toxins	Exposure	Chamorro people	2,4-diaminobutyric acid
6	Toxicity	Disease	Parkinsonism-dementia	Neurotoxin BMAA
7	Blooms	Neurodegeneration	Biomagnification	Mass-spectrometry
8	DAB	Neurotoxicity	ALS-PDC	Tandem mass-spectrometry
9	Neurotoxins	Acid	Amyotrophic lateral sclerosis	Beta-N-methylamino-l-alanine (BMAA)
10	Microcystins	Amino-acids	Cycad neurotoxins	Quantification

3. Analytical methods of BMAA

3.1. Analytical methods for BMAA between 2003 and early 2019

Bishop and Murch (2020) conducted a comprehensive review of analytical methodologies for BMAA analysis, examining 148 articles published from 2003 to 2019. Their findings revealed that 84% of these articles reported positive findings for BMAA in one or more samples. Furthermore, they noted a variance in detection rates among different analytical techniques. Of the studies reviewed, 92% of those employing RPLC reported BMAA-positive results, compared to only 57% of studies using hydrophilic interaction liquid chromatography (HILIC) and 71% of studies employing other methods, such as capillary electrophoresis (CE), ^{1}H nuclear magnetic resonance (NMR) spectroscopy, and enzyme-linked immunosorbent assay (ELISA) kits (Bishop and Murch, 2020). Notably, when cyanobacteria were used as the matrix, the disparity between HILIC and RPLC in the positive detection of BMAA became even more evident: 95% positive detection rate for RPLC and 25% for HILIC (Bishop and Murch, 2020). Among the various methods, RPLC with 6-aminoquinolyl-N-hydroxysuccinimidyl carbamate (AQC) derivatization is currently the only method verified under the AOAC™ Guidelines for Single Laboratory Validation (Glover et al., 2015). However, a comparison between RPLC with AQC and HILIC without derivatization in BMAA quantification has supported the validation of HILIC utilization (Wang et al., 2021).

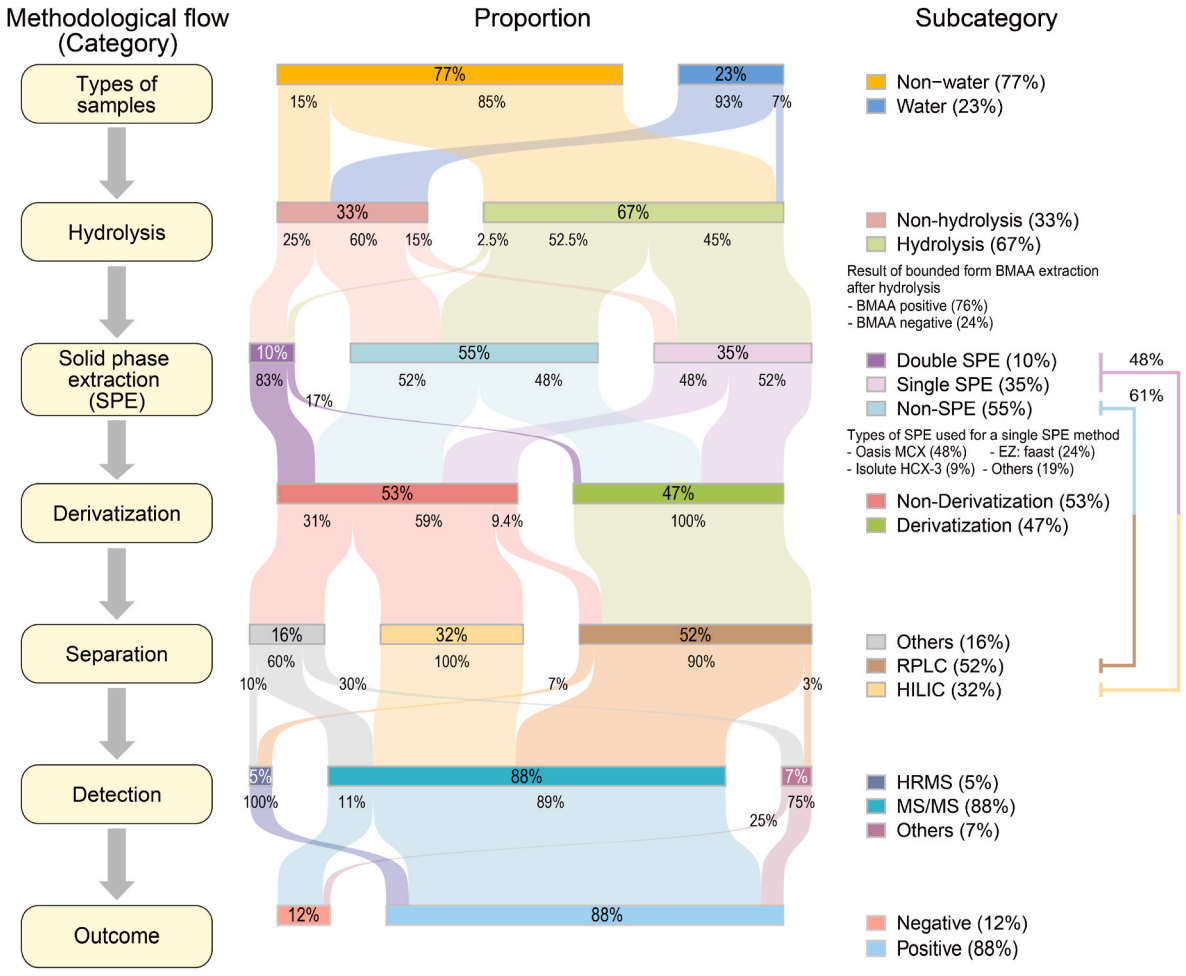

Fig. 2. Sankey diagram of methodological flow for BMAA analysis and its outcomes from reviewed articles from 2019 to 2024. Information on the reviewed articles is provided in Table S2.

3.2. Analytical methods for BMAA between 2019 and 2024

This review examines 60 papers published between 2019 and 2024, focusing on the extraction and analytical methods for detecting and quantifying BMAA. All studies are provided in Table S1 of the Supplementary Materials. The studies were reviewed to identify the detailed methods used for the extraction and analysis of BMAA, depending on sample types and their consequent outcomes. Samples were divided into non-water and water types (Fig. 2 and Table S1). If both types were analyzed in one article, each type was counted separately. For example, zebrafish, opossum shrimp, and the medium used for their cultivation were analyzed (Wang et al., 2020): zebrafish and opossum shrimp were classified as non-water samples and counted once, not twice; the medium was classified as a water sample and also counted once. If at least one sample was quantified as BMAA positive, the outcome was treated as BMAA positive. If more than one method was tested or utilized in a single article, each method was treated separately. For instance, Wang et al. (2021) used RPLC-MS/MS with AQC and HILIC-MS/MS to quantify BMAA in the same marine animal samples. Both methods were counted and listed in the table, even though the same samples were used. Sampling details, such as method and season, were not considered in the present study. A Sankey diagram, created using the ggsankey package by David Sjöberg in R (version 4.2.3), was used to vividly visualize methodological flows (Fig. 2). The methodological process was divided into six categories: sample types, hydrolysis, solid phase extraction (SPE), derivatization, chromatography, and detection.

3.3. Sample types and hydrolysis

A variety of samples were analyzed to verify the production and accumulation of BMAA, as well as the effectiveness of analytical methods. The linkage ratio of a subcategory (i.e., non-water and water) within a primary category (i.e., types of samples) to a corresponding subcategory (i.e., non-hydrolysis and hydrolysis) in the subsequent primary category (i.e., hydrolysis) is quantitatively represented by the numbers provided beneath each subcategory. Non-water samples represented the majority, accounting for 77% of all samples (Fig. 2 and Table S1). This category included terrestrial and aquatic animals, cells, dietary supplements, filtered air and ground, insects, microalgae, plants, etc. Water samples constituted the remaining 23%. Regardless of the analytical methods used, non-water samples were analyzed more frequently than water samples (Fig. S1b), yet fewer studies reported positive BMAA results in non-water samples compared to water samples (Fig. S1c). In non-water samples, the percentage of studies reporting BMAA-positive results was 88%, 83%, and 37% when using RPLC-MS/MS, HILIC-MS/MS, and other methods, respectively. In contrast, all studies assessing BMAA in water samples reported positive results. These findings suggest that the type of sample may influence BMAA detection, possibly due to differences in the sample matrix.

Furthermore, 85% of non-water and 7% of water samples were hydrolyzed, while the remainder were not. The associated or bounded form of BMAA, rather than the total form, was extracted and analyzed separately from the free form in 42% of the reviewed samples. Among these, 76% reported a positive result for BMAA, while 24% reported a negative result (Fig. 2 and Table S1). Employing acid hydrolysis on tissue samples can increase the extracted concentration of BMAA by 10 to 240-fold, highlighting the presence of two forms of BMAA (i.e., free and protein-associated) (Cox et al., 2003). The importance of hydrolysis was further demonstrated by identifying another form, soluble bound BMA, which exists in varying proportions depending on the samples analyzed (Faassen et al., 2016). In the same study, the authors debated the use of the term “protein-associated/bound form” due to the lack of BMAA incorporation into bacterial protein in vivo (Van Onselen et al., 2015), suggesting the term “precipitated bound BMAA” instead. Further research using hydrolysis to extract BMAA is essential to accurately quantify BMAA in various natural samples and better understand the forms in which BMAA exists and their proportions.

3.4. Clean-up, derivatization, and separation

The results of SPE for BMAA analysis have been controversial due to low recovery rates, necessitating careful optimization of the process (Esterhuizen-Londt and Downing, 2011; Yan et al., 2017). Bishop and Murch (2020) noted that before 2019, SPE was more commonly used for HILIC analysis (67%) than RPLC analysis (37%). The present review, categorizing studies based on their use of SPE into no SPE, single SPE, and tandem SPE (Fig. 2 and Table S1), found similar results. Studies conducted between 2019 and 2024 tended to use SPE in conjunction with HILIC rather than RPLC. Among the studies using SPE, 48% employed HILIC, while 44% used RPLC. In addition, among the studies not using SPE, 61% employed RPLC, suggesting that the higher usage rate of RPLC compared to HILIC may influence the adoption of SPE (Fig. 2). Among single SPE methods, Oasis MCX had the highest usage rate at 48%, followed by EZ:faast at 24% and Isolute HCX-3 at 9%. The combinations used for tandem SPE included Oasis HLB + Oasis MCX and Strata-X + Oasis MCX.

Derivatization in LC-MS results in extended retention times on RP columns, facilitating compound separation within the sample matrix and improving resolution for amino acid analysis (Cohen, 2012). RPLC-MS/MS with AQC, the only verified method for BMAA analysis under the AOAC™ Guidelines, was widely used between 2003 and 2019 (Bishop and Murch, 2020; Glover et al., 2015). Research from 2019 to 2024 shows a consistent pattern; the highest usage rate (47%) was observed for RPLC with derivatization (Fig. 2 and Table S1), followed by HILIC without derivatization (32%), other methods without derivatization (16%), and RPLC without derivatization (5%). RPLC and HILIC usage rates until 2019 were 70% and 19%, respectively. Between 2019 and 2024, RPLC remain the most widely used method at 52%, with HILIC at 32%. The comparison between the periods 2003–2019 and 2019–2024 revealed an increasing trend in HILIC usage. However, in 2019–2024, the use of RPLC and HILIC, together with MS/MS, varied significantly depending on the sample type (Fig. S1a). In non-water samples, 57% of the studies employed RPLC-MS/MS, while only 26% used HILIC-MS/MS. In contrast, for water samples, only 14% of the studies used RPLC-MS/MS, while 50% used HILIC-MS/MS. Based on the data and analysis results reporting BMAA-positive findings (Figs. S1a and S1c), it appears that the choice of analytical methods for water samples does not significantly affect the outcome. However, for non-water samples, the methods used seem to influence the detection of BMAA. RPLC-MS/MS yielded the highest percentage (88%) of BMAA-positive results and employed more quality controls (QCs) compared to studies using HILIC-MS/MS. Recent studies comparing BMAA concentrations using HILIC and RPLC have demonstrated comparable performance between the two methods (Banack, 2021; Beach et al., 2015; Kerrin et al., 2017; Wang et al., 2021). However, the validity of using HILIC (i.e., ZIC-HILIC) remains controversial due to its failure to meet the criteria for selectivity, sensitivity, and precision in BMAA analysis (Tymm et al., 2021). For broader applications, HILIC-MS/MS requires validation with a greater number of QCs, similar to RPLC-MS/MS.

3.5. Detection and quantification of BMAA

MS/MS has become the predominant detector for BMAA analysis (Bishop and Murch, 2020; Faassen, 2014). Before MS/MS emerged as the preferred choice, various detectors such as fluorescence detector (FD), spectrophotometer, ^{1}H NMR, and MS were tested and utilized (Bishop and Murch, 2020; Faassen, 2014). Initial studies identifying

Table 2
Reported cyanobacteria as producers and as non-producers of BMAA.

Genus	BMAA-positive species/strain	BMAA-negative species/strain
Marine or brackish water ecosystems		
Anabaena	sp. CCNP1406	sp. CCNP1407
Aphanizomenon	*flos-aquae*	–
Chroococcidiopsis	*indica* GQ2-7, GT-3-26	–
Cyanobium	LEGE06068, sp.	–
Dolichospermum	sp. CCNP0808	–
Leptolyngbya	aff. *bijugata*, sp. LEGE07085, 6069, 7080, 7084, 7091, 6070, 7075	–
Lyngbya	*majuscule*	–
Microcoleus	*chthonoplastes* LEGE 07092, *vaginatus* LEGE 07076	*chthonoplastes* LEGE 07092
Myxosarcina	*burmensis* GB-9-4, *concinna* GT-7-6, sp. LEGE 06146	–
Nodularia	sp. LEGE 06071	*spumigena* CCNP1401, 1402
Nostoc	CMMED01, 268, sp. LEGE06077, LEGE06078, LEGE06079	–
Phormidium	*animale* LEGE 06072, *chalybeum* LEGE 06078	sp. CCNP1301, 0909
Prochlorococcus	*marinus* CCMP1377	–
Symploca	PCC8002	PCC8002
Synechococcus	sp. LEGE07074	*elongatus* CCAP1479/1B, sp. TES 206V, TES 206R, TES 206H6, TES 206D8
Synechocystis	*salina* LEGE07073, LEGE06079, LEGE06083	CCNP1104
Trichodesmium	*thiebautii*, CCMP1985	–
Freshwater or terrestrial ecosystems		
Anabaena	sp., PCC7120, J241, 331, *variabilis* ATCC29413	*oumiana* ITEP26, *flos-aquae* SAG30.87, sp. FACHB1091, 1180, 12631, 1388, CCNP1408, 1409
Aphanizomenon	–	*flos-aquae* FACHB1171, 1249, 1290
Calothrix	PCC7103, C511	sp. FACHB154, 167. CCNP0907, 1410
Chlorogloeopsis	PCC6912	–
Chroococcus	sp.	
Cyanodictyon	R202	–
Cylindrospermopsis	*raciborskii* CR3	*raciborskii*, ITEP18
Fischerella	PCC7521	–
Dolichospermum	–	*planctonicum* CCNP0709
Leptolyngbya	B121, D351, J341, Q411, R203, PCC7310, sp.	PCC7310
Limnothrix	K901	–
Lyngbya	sp.	*maiussula* FACHB-866, *cryptovaginatus* FACHB-890
Merismopedia	sp.	–
Microcystis	PCC7806, 7820, D351, *aeruginosa*, *flos-aquae*	PCC7806, *aeruginosa* M905, 315, FACHB905, 315, CCNP1101, 1102, 1103, 0906, AB2005/17, 2005/19, 2005/22, 2005/26, 2005/28, 2005/30, 2005/31, 2005/32, 2005/33, 2005/40, 2005/41, 2005/42, 2005/43, 2005/45, 2005/46, 2005/47, NIES88, *flos-aquae*
Nodularia	–	*harveyana* FACHB259, 1490, *spumigena* 1983/300, 306, NSG01, 0205
Nostoc	*Pc*, enc, PCC9305, 7422, 9229, 8001, 8963, 8964, 6310, 7107	LBG1, PCC7120, 7107, 73102, 9401, sp. CCNP0907, FACHB 106, 973, 1042, 1043, 1053, 1135, 1145, 1149, 1154, 1155, 1159, 1162
Oscillatoria	C511, D241, D351, G401, J121, V203, sp.	–
Phormidium	sp., H602	*ambiguum* FACHB161, *foveolarum* FACHB239, *tenue* FACHB886, 1050, sp. FACHB1099, 1129, 1136, 1137
Planktothrix	D311, H602, S701, *agardhii* CCNP1303, NIES 595	*agardhii* CCNP1304, FACHB 1243, 1261
Plectonema	PCC73110	*phormidiodes* FACHB200
Pseudoanabaena	G227, K401, R203	CCNP1306
Scytonema	PCC7110	sp, FACHB625, 626, 628, 633, *javanicum* FACHB887
Synechococcus	PCC6301, Q131	FACHB1061
Synechocystis	PCC6803, J341	PCC6308, 6803

BMAA biomagnification and diverse cyanobacteria as BMAA producers used HPLC-diode array detector (DAD) and HPLC-FD, respectively (Cox et al., 2003, 2005). Faassen (2014) claimed, without providing evidence, that these methods were not specific, although they were considered state-of-the-art at the time. A spectrophotometer was used as the detector for ELISA, but controversial results, particularly false positives and a lack of linearity in the calibration curves of ELISA, have limited its adoption in recent studies (Bishop and Murch, 2020). Only 5% of all studies between 2019 and 2024 used ELISA and spectrophotometers (Table S1). ^{1}H NMR was used only once in 2009, with no subsequent studies employing this method due to its low sensitivity (Faassen, 2014). Since 2008, most studies have reported using either MS or MS/MS as the detector (Bishop and Murch, 2020; Faassen, 2014). MS/MS, with its high selectivity in choosing the transitions of both precursor and product ions, has established itself as the preferred method for BMAA study. Recent studies have shown that 88% employed MS/MS (Fig. 2).

4. Causative microalgae of BMAA

Cyanobacteria, diatoms, and dinoflagellates have been suggested as producers of BMAA (Cox et al., 2005; Jiang et al., 2014a; Lage et al., 2014). However, evidence for BMAA production in dinoflagellates is relatively scarce compared to that in cyanobacteria and diatoms (Tables 2 and 3, and S2). Consequently, most studies, including this review, have primarily focused on cyanobacteria and diatoms. In this review, cyanobacteria and diatoms proven to produce BMAA at the species or strain level from 2003 to 2024 were recategorized at the genus level, with details on specific species or strains included (Tables 2 and 3, and S2). To summarize previous studies, the following parameters were

Table 3
Reported diatoms as producers and as non-producers of BMAA.

Genus	BMAA-positive species or strains	BMAA-negative species or strains
Marine or brackish water ecosystems		
Asterionellopsis	–	*glacialis* CCMP 139
Chaetoceros	*calcitrans* CCMP1315, *diadema* MC2830, *decipiens* MC2501, *socialis* SCCAP K0550, sp.	*laevisporus* MC2835, *lauderi* MC2769, *tortissimus* MC2901, *pseudo-curvisetus* MC2880, *curvisetus* MC2873, *hirtisetus* MC2597, MC2701, sp. MC2677, *pumilum*
Coscinodiscus	*granii* SCCAP K1831	–
Ditylum	*brightwellii* strain 1 to 4	–
Halamphora	–	*coffeaeformis* CCAP1001/2
Minidiscus	–	*comicus* MC6310, *spinulatus* MC6313, *spinulosus* MC6341
Navicula	*pelliculosa* CCAP 1050/9	–
Odontella	–	*aurita* AC815
Phaeodactylum	*tricornutum* CCAP1055/1, SCCAP K-1280	–
Planktoniella	*blanda* MC6394	*blanda* MC6056
Pseudo-nitzschia	*lundholmiae* MC5134, *bipertita* MC4552, *simulans* MC4394, *delicatissima* MC4034, sp. MC4630, *fraudulenta* MC4616, *multiseries* MC4451, MC4185, *caciantha* MC4584	*delicatissima* P5C1, *dolorosa* MC4588, *taiwanensis* MC5109, *unseriata* MC4196, *americana* MC4127, *qiana* MC4418, *pungens* MC3052, *bipertita* MC4557, *nanaoensis* MC4215, *multiseries* MC4427, *caciantha* MC4537
Skeletonema	*marinoi* SCCAP K0669, SAAE08603, ST28	*marinoi* CCMP1332, *pseudocostatum*
Thalassiosira	*allenii* MC6441, *andamanica* MC6523, *gravida* MC6463, *ludiana* MC6465, *minima* MC6475, *sinica* MC6025, *tealata* MC6127, *tenera* MC6420, *weissflogii* GUMACC123, 162, *pseudonana* CCMP1015	*allenii* MC6101, *andamanica* MC6524, *binata* MC6016, *delicatula* MC6404, *eccentrica* MC6091, *flabellata* MC6215, *gravida* MC6093, *minima* MC6447, *minuscula* MC6361, *nordenskioeldii* MC6069, *oceanica* MC6331, *pseudonana* MC124, *punctigera* MC6090, *tenera* MC6354, *weissflogii* CCMP1336
Freshwater ecosystems		
Aulacoseira	sp.	–
Cyclotella	sp.	–
Fragilaria	–	sp.
Tabellaria	sp.	–

considered: 1) the concentration of BMAA in ng g^{-1} dry weight (dw) (Table S2), and 2) the origin of microalgae (marine or brackish water ecosystems or freshwater or terrestrial ecosystems) (Tables 2 and 3 and S2). If the origin of algal culture was unclear, it was determined based on the salinity of the culture medium. Three algal species/strains with unknown origins were included in the freshwater or terrestrial ecosystems category, and their origin was listed as "unknown" in Table S2.

Cyanobacteria from marine or brackish water ecosystems were categorized into 17 genera, while those from freshwater or terrestrial ecosystems were grouped into 24 genera (Baptista et al., 2011, 2015; Błaszczyk et al., 2021; Cervantes Cianca et al., 2012; Cox et al., 2003, 2005; Esterhuizen and Downing, 2008; Fan et al., 2015; Krüger et al., 2010; Kubo et al., 2008; Lage et al., 2015; Li et al., 2010; Murch et al., 2004; Réveillon et al., 2014, 2015; Violi et al., 2019b; Wang et al., 2023) (Table 2 and S2). Among these, ten genera were common across both environments, while others were unique to their respective ecosystems. The genera reported as BMAA producers exclusively in marine or brackish water ecosystems included *Chroococcidiopsis*, *Cyanobium*, *Microcoleus*, *Myxosarcina*, *Prochlorococcus*, *Symploca,* and *Trichodesmium* (Baptista et al., 2011; Cervantes Cianca et al., 2012; Cox et al., 2005). In contrast, the genera associated with BMAA production in freshwater or terrestrial ecosystems were *Calothrix*, *Chlorogloeopsis*, *Chroococcus*, *Cyanodictyon*, *Cylindrospermopsis*, *Fischerella*, *Limnothrix*, *Merismopedia*, *Microcystis*, *Oscillatoria*, *Planktothrix*, *Plectonema*, *Pseudoanabaena*, and *Scytonema* (Błaszczyk et al., 2021; Cox et al., 2005; Esterhuizen and Downing, 2008; Violi et al., 2019b). The ten genera common to both environments were *Anabaena*, *Aphanizomenon*, *Dolichospermum*, *Leptolyngbya*, *Lyngbya*, *Nodularia*, *Nostoc*, *Phormidium*, *Synechococcus*, and *Synechocystis* (Baptista et al., 2011; Błaszczyk et al., 2021; Cervantes Cianca et al., 2012; Cox et al., 2003, 2005; Esterhuizen and Downing, 2008; Lage et al., 2015; Murch et al., 2004; Violi et al., 2019b). Notably, several genera, including *Anabaena*, *Calothrix*, *Cylindrospermopsis*, *Dolichospermum*, *Leptolyngbya*, *Lyngbya*, *Microcoleus*, *Microcystis*, *Nodularia*, *Phormidium*, *Symploca*, *Synechococcus*, and *Synechocystis*, have also been reported not to produce BMAA (Błaszczyk et al., 2021; Cox et al., 2005; Fan et al., 2015; Krüger et al., 2010; Kubo et al., 2008; Li et al., 2010; Réveillon et al., 2014, 2015; Wang et al., 2023).

Diatoms were categorized into 13 genera from marine or brackish water ecosystems and four genera from freshwater or terrestrial ecosystems, with no genera common to both environments (Jiang et al., 2014a; Lage et al., 2016a, 2016b, 2019; Réveillon et al., 2015, 2016a, 2016b; Violi et al., 2019a; Wang et al., 2021). Among them, 12 genera were known to produce BMAA, including *Chaetoceros*, *Coscinodiscus*, *Ditylum*, *Navicula*, *Phaeodactylum*, *Planktoniella*, *Pseudo-nitzschia*, *Skeletonema*, and *Thalassiosira* from marine or brackish water ecosystems, and *Aulacoseira*, *Cyclotella*, and *Tabellaria* from freshwater ecosystems (Jiang et al., 2014a; Lage et al., 2016a, 2016b, 2019; Réveillon et al., 2015, 2016b; Violi et al., 2019a; Wang et al., 2021). However, it should be noted that several of these genera, such as *Chaetoceros*, *Planktoniella*, *Pseudo-nitzschia*, *Skeletonema*, and *Thalassiosira*, were also found not to produce BMAA (Réveillon et al., 2015, 2016a; Wang et al., 2021). Additionally, *Halamphora*, *Minidiscus*, and *Odontella* from marine or brackish water ecosystems, and *Fragilaria* from freshwater ecosystems were identified as non-producers of BMAA (Réveillon et al., 2016a; Wang et al., 2021). These findings underscore the complexity of BMAA production among cyanobacteria and diatoms. Although many genera across diverse ecosystems have the potential to produce BMAA, not all species or strains within these genera exhibit this trait, highlighting the variability of BMAA production.

5. Geographic distributions of BMAA across diverse ecosystems

BMAA research began in the 1960s when it was isolated from the cycad tree *Cycas circinalis* in terrestrial ecosystems (Vega and Bell, 1967). Following the discovery of BMAA biomagnification in Guam (Cox et al., 2003), Metcalf et al. (2008) reported the first detection of BMAA in freshwater and brackish water ecosystems in the UK, based on analyses of water samples collected between 1990 and 2004 from sources designated for drinking or recreational purposes. The earliest report of BMAA in freshwater organisms was in the cyanobacterium *Nostoc commune* in Peru (Johnson et al., 2008). By 2010, BMAA had also been detected in marine ecosystems, specifically in Biscayne and Florida Bays in South Florida, where it accumulated in various animals (Brand et al., 2010), and in the Baltic Sea, where BMAA biomagnification occurred across trophic levels (Jonasson et al., 2010). Subsequent reports have documented BMAA in diverse sample types from multiple countries, including water, organisms, and dietary supplements (Tables S3 and S4). BMAA has been detected in water samples from Canada, Egypt, the UK, the USA, and Sweden (Al-Sammak et al., 2014; Almuhtaram et al., 2018; Lage et al., 2015; Metcalf et al., 2008; Mohamed et al., 2024; Vo Duy

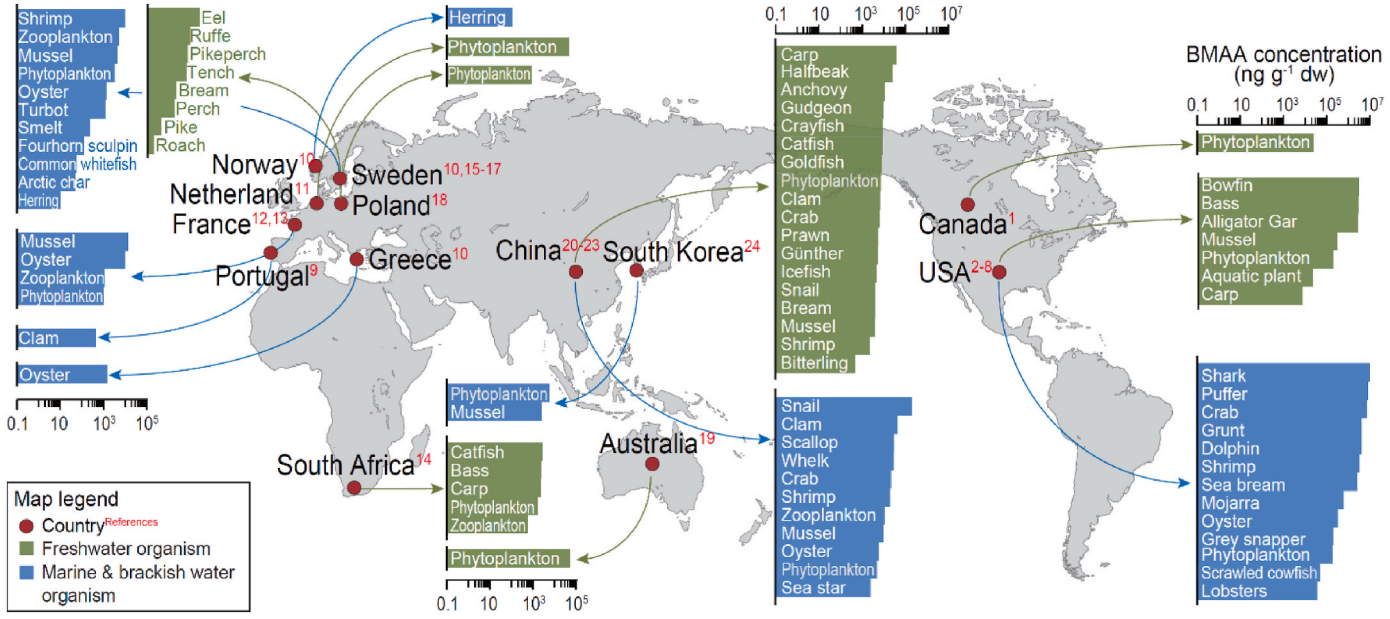

Fig. 3. Geographic distributions of BMAA in organisms collected from various aquatic ecosystems. The concentrations of BMAA, expressed in ng g^{-1} dry weight and quantified by LC-MS/MS, were selected solely for comparison between organisms and between countries. Information on the reviewed articles regarding the distribution is provided in Table S4 [[1] Bishop et al. (2018); [2] Brand et al. (2010); [3] Al-Sammak et al. (2014); [4] Metcalf et al. (2021a); [5] Davis et al. (2019); [6] Banack et al. (2015); [7] Banack et al. (2014); [8] Mondo et al. (2012); [9] Lage et al. (2014); [10] Jiang et al. (2014a); [11] Faassen et al. (2009); [12] Réveillon et al. (2014); [13] Réveillon et al. (2015); [14] Scott et al. (2018); [15] Lage et al. (2015); [16] Zguna et al. (2019); [17] Jonasson et al. (2010); [18] Błaszczyk et al. (2021); [19] Main et al. (2018); [20] Jiao et al. (2014); [21] Wu et al. (2019); [22] Li et al. (2018); [23] Wang et al. (2021); and [24] Kim et al. (2024a)].

et al., 2019) (Table S3). All these samples were sourced from freshwater ecosystems except for brackish water in the UK (Metcalf et al., 2008). Additionally, algal samples collected from diverse ecosystems have tested positive for BMAA. These samples originated from Australia, Canada, China, Egypt, France, the Netherland, Peru, Poland, Qatar, South Africa, Sweden, and the USA (Bishop et al., 2018; Błaszczyk et al., 2021; Cox et al., 2009; Faassen et al., 2009; Jiao et al., 2014; Johnson et al., 2008, 2010; Main et al., 2018; Metcalf et al., 2015, 2021a; Mohamed et al., 2024; Réveillon et al., 2015; Scott et al., 2018; Spáčil et al., 2010; Wang et al., 2021; Zguna et al., 2019) (Table S4), as well as South Korea (Kim et al., 2024a). BMAA has been detected in plankton at the lowest trophic level and higher trophic level organisms such as zooplankton and various animals, collected from ecosystems or markets (Al-Sammak et al., 2014; Amzil et al., 2023; Banack et al., 2014, 2015; Braga et al., 2017; Brand et al., 2010; Christensen et al., 2012; Cox et al., 2003; Davis et al., 2019; Hammerschlag et al., 2016; Jiang et al., 2014b; Jiao et al., 2014; Jonasson et al., 2010; Kim and Rydberg, 2020; Lage et al., 2014, 2015; Li et al., 2016, 2018; Masseret et al., 2013; Mondo et al., 2012, 2014; Murch et al., 2004; Réveillon et al., 2014, 2015, 2016a, 2016b; Scott et al., 2018; Wang et al., 2021; Wu et al., 2019; Zguna et al., 2019) (Table S4).

5.1. BMAA concentrations in aquatic ecosystems using LC-MS/MS: data editing

We reviewed the geographic distribution of BMAA in organisms from freshwater and marine or brackish water ecosystems using data quantified by LC-MS/MS and expressed in ng g^{-1} dw or μg g^{-1} dw (Fig. 3 and Table S4). Sample origins were based on collection sites, not the affiliations of the authors. Concentrations reported as wet weight basis were converted to dry weight basis using a 5:1 conversion factor (Table S4). If studies did not specify the concentration basis (wet or dry weight), it was assumed to be dry weight. Organisms were categorized by trophic traits (producer, herbivore, planktivore, omnivore, detritivore, carnivore, insectivore, filter feeder, piscivore) and reported countries to assess the cumulative probability of BMAA (Fig. 4 and Table S4). The highest reported BMAA concentrations detected in each trophic trait from each country were used to determine cumulative probabilities (Fig. 4) and to calculate ratios of BMAA concentrations among organisms within the trophic trait (Table S5).

5.2. Distribution of BMAA in freshwater ecosystems

BMAA distribution in freshwater ecosystems has been documented in Australia, Canada, China, Poland, the Netherlands, Sweden, South Africa, and the USA (Al-Sammak et al., 2014; Banack et al., 2015; Bishop et al., 2018; Błaszczyk et al., 2021; Brand et al., 2010; Faassen et al., 2012; Jiao et al., 2014; Lage et al., 2015; Main et al., 2018; Metcalf et al., 2021a; Scott et al., 2018; Wu et al., 2019) (Fig. 3). BMAA concentrations ranged from 0.2 to 2,559,000 ng g^{-1} dw, showing no specific pattern of cumulative probability among organisms, but notable differences among countries (Figs. 3 and 4). Diverse organisms in China, South Africa, Sweden, and the USA tested positive for BMAA, with concentrations of 440 to 35,910 ng g^{-1} dw, 500 to 2500 ng g^{-1} dw, 0.2–22 ng g^{-1} dw, and 6400 to 2,559,000 ng g^{-1} dw, respectively (Al-Sammak et al., 2014; Banack et al., 2015; Brand et al., 2010; Jiao et al., 2014; Lage et al., 2015; Scott et al., 2018; Wu et al., 2019) (Figs. 3 and 4, Table S4). The highest concentrations of BMAA were observed in the USA (North America), followed by China (Asia), South Africa (Africa), and Sweden (Europe). Concentrations of BMAA in phytoplanktons varied by country (Bishop et al., 2018; Błaszczyk et al., 2021; Faassen et al., 2009; Jiao et al., 2014; Main et al., 2018; Metcalf et al., 2021a; Scott et al., 2018), with most values exceeding the median concentration of 4955 ng g^{-1} dw, indicating that BMAA in freshwater ecosystems may have low potential for accumulation and biomagnification in higher trophic levels (Figs. 3 and 4).

5.3. Distribution of BMAA in marine or brackish water ecosystems

The distribution of BMAA in marine or brackish water has been

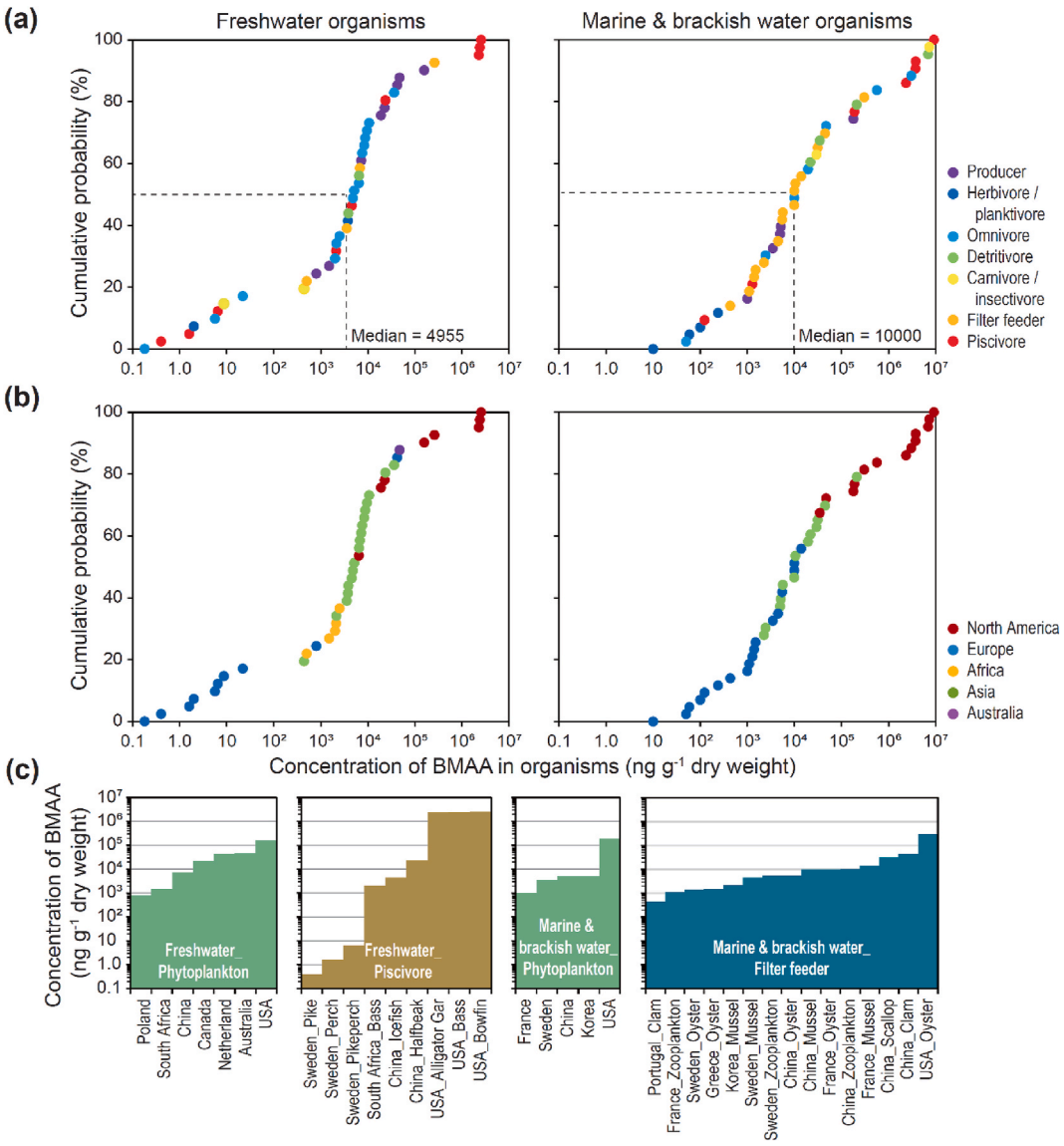

Fig. 4. Cumulative probability of BMAA in organisms based on **(a)** trophic traits and **(b)** countries. **(c)** The concentration of BMAA in phytoplankton, piscivores, and filter feeders in aquatic ecosystems. Related information is provided in Table S4.

reported in China, France, Greece, Norway, Portugal, South Korea, Sweden, and the USA (Banack et al., 2014; Braga et al., 2017; Brand et al., 2010; Christensen et al., 2012; Davis et al., 2019; Jiao et al., 2014; Jonasson et al., 2010; Lage et al., 2014; Li et al., 2018; Metcalf et al., 2021a; Mondo et al., 2012; Masseret et al., 2013; Réveillon et al., 2014, 2015; Wang et al., 2021; Zguna et al., 2019; Kim et al., 2024a) (Fig. 3). Reported BMAA concentrations ranged from 10 to 9,180,000 ng g^{-1} dw, showing a broader range compared to freshwater ecosystems, which ranged from 0.2 to 2,559,000 ng g^{-1} dw (Figs. 3 and 4, Table S4). The cumulative probability pattern by country was similar to freshwater ecosystems but differed by organism trophic trait (Fig. 4). In marine or brackish water ecosystems, the highest cumulative probability was found in North America, followed by Asia and Europe. BMAA concentrations in most phytoplankton samples were lower than the median concentration of 10,000 ng g^{-1} dw (Jonasson et al., 2010; Metcalf et al., 2021a; Réveillon et al., 2015; Wang et al., 2021; Zguna et al., 2019; Kim et al., 2024a) (Fig. 4a), while concentrations in half of the samples were higher (Banack et al., 2007; Brand et al., 2010; Christensen et al., 2012; Davis et al., 2019; Li et al., 2018; Mondo et al., 2012; Réveillon et al., 2014; Wang et al., 2021; Zguna et al., 2019). Recent studies in China indicated lower biomagnification potential in freshwater ecosystems compared to marine ecosystems (Wang et al., 2021; Wu et al., 2019). In marine or brackish water ecosystems, the ratio of BMAA concentrations between producers and piscivores (i.e., BMAA concentration in piscivores/BMAA concentration in producers) ranges from a minimum of 6.89×10^{-4} to a maximum of 9.18×10^{3} (Table S5). In contrast, in freshwater ecosystems, this ratio ranges from 2.53×10^{-6} to 3.20×10^{3}. Similar trends are observed in omnivores, detritivores, and carnivores/insectivores, where marine or brackish water ecosystems exhibit higher ratio ranges compared to freshwater ecosystems (Table S5). For filter feeders, comparable ranges are observed across both ecosystem types, while herbivores/planktivores show lower ranges in marine or brackish water ecosystems. Overall, these findings suggest that BMAA is more likely to accumulate and biomagnify in higher trophic-level organisms in marine or brackish water ecosystems, indicating greater potency than in freshwater ecosystems.

6. Summary and future directions

This study has systematically reviewed the neurotoxin BMAA, with an emphasis on its analytical methodologies, primary algal sources, and geographic distribution across diverse ecosystems. From 2019 to 2024,

LC-MS/MS, in combination with hydrolysis, has become the preferred method for BMAA analysis. However, the usage rates of different LC-MS/MS methods and their positive detection rates for BMAA varied depending on the sample types, with RPLC-MS/MS showing the highest percentage of positive results. Additionally, employing as many QCs as possible is essential to ensure accurate quantification across various environmental matrices. The concentrations of BMAA exhibit significant variability depending on the detection method employed, as well as the genus and origin of the microalgae. The widespread presence of BMAA in diverse ecosystems highlights its pervasive nature and potential global risk. The propensity for higher accumulation and bio-magnification of BMAA in marine or brackish water ecosystems, compared to freshwater ecosystems, suggests a need for increased research focus on the former. Future research endeavors should consistently employ the most sensitive and precise methods for BMAA detection to ensure the reliability and comparability of results. Expanding investigations to identify new algal producers and previously unreported geographic areas will be crucial in enhancing our understanding of the environmental distributions and impacts of BMAA. Furthermore, the following subjects should be intensively researched to better understand BMAA production and its environmental distribution: the effect of individual and multiple biotic and abiotic stress factors on BMAA production in causative algae, and the half-life of BMAA in various organisms.

CRediT authorship contribution statement

Sea-Yong Kim: Writing – original draft, Visualization, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Mungi Kim:** Writing – review & editing, Investigation, Data curation. **Kiho Park:** Investigation, Data curation. **Seongjin Hong:** Writing – review & editing, Visualization, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chemosphere.2024.143487.

Data availability

Data will be made available on request.

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Supplementary Figure

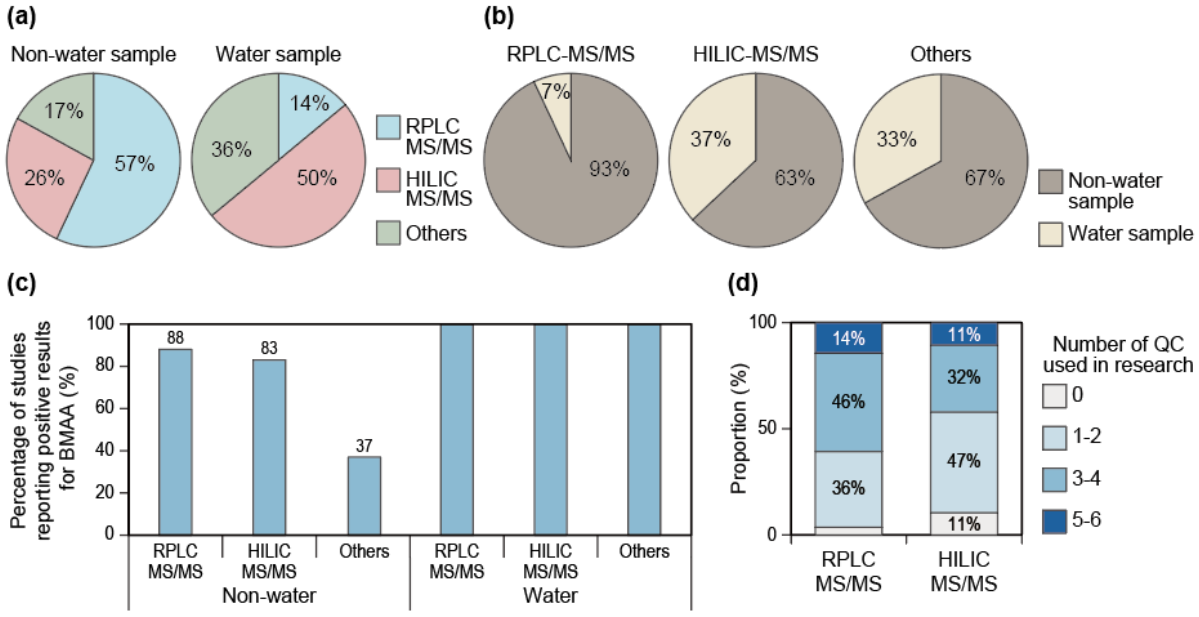

Fig. S1. Proportion of **(a)** analytical methods used depending on sample types, and **(b)** sample types depending on analytical instruments. **(c)** Percentage of studies reporting positive results for BMAA, and **(d)** proportion of the number of quality control (QC) methods used in research.