

Review

Trace Metals in Phytoplankton: Requirements, Function, and Composition in Harmful Algal Blooms

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Abstract: In a constantly changing environment brought about by the climate crisis and escalated anthropogenic perturbations driven by the growing population, harmful algal bloom dynamics and their impacts are expected to shift, necessitating adaptive management strategies and comprehensive research efforts. Similar to primary productivity, HABs have been thought to be driven primarily by major nutrients such as N, P, and Si. However, recent investigations on the role and importance of micronutrients as limiting factors in aquatic environments have been highlighted. This paper provides a review of metal and phytoplankton interactions, with a specific emphasis on pertinent information on the influence of trace nutrients on growth, toxin production, and other underlying mechanisms related to the dynamics of HABs. Low to near-depleted levels of essential nutrients, including Fe, Cu, Zn, Se, Mn, Co, and Mo, negatively impact cell growth and proliferation of various marine and freshwater HAB species. However, evidence shows that at elevated levels, these trace elements, along with other non-essential ones, could still cause toxic effects to certain HAB species manifested by decreased photosynthetic activities, oxidative stress, ultrastructure damage, and cyst formation. Interestingly, while elevated levels of these metals mostly result in increased toxin production, Co (i.e., yessotoxins, gymnodimine, and palytoxins) and Mn (i.e., isodomoic acid, okadaic and diol esters) enrichments revealed otherwise. In addition to toxin production, releasing dissolved organic matter (DOM), including dissolved organic carbon (DOC) and humic substances, was observed as an adaptation strategy, since these organic compounds have been proven to chelate metals in the water column, thereby reducing metal-induced toxicity. Whilst current research centers on free metal toxicity of specific essential elements such as Cu and Zn, a comprehensive account of how trace metals contribute to the growth, toxin production, and other metabolic processes under conditions reflective of in situ scenarios of HAB-prone areas would yield new perspectives on the roles of trace metals in HABs. With the growing demands of the global population for food security and sustainability, substantial pressure is exerted on the agriculture and aquaculture sector, highlighting the need for effective communication of information regarding the interactions of macro- and micronutrients with HABs to improve existing policies and practices.

Keywords: metal bioavailability; toxin production; nutrient limitation; harmful algal bloom dynamics; metal contamination; metal–phytoplankton feedback interaction



Citation: Manic, D.C.; Redil, R.D.; Rodriguez, I.B. Trace Metals in Phytoplankton: Requirements, Function, and Composition in Harmful Algal Blooms. *Sustainability* **2024**, *16*, 4876. <https://doi.org/10.3390/su16124876>

Academic Editor: José Carlos Magalhães Pires

Received: 2 May 2024

Revised: 3 June 2024

Accepted: 4 June 2024

Published: 7 June 2024



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1. Introduction

Harmful algal blooms (HABs) have been an ever-evolving concern globally and are characterized by their unpredictable occurrences, diverse impacts, and complex underlying mechanisms [1–4]. As drastic changes in climate patterns, coupled with increasing anthropogenic disturbances, continue, the frequency, intensity, duration, and distribution of HAB events are expected to shift, leading to deleterious consequences in aquatic ecosystems [5–8]. These outcomes include oxygen depletion, mechanical damage (e.g., disruption of fish gills), and production of toxic substances affecting not only their immediate consumers but also those in higher trophic levels and even inflicting fatalities on humans [4,9]. Persistent HAB

events can shut down aquaculture facilities as well as economically important fishing zones over a long period, resulting in massive economic losses [10,11], highlighting the need for further development of robust detection tools.

While progress has facilitated thorough research on mitigating the impacts of HABs, obstacles to the advancement of early warning systems persist. For instance, most detection models to date primarily utilize oceanographic data that are combined solely with macronutrient loading data [12–14]. Recent investigations on the role and importance of micronutrients as limiting factors in aquatic environments have been highlighted [1,15–17]. Hence, the lack of inclusion of these parameters could lead to potential gaps in the overall species-specific prediction of HAB events. Advancements in monitoring technologies and analytical capability constantly reveal new insights into the drivers and dynamics of HABs. The dynamic nature of HABs underscores the need for adaptive management strategies and multi-pronged research efforts to mitigate their impacts on the environment, public health, and economies worldwide.

In this review, we will expand the current knowledge base for the dynamics of HABs, focusing on the roles of trace nutrients on growth, toxin production, and other underlying mechanisms related to bloom dynamics.

2. Frequency and Diversification of HABs

While extensive discussions about the worldwide spread of HABs only began recently, historical records dating back centuries document HAB occurrences and HAB-associated poisoning [18–20]. Through the years, some factions in the scientific community have been skeptical about the persistence of HABs as a global phenomenon as supported by the argument that the increase in reported incidence is due to heightened awareness and monitoring efforts (see Figure 1) [1,3,4,21,22].

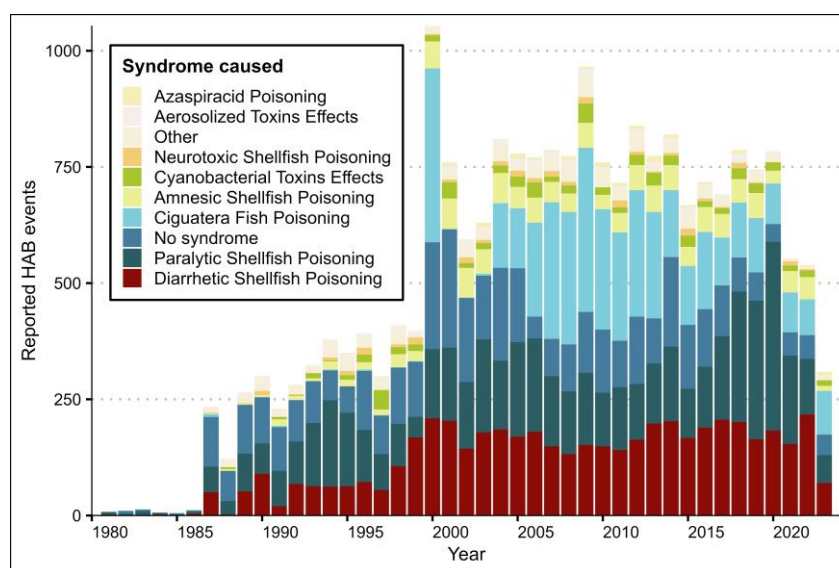


Figure 1. Number of reported HAB events and syndromes caused from 1980 to 2024. Presented data include the following: water discoloration, seafood toxins, coastal foam/mucilage, high phytoplankton concentration, and mass mortalities. Retrieved 29 April 2024, from <https://data.hais.ioc-unesco.org/>.

Interestingly, a recent statistical analysis on global HAB events has found that once distribution data were normalized against variations in regional monitoring activities conducted, no uniform global trend exists, suggesting that observable trends should be considered on a regional scale as well as on a species level [3]. Despite debates surrounding HAB frequencies, a pattern of diversification in HAB occurrences over time has been noted across various regions [23–26]. This phenomenon impacts new sites and is attributed to

climate change and intensified anthropogenic disturbances, which in turn contribute to the persistence of HABs in coastal and freshwater ecosystems (Figure 2).

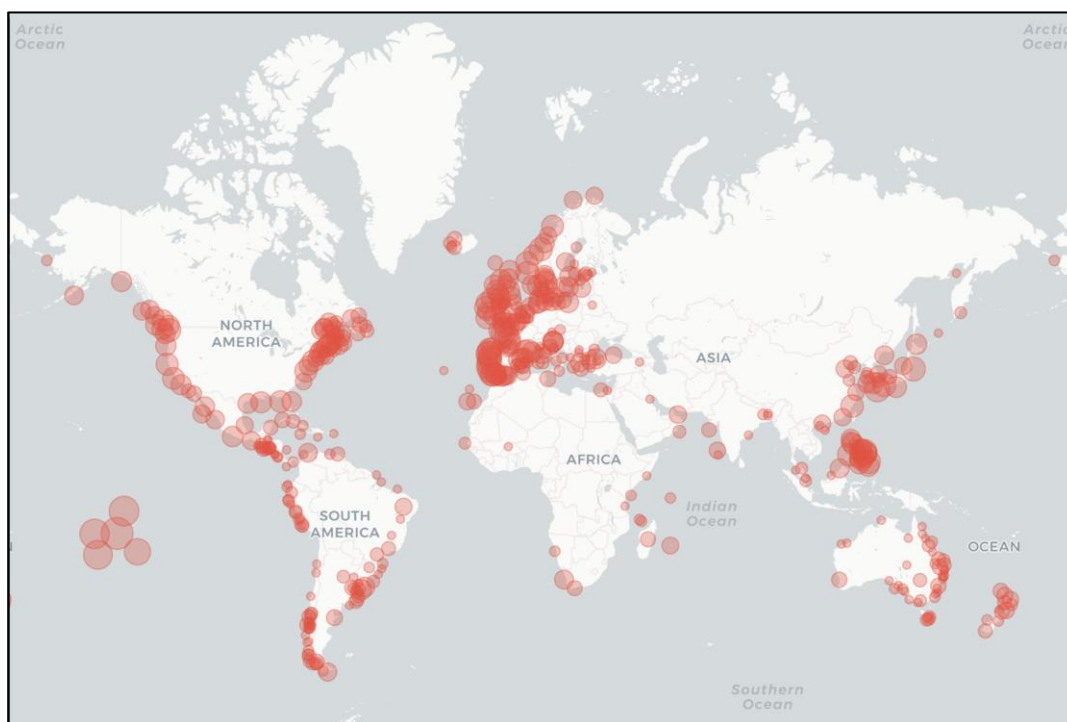


Figure 2. Global distribution of HAB events from 1980 to 2024. Map showing location of reported HAB events generated from IOC-UNESCO Harmful Algae Information System. Retrieved 29 April 2024, from <https://data.hais.ioc-unesco.org/>.

2.1. Major Drivers: Changing Climate and the Global Population

Occurrences of algal blooms and the natural succession in phytoplankton community structure are shaped by nutrient loading from seasonal rains, flooding, upwelling [9,27], and atmospheric deposition from major deserts [28]. In oligotrophic oceans where nitrogen is limited, the bloom and bust of nitrogen-fixing organisms initiate the succession of organisms up to higher trophic levels. The imbalance in some key physicochemical parameters necessary for growth initiates harmful blooms, which are associated with the climate crisis, coupled with increased anthropogenic perturbations that exacerbate the impact of algal blooms across regions [5,7,8,29]. Drastic changes in global climate patterns affecting temperatures [30,31], sea levels [11], rainfall and precipitation [32,33], atmospheric CO₂ concentrations [34], acidification [35,36], and water stratification [37,38] influence species-specific algal bloom dynamics. This outcome is best illustrated by algal blooms following volcanic eruptions or inundation brought by typhoons.

Furthermore, apart from the direct impacts of urbanization and expanding human settlements, the increasing global population has led to massively growing demands for sustainable food production, placing substantial pressure primarily on the agriculture and aquaculture sectors. Under varied socio-economic and climate change scenarios, the projected global food demand is expected to increase from 35% to 56% between 2010 and 2050 [39]. Currently, such demands are met by expansion and increased productivity in both sectors. According to FAO in 2003, fertilizer consumption will increase by 1% per annum from 138 million tons in 1997/99 to 188 million tons in 2030 [40]. As of 2022, however, the demand for fertilizer already exceeded the 2030 prediction and was reported at 200 million tons [41]. The heavy use and reliance on fertilizer has an unwanted outcome because poorly managed agricultural nutrient enrichments lead to higher levels of nutrient run-off, including key elements like nitrogen [42–45] and phosphorus [46–49], entering

bodies of water. Similar trends in market demands for commercial feeds for livestock and aquaculture facilities were observed [50]. Interestingly, these demands are met by around 30% of cereal crop production, utilizing about 40% of the world's arable land [51,52], and around 23% of capture fisheries [53]. This complex competition between feed and food production is deemed as one of the major bottlenecks in achieving sustainable food production systems [50]. Moreover, excess macronutrients, trace elements, and other chemicals from the unregulated use of feed products contribute further to eutrophication, impacting various aquatic ecosystems [54,55].

2.2. Roles of Macronutrients in Bloom Dynamics

Eutrophication has been identified as one of the major culprits of algal bloom events since macronutrients from agricultural runoff and aquaculture waste, including nitrogen, phosphorus, and to some extent silica, play critical roles in the species-specific bloom dynamics of phytoplankton species. Variations in the concentration and ratio of these major nutrients lead to diverse plankton community compositions, potentially giving rise to either HAB or non-HAB bloom formations.

Nitrogen (N) plays a fundamental metabolic role in phytoplankton physiology, serving as a building block for various cellular components such as nucleic acids, proteins, and chlorophyll, which are essential for algal growth and biomass production [56,57]. Various nitrogen enrichment experiments recorded high cell densities and faster growth rates of different microalgal species [56,58,59]. In addition, phytoplankton community structure shifts were reported as a result of increased nutrient loading, primarily N [60–63]. In oligotrophic areas such as the tropical Pacific [64,65] and the North Atlantic [66], phytoplankton biomass has increased after the addition of N during in situ enrichment studies. Although several studies have shown that fast-growing diatoms and cyanobacteria dominate marine [61,62] and estuarine ecosystems [67] with high N concentrations, other phytoplankton taxa were also found to dominate in certain areas. Aquatic ecosystems with high N:P ratios were found to have dinoflagellates as primary producers [68,69], whilst other cultivation experiments reported that N:P ratios have no significant effect on cell abundance, reiterating that it is the N sources alone that significantly affect growth [59,70]. Apart from the fundamental role of N in cell division and growth, as well as in macromolecule synthesis, N is also essential for dinoflagellate toxin metabolism, which has been of interest over the years due to deleterious impacts on the environment and public health [71–76].

Phosphorus (P) has several key roles in cellular metabolism, particularly in processes related to energy transfer, nucleic acid synthesis, and cell membrane structure [77]. It serves as a key constituent of adenosine triphosphate (ATP), which fuels cellular metabolism by providing energy for biochemical reactions within cells [78]. P is also essential for the synthesis of nucleic acids (DNA and RNA), which are crucial for cell growth, cell division, and protein synthesis [79]. Furthermore, P is a structural component of cell membranes, phospholipids, and various cellular molecules that contribute to the integrity and fluidity of cell membranes. Ding et al. [80] demonstrated the ability of P limitation to change nutrient-limiting conditions for HAB formation. These metabolic functions underscore its significance as a limiting nutrient in marine ecosystems, with implications for phytoplankton productivity and ecosystem dynamics [66,81,82].

Silica (Si) has a more species-specific role in phytoplankton, particularly in diatoms. It serves as a structural component of their frustules, which are external siliceous cell walls providing mechanical support and protection from predators. These siliceous structures also regulate the uptake and transport of essential nutrients such as nitrogen, phosphorus, and carbon through specialized silica transporters [83,84]. Silica metabolism is closely linked to photosynthesis and carbon fixation processes in phytoplankton, ultimately impacting primary productivity and the biogeochemical cycling of nutrients in aquatic ecosystems [85–87].

These variations in species-specific responses to the major nutrient enrichments can generally be explained by differences in the species physiology [61], theory of resource

competition [88], and the widely observed Redfield ratio, stating that elemental composition of phytoplankton biomass across environments follows a ratio of 106:16:1 for C:N:P [89–91]. Under sufficient N and P supply in marine environments, maximum phytoplankton growth rate can be achieved with the Redfield ratio [92]. However, it has been reported that nutrient requirements by phytoplankton result in deviations from the Redfield ratio [60,91]. As such, the silicate requirement by diatoms merits the inclusion of Si as part of this ratio [93].

Backed by global documentation, primary productivity was always thought to be driven by the availability of macronutrients, primarily N, P, and Si. However, results from research spanning the past decades revealed that trace nutrient availability also impacts productivity and phytoplankton community structure in marine and freshwater environments across the globe [94–98]. Advancements in monitoring technology and analytical tools have permitted exploring the influence of trace elements on algal productivity and various cellular and biochemical processes. Gathered data from such investigations hold the potential to enhance our understanding of HAB dynamics.

2.3. Current Efforts for Algal Bloom Detection

In the pursuit of mitigating the detrimental impacts of HABs, there has been a substantial focus on the development and enhancement of HAB prediction, detection, and other early-warning systems. Current methods involve the use of satellite imagery, bathymetry data, in situ physicochemical data, and even machine learning for algorithms used in modeling [13,99–101]. In marine environments, physicochemical parameters such as DO, temperature, salinity, Chl A, and pH are the few primary considerations for in situ prediction of HABs. These factors are most often selected due to their high correlation with HAB occurrences, the availability of data during all periods of fish kill or toxic bloom, and the capacity to obtain real-time parameters [102]. Recently, the inclusion of macronutrients such as N, P, and Si in the regular monitoring of HAB-prone areas as additional prediction parameters has been highlighted [103]. Incorporating nutrient loads of particulate phosphorus (PP) into other physicochemical parameters improved prediction models in HAB formation in Lake Erie [104]. Furthermore, nitrogen (N) loads were also found to be a valuable parameter in the prediction of HAB formation in the same lake [105]. More complex models utilize different sources and types of nutrients as part of the predictive drivers for the modeling of cyanobacterial HABs [106]. The contribution of nutrient loading to eutrophication in coastal systems has been demonstrated and has warranted its inclusion as a predictive driver in several HAB modeling papers [42,107]. The predictive capabilities of models are reliant on existing data, which includes results from bottle incubation and mesocosm experiments. However, continuous and long-term in situ observations are still necessary in fine-tuning these models, especially in a changing climate [14]. Increasing evidence of the roles of metals in the initiation and development of HABs underscores the importance of their inclusion in long-term monitoring [12,108]. Furthermore, studies detailing the effects of metals on growth, toxin production, and allelopathic effects may improve prediction models. This is especially true for those involving complex biological systems that not only consider the growth of a species capable of forming harmful blooms but also trophic succession and the upstream risks that come with HAB events.

3. Trace Metals

3.1. Overview of Trace Metal Distribution and Bioavailability

Concentrations of many trace metals typically increase with depth of the water column and proximity to terrestrial ecosystems [109–111] due to natural and anthropogenic inputs such as continental dust [44,112–115], shelf sediments [116–118], hydrothermal circulation at ocean ridges [119–121], glaciers [122–124], atmospheric ash [125–127], coastal sediments, and riverine outputs [128–130]. Interestingly, recent studies have also explored the potential contribution of fecal materials of marine mammals, seabirds, and other migratory animals in trace metal deposition in the oceans [131–133].

Most metals, including iron (Fe), zinc (Zn), copper (Cu), nickel (Ni), selenium (Se), and cadmium (Cd), have a typical nutrient-type distribution similar to macronutrients [111,134,135]. These metals generally increase in concentrations with depth and proximity to landmasses [136]. Cobalt (Co), similar to Fe, has a nutrient-like profile. However, its concentrations in deep waters do not necessarily increase due to organic complexation [137–139].

Other metals such as manganese (Mn), chromium (Cr), molybdenum (Mo), and vanadium (V) have different behaviors in seawater and are largely conservative [140–143]. Mn has an established maximum layer in surface waters and in the oxygen minimum zone, while the lowest concentrations are in deep waters [140]. Cr is found to be slightly depleted in subsurface waters. However, it was found that decoupling of Cr happens in deeper waters as observed in subtropical North Atlantic [144]. Mo and V are under-explored elements due to their largely conservative nature. Mo concentration, in the form of molybdate (MoO_4^{2-}), is influenced by salinity rather than depth and shows little to no differences in its vertical distribution [145,146]. However, recent studies have reported the non-conservative nature of Mo, especially in its horizontal distribution [146]. In some cases, dissolved V concentrations are presented as non-conservative oceanic profiles, but variability is generally observed across ocean basins. The variations are attributed to factors such as riverine inputs, reducing shelf environments, and chemically driven particle interactions, all of which highlight the call to further investigate the V cycle [147].

In most freshwater lakes, the seasonal release of macronutrients and Fe species from sediments occurs due to thermal stratification, upwelling, and mixing [148–150]. However, anthropogenic sources such as wastewater discharge, mining, and changing land-use practices caused by urbanization have impacted metal deposition in such habitats [151,152]. Wastewater discharge from human settlements contributes to the accumulation of Cd, Ni, and Zn, with 60% of the total claimed to be recycled by phytoplankton [152,153]. In these ecosystems, the spatiotemporal distribution of trace nutrients exhibits significant variability owing to variations in bathymetry, mixing patterns, temperature regimes, and other physicochemical parameters [154–156]. Ultimately, this variability is influenced by fluctuating levels of disturbances from nearby anthropogenic settlements, e.g., water runoffs, aerosols, etc. [153,157].

Trace metal elements exist in several chemical species, influencing their chemistry, biological availability, and hence status as a limiting nutrient [15]. Most metals occur as cations in complexes with inorganic or organic ligands. Essential trace elements, such as Fe, Cu, Mn, and Co, exist in more than one oxidation state, resulting in varied reaction energy requirements and reaction rates affecting their bioavailability [111,158]. For example, the most biologically available form of Fe is ferrous iron (Fe^{2+}), which is highly soluble in anoxic waters. However, it can be rapidly oxidized to weakly soluble ferric iron (Fe^{3+}) in neutral to slightly alkaline oxygenated waters [159–161]. Other metals, including Zn, Ni, and Cd, exist as soluble divalent cations complexed with inorganics such as chlorides, hydroxides, carbonates, and other organic chelators (binding agents). The chemical speciation of these trace metals in the water column affects their biological availability for phytoplankton uptake and assimilation [162].

3.2. Overview of Roles of Trace Metals in Photosynthetic Microorganisms

Bioavailable trace elements are essential for phytoplankton growth and metabolism, resulting in varied productivities across ocean basins, coastal regions, and other aquatic ecosystems. A growing number of studies (Table 1) demonstrate the roles of essential trace metals, Fe, Mn, Ni, Co, Cu, and Zn, as well as species-specific essential metals, including Se, Cd, Mo, and V, based on their function as active centers or structural support in enzymes involved in various biochemical pathways [96,98,163–170].

Table 1. List of metals and associated metalloenzymes in photosynthetic microorganisms.

Metal	Metalloenzyme	Metal	Metalloenzyme
Fe	Fe-S proteins (e.g., aconitase)	Mn	Oxygen-evolving enzymes
	Ferredoxin		Superoxide dismutase
	Superoxide dismutase		Arginase
	Nitrate reductase		Phosphotransferases
	Nitrite reductase	Cu	Plastocyanin
	Chelatase		Ferrous oxidase
Zn	Peroxidase		Amine oxidase
	Carbonic anhydrase		Cytochrome oxidase
	Alkaline phosphatase		Ascorbate oxidase
	RNA polymerase		Superoxide dismutase
	tRNA synthase	Co	Carbonic anhydrase
	Reverse transcriptase		Cobalamin
	Carboxypeptidase	Se	Alkaline phosphatase
Ni	Superoxide dismutase		Glutathione peroxidase
	Alcohol dehydrogenase	V	Bromoperoxidase
	Aminoamidase		Nitrogenase
Ni	Urease	Cd	Carbonic anhydrase
	Superoxide dismutase		Alkaline phosphatase

Fe is widely accepted as a key micronutrient that limits phytoplankton productivity in vast oceanic regions [171] and this can be attributed to the high Fe requirements of various phytoplankton species [95,96]. Fe serves as a cofactor for a wide range of essential enzymes required in different metabolic processes. It is integral to the structure and function of pigments, electron transport systems, and other components of the photosynthetic machinery. Additionally, Fe-containing enzymes are crucial for nutrient acquisition and assimilation, respiration, and RNA and DNA synthesis. All these processes comprise a pipeline for the conversion of nutrients into biomass and energy, hence influencing ecosystem-level interactions and various biogeochemical cycles.

Moreover, Fe, along with other trace elements (Table 1), contributes to various antioxidant defense mechanisms and other metabolic processes to ensure phytoplankton survival and growth, thus shaping ecosystem dynamics [96,97,167,172]. Although a wide range of metabolic roles in phytoplankton have been well documented during the past decades, the foundations of phytoplankton metal physiology mostly come from studies on diatoms [97,168,173–181] and, recently, cyanobacteria, including *Prochlorococcus* [182–184], *Synechococcus* [185], *Crocospira* [186,187], *Cyanothece* [188], *Trichodesmium* [186,189–192], and several others.

In recent years, investigations on the effects of trace metal concentrations on photosynthetic microorganisms have expanded to other taxa such as picoeukaryotes, dinoflagellates, green algae, prymnesiophytes, and other nano-picophytoplankton due to their significant roles in biogeochemical cycles. Studies have shown that metal requirements vary among different phytoplankton functional types, suggesting that the current understanding of metal functions in diatoms and diazotrophs might not apply to others. For example, in similarly designed studies conducted on diatoms and a picoeukaryote, *Pelagomonas calceolata*, the Fe quotas exhibited a 100-fold difference, with *P. calceolata* showing minimal physiological plasticity [193]. Similar observations were reported with another picoeukaryote, *Ostreococcus lucimarinus*, wherein iron limitation resulted in 68% reduction in iron quota, which is just a fraction of the plasticity reported in diatoms [184]. In a study investigating the metal composition of 15 major marine phytoplankton groups, systematic differences were observed in diatoms, chlorophytes, and coccolithophores [95]. Differences were also observed between strains isolated from coastal and oceanic regions [194]. Moreover, several members of *Symbiodiniaceae*, a family of marine dinoflagellates that are notable for

their symbiotic relationships with reef-building corals [195], have shown different metal requirements when subjected to various metal conditions, indicating the complex roles of trace nutrients in their growth [57,189–191] and other metabolic processes [196].

The variations in trace metal quotas and metal requirements of these taxa reflect the complexity of phytoplankton metal physiology, highlighting the need for further investigations of trace elements and their roles in phytoplankton growth, metabolic processes, bloom dynamics, and other ecosystem-level interactions.

4. Trace Metals and Harmful Algal Blooms

The diverse roles of metals in the physiology of phytoplankton indicate numerous possibilities on how they would affect HAB events and their causative species. Discerning the effects of metals on HABs is complicated as they can affect either the individual cells or the HAB events. Aside from their usual effect on growth, metals may also be vital in other processes that support the proliferation of HABs, such as toxin production, dissolution of and protection against other metals, and synergistic effects with other compounds produced [175,197–200]. Several pieces of evidence reveal that the relationship between metals and HABs is not unidirectional, since some species can produce compounds that affect the bioavailability of metals in the environment [175,201]. Nonetheless, exposure to high concentrations can still lead to toxicity [202,203]. Describing the effects of metal on these organisms entails a meticulous degree of planning and experimentation to elucidate underlying mechanisms.

A growing number of bottle incubation experiments, mesocosm studies, and field investigations have been reported to visualize the role of trace metals on certain marine and freshwater HAB species (see Tables 2 and 3). Bottle incubation experiments entail culturing HAB-causing species, aiming to uncover how certain species respond physiologically to various growth factors like metals, macronutrients, micronutrients, or their combinations. Meanwhile, mesocosm experiments, conducted on a larger scale, strive to replicate real-world conditions more closely while maintaining adequate control to distinguish responses among treatments. While these approaches enable researchers to delve into fundamental biological inquiries, these may only infer the complex interconnectivity of processes involved in actual HAB occurrence and persistence. Thus, regardless of logistical challenges, emphasis is placed on in situ investigations such as metal concentration monitoring before, during, and after the onslaught of HABs. Complementing bottle incubations with mesocosm and field investigations on various physicochemical parameters can provide more extensive elucidation of bloom dynamics in a feedback loop.

Table 2. List of research focusing on trace metals in specific HAB species in marine and brackish ecosystems.

Species	Metals	References
<i>Akashiwo sanguinea</i>	Co (Vitamin B ₁₂)	[204]
<i>Alexandrium</i>	Zn	[205]
	Cu, Sn (as butyltin)	[206]
	Cu, Cd	[207]
<i>Alexandrium catenella</i>	Zn, Pb	[208]
	Fe	[209]
	Co (Vitamin B ₁₂)	[204]
	Fe, Cu	[197]
<i>Alexandrium minutum</i>	Se	[210]
	Cu	[211]
	Co (Vitamin B ₁₂)	[204]

Table 2. Cont.

Species	Metals	References
<i>Alexandrium tamarense</i>	Fe	[212]
<i>Amphidinium carterae</i>	Cu	[213]
<i>Aureococcus anophagefferens</i>	Zn, Cu, Ni, Cd	[214]
	Se	[215]
	Co (Vitamin B ₁₂)	[204]
	Fe	[216]
<i>Aureoumbra lagunensis</i>	Co (Vitamin B ₁₂)	[204]
<i>Chaetoceros compressus</i>	Cu	[217]
<i>Chatonella antiqua</i>	Fe	[218]
<i>Chatonella marina</i>	Zn, Cu, Cd, Pb, Hg	[219]
	Co (Vitamin B ₁₂)	[204]
<i>Chatonella ovata</i>	Zn, Cu, Cd, Pb, Hg	[219]
<i>Choomonas</i>	Cu, As	[220]
<i>Cochlodinium polykrikodes</i>	Cu	[221,222]
	Cu and Pb	[223]
	Co (Vitamin B ₁₂)	[204]
<i>Dinophysis acuminata</i>	Cu	[217]
<i>Fibrocasa japonica</i>	Co (Vitamin B ₁₂)	[204]
<i>Gymnodinium aureolum</i>	Co (Vitamin B ₁₂)	[204]
<i>Gymnodinium breve</i>	Cu, Ti, Zr	[224]
<i>Gymnodium catenatum</i>	Se	[210,225]
	Fe, Cu, Se	[226]
	Zn, Cu, Cd, Pb, Hg	[219]
<i>Gymnodinium instriatum</i>	Co (Vitamin B ₁₂)	[204]
<i>Gymnodinium nagasakiense</i>	Se	[227,228]
<i>Gymnodinium sanguineum</i>	Fe	[229,230]
	Zn, Cu, Cd, Pb, Hg	[219]
<i>Heterosigma akashiwo</i>	Fe	[218]
<i>Heterocapsa artica</i>	Co (Vitamin B ₁₂)	[204]
<i>Heterocapsa circularisquama</i>	Fe	[218]
<i>Heterocapsa triquetra</i>	Cu	[217]
	Co (Vitamin B ₁₂)	[204]
<i>Karenia brevis</i>	Fe, Cu, Co, Cd, Hg	[201]
<i>Karenia mikimotoi</i>	Co (Vitamin B)	[204]
<i>Karenia selliformis</i>	Mn, Zn, Cu, Co, Se	[231]
<i>Karlodinium veneficum</i>	Co (Vitamin B ₁₂)	[204]
<i>Katodinium rotundatum</i>	Cu, As	[220]
<i>Lingulodinium polyedrum</i>	Fe	[209]
	Cd	[232]
	Mo	[233]
<i>Ostreopsis cf. ovata</i>	Cu, Sn (as butyltin)	[206]

Table 2. Cont.

Species	Metals	References
<i>Ostreopsis siamensis</i>	Mn, Zn, Cu, Co, Se	[231]
<i>Phaeocystis globosa</i>	Co (Vitamin B ₁₂)	[204]
<i>Polykrikos hartmannii</i>	Co (Vitamin B ₁₂)	[204]
<i>Protoceratium reticulatum</i>	Mn, Zn, Cu, Co, Se	[231]
	Fe, Co, Se	[234]
<i>Prorocentrum dentatum</i>	Fe	[235]
<i>Prorocentrum donghaiense</i>	Co (Vitamin B ₁₂)	[204]
<i>Prorocentrum lima</i>	Mn, Zn, Cu, Co, Se	[231]
<i>Prorocentrum micans</i>	Cu	[213]
<i>Prorocentrum minimum</i>	Co (Vitamin B ₁₂)	[204]
<i>Pseudo-nitzschia</i> sp.	Fe, Cu	[175,198]
<i>Pseudo-nitzschia australis</i>	Mn, Zn, Cu, Co, Se	[231]
	Fe, Cu	[236]
<i>Pseudo-nitzschia delicatissima</i>	Fe, Cu	[237]
	Cu	[238]
	Fe	[239]
<i>Pseudo-nitzschia multiseriata</i>	Cu	[240,241]
	Co (Vitamin B ₁₂)	[204]
<i>Pseudo-nitzschia pungens</i>	Co (Vitamin B ₁₂)	[204]
<i>Rhizosolenia setigera</i>	Cu	[217]
<i>Scrippsiella trochoidea</i>	Fe	[242]
	Co (Vitamin B ₁₂)	[204]
<i>Skeletonema costatum</i>	Fe	[235]
<i>Takayama acrotricha</i>	Co (Vitamin B ₁₂)	[204]
<i>Thalassiosira pseudonana</i>	Cu, As	[220]
<i>Trichodesmium</i>	Ni	[190,243]

Table 3. List of research focusing on trace metals in specific HAB species in freshwater ecosystems.

Species	Metals	References
<i>Anabaena lemmermannii</i>	Cu	[199]
<i>Anabaenopsis</i> sp.	Cu	[244]
<i>Aphanizomenon schindlerii</i>	Fe	[245]
<i>Aphanizomenon</i> sp.	Cu	[199]
<i>Chlamydomonas reinhardtii</i>	Cu	[199,246]
<i>Cylindrospermopsis raciborskii</i>	Cu	[199]
<i>Closterium ehrenbergii</i>	Cu	[247]
<i>Desmodesmus</i>	Cu, Fe	[248]
<i>Gonyostomum semen</i>	Fe	[249,250]
<i>Lyngbya wollei</i>	Cu	[251]
<i>Microcystis</i> sp.	Cu, Fe	[248]
	Fe	[252]
	Zn	[253]

Table 3. Cont.

Species	Metals	References
<i>Microcystis aeruginosa</i>	Fe, Zn, Al, Cd, Cr, Cu, Mn, Ni, and Sn	[254]
	Co, Cu, Fe, Mn, Mo	[255]
	Ca, Cu, Pb, Cd	[256]
	Fe, Mn, As	[257]
	Fe, Zn	[258]
	Fe, Cu	[200]
	Cu, Zn	[202,259]
	Zn, Cd	[260]
	Ni	[261]
	Fe	[262–264]
	Cu	[199,202,203,244,265–268]
	Zn	[269,270]
	As	[271]
<i>Oscillatoria</i> sp.	Cu	[199]
<i>Pseudokirchneriella subcapitata</i>	Cu	[199]

This section will highlight conducted research focused on how metal availability influences HABs and HAB-causing organisms (Tables 2 and 3). Discussions will mainly focus on Fe, Co, Zn, Se, and other metals, both essential and non-essential.

4.1. Iron (Fe)

Among metals, Fe is the most heavily studied in terms of its effects on the physiology of HABs. Growth studies indicate that Fe is an essential metal for both marine and freshwater HAB causative species [16,242,272,273]. Phytoplankton are heavily reliant on Fe for its role on the major photosynthetic complexes and as cofactors for many physiologically important enzymes. Bottle experiments show that decreasing Fe concentrations causes a decrease in physiological activities related to growth and proliferation. Specifically, Fe depletion or low Fe conditions have been observed to decrease cell density and growth rate on freshwater *Microcystis aeruginosa* [212,248,254,255,264] and *Gonyostomum semen* [249,250] and marine HAB species *Alexandrium minutum* [197,212], *Alexandrium catenella* [209], *Protoceratium reticulatum* [234], *Pseudo-nitzschia australis* [236], *Chattonella antiqua* [218], *Heterosigma akashiwo* [218], *Heterocapsa circularisquama* [218], *Scrippsiella trochoidea* [242], and *Gymnodinium sanguineum* [229,230]. Interestingly, synergistic effects of Fe and humic compounds in improving growth rates have been established for *M. aeruginosa* [264]. Nevertheless, elevated Fe concentrations can still result in toxicity for certain HAB species [209,212]. The role of Fe in enzymes essential for photosynthetic activities and various metabolic processes, including nutrient uptake and assimilation, underscore its significance in the universal requirements of phytoplankton for Fe [94,171]. Hence, mitigation strategies targeting HABs should consider the significance of Fe in phytoplankton physiology.

Moreover, increasing correlations between Fe levels and toxins produced by specific HAB species were reported. The freshwater *M. aeruginosa*, a known cyanoHAB species, is capable of producing microcystin, a hepatotoxic and carcinogenic compound [274,275]. Incubation experiments revealed contrasting trends for its production of microcystin in relation to Fe. Lukač and Aegerter [254] have shown increased toxin production at lower or reduced Fe concentrations, while other investigations on the same species presented otherwise. Facey et al. [255] reported reduced microcystin-LR in Fe-deficient media after 20 days. Moreover, Alexova et al. [262] have shown decreased toxin levels in increasing Fe concentrations. This evidence highlights the complex yet potential role of Fe on microcystin production, which stipulates further studies to elucidate this relationship. Nonetheless, the possible role and importance of Fe in the alleviation of damage caused by *M. aeruginosa* is highlighted.

Other forms of toxic substances produced by HAB species shed some light on the potential metabolic role of Fe on toxin production. Alterations in toxin production associated with Paralytic Shellfish Poisoning (PSP) were also observed in different *Alexandrium* species. Decrease in Fe leads to increased PSP toxin content and PSP toxicity per cell, and changes in the PSP toxin profile of *Alexandrium tamarense* [212]. Interestingly, a gradient of Fe concentrations tested on *A. catenella* and *A. minutum* revealed the highest toxin levels were observed not in the lowest Fe treatment tested but at the most optimal [197,209]. Comparison between the three studies shows that the highest PSP toxin concentration per cell was observed at 1 nmol L⁻¹ Fe for *A. tamarense*, while it was at 1000 nmol L⁻¹ Fe for *A. catenella* [209,212]. Although the PSP toxin profile was elucidated for both strains, changes to the PSP toxin profile were observed only in *A. minutum* with an increase in GTX 1 + 4 and decrease in both STX and GTX 2 + 3 [197]. *A. catenella* was only able to produce GTX 1 to 4, with the ratios of these toxins being similar throughout Fe treatments [209]. These findings show the different requirements and sensitivities of varying *Alexandrium* species towards Fe. Elevated PSP toxin generation in low-Fe conditions may serve as a stress response, with heightened toxin production serving as a method for alternative Fe storage through metal-ligand interactions, where the toxin itself acts as a ligand. However, the observed decrease in toxin production at high Fe levels can be attributed to toxicity effects exerted by Fe and the subsequent decrease in related physiological activities. Further studies are needed to pinpoint the exact mechanism on how Fe affects PSP toxin production.

Though we see that Fe affects the toxin production of some HABs species, this is not necessarily true for all. *P. reticulatum*, a known yessotoxin (YTX) producer, requires Fe for its production. However, cells subjected to increasing Fe levels have shown neither increase nor decrease in YTX production [234]. Congruent with other toxic HAB species, an increase in the production of domoic acid was observed for both *Pseudo-nitzschia multiseriata* and *P. australis* under Fe-limited treatments [236]. In contrast, an argument on the importance of Fe in the production of domoic acid (DA) by *Pseudo-nitzschia* was raised due to positive correlations between increasing Fe concentrations and domoic acid production [276]. This is further evidenced by the Fe-deplete treatments that reveal comparatively lower DA. Although the two studies give contrasting results, this may be due to interspecific variability between different strains of the species. Consequently, it was shown by Sobrinho et al. [239] that both excessive Fe amendments and Fe deficiency would lead to comparatively higher DA concentrations between treatments. These findings suggest that increases in DA production are mediated by either Fe deficiency or Fe-mediated toxicity. Upregulated DA production under scarcity conditions may be a means of self-protection for *Pseudo-nitzschia* as observed in other nutrient-deplete experiments [277–279]. On the other hand, the surge in DA production under high Fe stress can also be seen as a survival response as evidenced by the chelating capabilities of DA towards several different metals [175,198,236].

Investigations of the relationship between toxin production and Fe concentrations reveal complexity and specificity of responses not only among species but also among specific strains within these species. Furthermore, the repercussions of toxin production and its concentration cascade towards higher trophic organisms. Understanding the influences of Fe in toxin production would help deepen understanding of HABs and how they affect other organisms in the field.

The utilization of toxins and other compounds produced by HABs is not only limited to their allelopathic effects against other phytoplankton but may also provide other environmental advantages for the organism. Domoic acid produced by several species of *Pseudo-nitzschia* is capable of chelating Fe and other metals [175]. This chelating mechanism of domoic acid helps in the provision of bioavailable Fe and in the decrease in Cu concentrations to pre-toxic levels [175,236]. Though the mechanism of Fe chelation by domoic acid may control and reduce bioavailable Fe, several strains of *Pseudo-nitzschia* have been shown to perform high-affinity Fe acquisition with the aid of Cu and domoic acid [198]. Microcystins, brevetoxins, okadaic acid, and pahayokoides were found to form complexes with Fe, suggesting the ability of HABs to control bioavailability of metals within their

environment [201]. Production of other substances such as extracellular glycans, mucilage, dissolved organic matter, and humic substances also aid in the access of phytoplankton to trace metals [137,264,280–282]. Capsular polysaccharides exuded by *Microcystis* sp. were shown to reduce the effects of Fe deficiency in colony-forming variants as compared to the unicellular form by binding Fe and acting as a storage mechanism [252]. Aside from their roles in metal sequestration, the produced compounds may also help in colony formation and aggregation of certain cyanobacterial HABs and may exacerbate the damage during blooms. Both microcystins [283–285] and organic matter [252,264] contribute to the scum formation of *Microcystis* sp. The consequence of Fe concentrations towards both toxin and organic matter production described earlier spill over to aggregation and scum formation during blooms, effectively heightening the threat posed by colony-forming HABs.

The dependence of HABs on Fe concentrations provides a possible means for the suppression of cyanobacterial blooms. The greater Fe requirement of cyanobacteria as compared to other algae proves perilous under low concentrations of Fe [162,272,286,287]. Additionally, the role of phosphorus itself and in conjunction with Fe in the triggering of cyanobacterial HABs has also been well established [288–290]. Several contrasting studies have described the use of Fe and phosphorus in the control of HABs through various mechanisms. Orihel et al. [291] showed through mesocosm experiments that additional Fe concentrations in eutrophic lakes lead to reduced pore water P concentrations. Decreased P concentrations were then shown to be directly correlated to decreased phytoplankton and periphyton growth. In contrast, direct addition of Fe chelators to a eutrophic lake has been proposed to control cyanobacterial growth. This exploits the direct relationship between Fe and cyanobacterial growth [245]. Further evidence from Leung et al. [289] demonstrates the drawdown of dissolved Fe during peak growth times of cyanobacterial HABs, indicating the necessity of Fe in the growth of cyanobacterial blooms. However, in the same paper, the role of increasing phosphorus concentrations was also attributed to the triggering of the bloom event. These studies suggest the complexity of bacterial blooms in the field and the control of nutrients that limit them.

Comprehension of Fe concentrations in the field and their relationship to blooms is necessary in understanding the dynamics and triggers of HABs. Concentration of Fe in the environment has been established as one of the driving factors in the progress and proliferation of HABs. Linkages between atmospheric transport of Fe and algal blooms have already been substantiated [235]. As an essential nutrient needed by planktonic blooms, drawdown of Fe to produce biomass has been observed in several studies as a negative correlation between biomass and dissolved Fe concentrations [198,218,292]. The lowest dissolved Fe concentrations were observed during peak biomass of a cyanobacterial HAB event [289]. Algal bloom sites showed reduced Fe concentrations, which include the exchangeable/acid-soluble fraction, reducible fraction, and residual fraction, as compared to sites without algal blooms [293]. However, no differences in patterns among the three Fe fractions were observed during algal bloom formation. These field studies demonstrate the necessity of Fe in the progress of these blooms.

Aside from the drawdown of Fe by phytoplankton as a requirement for their growth, massive algal blooms also alter the physical parameters of the environment in which they exist. Thamdrup et al. [294] have outlined the effects of algal blooms on Fe concentrations as follows. Heterotrophic organisms devour the organic matter provided by the bloom, which leads to anoxic conditions at the topmost layer in shallow coastal sediments. The lack of oxygen causes bacterial organisms to use Mn-oxide and Fe-oxide as oxidizing agents, resulting in dissolution of Fe and Mn. Interactions of Fe and H₂S during algal blooms also lead to control of available Fe during algal blooms [295]. Subsequent anaerobic experiments derived from algal bloom-simulated conditions prove the dissolution of metals from sediments, most notably Fe [80,253,296]. The indirect effects of HABs on Fe introduce a layer of complexity in the dynamics and interactions of the two. Further studies are needed to substantiate other possible indirect effects that may exist.

The relationships between Fe and HABs have been described in terms of the metal effect on growth, senescence, and toxin production. The compounds produced by HABs and algal bloom events affect the bioavailability of Fe, which shows their two-way relationship. The universal need for Fe by phytoplankton reveals the possible use of the metal in the mitigation of HABs. Differences in the reaction of varying species towards Fe merit continuous research on the topic, and sustained data gathering would fine-tune our understanding of HAB dynamics.

4.2. Copper (Cu)

Copper has long been established as an essential nutrient for phytoplankton growth. The role of Cu as a metal center for plastocyanin and for other oxidative stress enzymes highlights the importance of the metal in the physiology of HABs. Several studies have shown correlations between the growth of marine HAB species like *Pseudo-nitzschia australis* [231], *Pseudo-nitzschia delicatissima* [237], *Alexandrium minutum* [197], and *Aureococcus anophagefferens* [214] and adequate Cu concentrations. Furthermore, Cu has been observed to be a limiting agent for HAB occurrences in a hypereutrophic lake [297]. Under Cu starvation, multiple strategies are deployed for the compensation and conservation of physiological functions. For some HABs, most of these strategies aim to preserve survival of the organism. The stabilization and maintenance of photosynthesis at the PSII step [298] and preference for pigment and lipid reconstruction [238] were observed for *P. delicatissima*. This alludes to be a compensation for the role of Cu in plastocyanin in the electron transfer chain of photosynthesis. Transcriptome modifications involving lipid pathways were observed for *Chlamydomonas reinhardtii* under Cu-deficient stresses [299]. Cu as a nutrient is required by HABs for growth at the cellular level, and they must adjust when facing Cu starvation. However, the high reactivity of Cu dictates a need for optimal concentrations of this nutrient for it to be most effective. Toxicity occurs when concentrations exceed the threshold an organism can be exposed to.

The sensitivity of phytoplankton to high Cu concentrations is evidenced by decreasing population growth with increasing Cu levels. Marine and estuarine populations of *Gymnodinium breve* [224], *A. minutum* [197,211], *Pseudo-nitzschia* sp. [175,198], *Pseudo-nitzschia multiseriata* [240,241], *P. delicatissima* [237,238], *P. australis* [236], *Amphidinium carterae* [213], *Prorocentrum micans* [213], *Alexandrium catenella* [206,207], *Ostreopsis ovata* [206], *Cochlodinium polykrikoides* [221–223], and *Karenia brevis* [201] have exhibited toxicity to high Cu concentrations. Furthermore, some freshwater HAB species such as *A. anophagefferens* [214], *Anabaenopsis* [244], *Closterium ehrenbergii* [247], *Lyngbya wollei* [251], and *Microcystis aeruginosa* [65,203,244,248,254–256,267,268] also show decreased growth in high Cu concentrations. Aside from its senescent capabilities, induction of temporary cyst formation was observed in both *O. ovata* and *A. catenella* upon exposure to high Cu concentrations [206,207].

Responses to varying Cu concentrations were different for toxin-producing HAB species. Increasing Cu concentrations induced lower production of YTX by *Protoceratium reticulatum*, along with decreased growth [231]. Instances wherein Cu concentrations did not significantly affect toxin production were observed in microcystin production by *M. aeruginosa* [254], gymnodimine production by *Karenia selliformis* [231], and PSP toxin production in *A. catenella* [206]. However, PSP toxin production in a different species, *A. minutum*, was found to be maximized at optimal Cu concentrations and both low- and high-concentration Cu treatments induced lower toxin production [197]. Increasing Cu concentration caused higher okadaic acid production in *Prorocentrum lima* [231] and palytoxin and related compounds in both *Ostreopsis siamensis* [231] and *O. ovata* [206]. This increase can also be seen in the production of domoic acid by *Pseudo-nitzschia*. This toxin is documented to form complexes with metal ions and is considered as a means of surviving Cu toxicity by several *Pseudo-nitzschia* species [175,198,241]. Furthermore, compounding requirements of silicate and Cu also lead to an increase in domoic acid production in *Pseudo-nitzschia* sp. [240]. Aside from domoic acid, other HAB-produced toxins, such as microcystin, palytoxin, brevetoxins, and okadaic acid, were able to form

complexes with Cu and other metal ions [201,300–302]. This further indicates the capability of numerous HAB species to control and mitigate metal toxicity in the environment. Aside from their toxins, dissolved organic matter (DOM) and dissolved organic carbon (DOC) produced by phytoplankton may also function as metal chelators in the environment through their organic ligands [15,137,282]. DOC production by *M. aeruginosa* [202] and *A. minutum* [207] was enhanced under moderate Cu exposure. Although the DOC may play a role in decreasing Cu toxicity, it is highlighted in both studies that the highest concentrations of Cu used exhibited total inhibition for both the organisms. This suggests that production of DOC cannot entirely negate the effects of Cu toxicity. HAB species may utilize this characteristic of the toxins they produce to chelate metals in their environment, alleviating effects of toxic metals like Cu [236].

Consequences of Cu and its toxicity towards phytoplankton at high concentrations have paved the way for its possible use as an algicide in the control of HABs. *M. aeruginosa* was determined to be sensitive to high concentrations of Cu [265]. Exposure to high doses of Cu was seen with cell lysis-related release of K⁺ ions, increased reactive oxygen species production, increased superoxide dismutase and catalase activity, and upregulation of H₂O₂ treatment genes that are highly associated with oxidative stress [267,268]. Consequently, several studies have already outlined the use of copper sulfate as a means to control HAB blooms of *M. aeruginosa* [202,203,244,266,303]. This mitigative measure was also applied to other HAB-causing organisms. Reduced photosynthetic ability and increases in reactive oxygen species were perceived in both *C. ehrenbergii* [247] and *C. polykrikoides* [221]. Downregulation of photosystem genes and upregulation of mitochondrial genes and other genes that are involved in translation, spliceosome, and/or signal transduction were also further identified in *C. polykrikoides* [222]. Blooms of *Anabaenopsis* were also deemed susceptible to Cu algicide treatments [203]. In the mat forming *Lyngbya wollei*, decreased filament viability was discovered upon exposure to high Cu concentrations [251], countering the mechanism in which *L. wollei* usually causes harm to the environment.

The description of the roles of Cu as both an essential and extremely toxic metal help us understand its unique dynamics with HABs. Studies regarding its use as an algicide are plentiful and provide us useful information on ways to mitigate these deleterious events. Although several papers have already described the effects of Cu starvation, its role as an essential nutrient should be further explored.

4.3. Zinc (Zn)

Zinc has been widely regarded as an important micronutrient due to its function in metalloenzymes for photosynthetic (carbonic anhydrase), translational (RNA polymerase, tRNA synthetase, reverse transcriptase), and antioxidative activities (superoxide dismutase, alcohol dehydrogenase) (Table 1). Zn is observed to be a necessary component in the growth of both freshwater HAB species such as *Aureococcus anophagefferens* [214], and *Microcystis aeruginosa* [254] and marine HABs like *Pseudo-nitzschia* [231], *Karenia selliformis* [231], and *Protoceratium reticulatum* [231].

Although many physiological functions provided by Zn promote growth and relief from oxidative stress, high concentrations of Zn may still cause toxicity to organisms. In *M. aeruginosa*, high concentrations of Zn inhibited its growth [269]. This is further substantiated by an increase in dissolved organic carbon production [65], increase in toxin production [254], and upregulation of genes responsible for the production of microcystin [270]. Dissolved organic carbon and microcystins are capable of metal chelation—this adaptation of the organism is exhibited to decrease toxicity, possibly exerted by Zn [207,236]. Synergistic effects of Zn and Cu [259] and Zn and Cd [260] toward decrease in cell division and photosynthetic activity were also described. Adaptations for oxidative stress response such as enhanced esterase and superoxide dismutase activity and increase in malondialdehyde content were noted as a response to Zn toxicity [260].

Marine HAB species also exhibited Zn stress-specific responses as an adaptation to toxicity. Increase in the domoic acid isomer-C production was observed in *Pseudo-nitzschia*

under optimal Zn conditions [231]. Alternatively, elevated Zn levels decreased domoic acid production, which is contrasting to responses by *Pseudo-nitzschia* under stress toxicity by other metal ions [238,240,241]. Decrease in toxin production was also observed for *P. reticulatum* [231]. Interestingly, *Alexandrium minutum* was observed to increase its release of fluorescent dissolved organic matter in response to moderate Zn concentrations [205]. These compounds have been documented to be capable of metal chelation, which was seen as a response to metal toxicity. Ultimately, Zn levels above the threshold still lead to toxicity, as evidenced by the formation of temporary cysts. Inspection of protein components under Zn toxicity in *Alexandrium catenella* reveals that Zn toxicity targets photosynthetic (Rubisco, peridinin chlorophyll-A, and ferredoxin NADP reductase), cellular signaling (calmodulin), and antioxidative processes (superoxide dismutases) [208].

Zn concentrations in the environment are also greatly affected during algal bloom development, duration, and decay. It has been established that drawdown of Zn by phytoplankton causes reduced concentrations during the onset of an algal bloom [153,253,304]. PCA component analysis suggests careful reconsideration of the relationship between Zn and algal bloom formation [305]. Inconsistent concentrations of Zn during onset are proof of other underlying mechanisms that govern environmental Zn concentrations. A possible substitution of Co instead of Zn in carbonic anhydrase [96] may diminish the need for Zn during algal blooms. Subsequently, the decay of blooms reintroduces Zn into the system via reductive dissolution of Mn oxides in sediments [253,305]. This is supported by positive correlation of Zn concentrations and bloom-related DOC levels [306].

Much like Cu, several studies have already detailed the distinctive capabilities of Zn as both an essential nutrient and a toxic metal. Optimal concentrations reveal the benefits Zn poses towards HABs and their toxin production. However, utilization and concentrations of the metal during blooms remain poorly understood. Subsequent studies should be established to further divulge the relationship between Zn and HABs and their interactions.

4.4. Selenium (Se)

The biochemistry of Se has piqued interest due to intrinsic requirements by diverse organisms in different trophic levels. Phytoplankton necessitates an optimum Se concentration to support growth, and this requirement is attributed to the production of Se-containing proteins [307]. There is limited work performed on the investigations of the interdependence of Se availability and phytoplankton growth. The limited reports, however, still clearly present effects by Se on algal growth and the dynamics of phytoplankton blooms [225,227,308,309]. Two pioneering works performed on *Gymnodinium nagasakiense*, a dinoflagellate species persistent in Japanese waters, reflected good correlation between Se concentrations backed by enhanced cell growth when bay waters were amended with Se [227,308]. Subsequent work on other organisms, as detailed in a review by Araie and Shiraiwa [307] (and references therein), show the relevance of Se but highlighted the need for further studies to better understand the mechanisms and bring to light its biological relevance.

The complexity of Se biochemistry in microalgae is depicted in the study on the intraspecific variabilities of *Gymnodinium catenatum* [225]. Se exists in nature with different isotopes and speciation ranging from the inorganic (selenite and selenate) to organic forms, including selenomethionine, selenocysteine, and other selenoproteins. Phytoplankton preferentially takes up selenite, Se(IV), over selenate, Se(VI), using an ATP-dependent high-affinity transporter that functions as an active transport system [215,307,309–311]. In the study by Doblin et al. [225], five strains from multiple origins were subjected to Se enrichment experiments, and the physiological responses of Se-treated strains were compared with non-Se-amended treatments. The results show variability in the growth performance of strains collected from different years and localities. These findings underscore the discrepancies in Se requirements, which is tempting to use to infer the possible requirements for other trace metals as well. But, what this clearly shows is that the Se requirement of different bloom-forming organisms needs to be further investigated.

Se is introduced to the environment through natural and anthropogenic sources with remarkably low concentrations. In open waters, selenite concentrations often range between 0.1 to 0.2 nM, while selenate concentrations may be from 0.1 to 1.0 nM [312]. The narrow concentration ranges at which Se occurs in aquatic environments may have dictated the window of essentiality of the metal for phytoplankton use because photosynthetic organisms need an optimum selenite supply of about 1 nM, beyond which Se begins to exert toxic effects on the organism [311]. Se is notable among trace metals because of this narrow usability for biological functions. The natural distribution of Se and its biogeochemical cycling in open waters is heavily influenced by phytoplankton because of the preferential uptake of selenite, the reduction and incorporation into proteins inside the cells of primary producers, and the complex regeneration from organic to inorganic Se compounds during algal decomposition [312]. In the many steps of Se transformations performed by microalgae, the role of excreted compounds, comprising 80% of dissolved Se in the ocean, is poorly characterized [313–315].

In terms of Se requirement of HAB-forming organisms, an excellent study organism is *Aureococcus anophagefferens* because it has the distinction of having the largest and most diverse known selenoproteome [215]. In ecophysiological studies conducted on the harmful pelagophyte that included cell cultures, genomic analyses, and ecosystem studies, it was demonstrated that dissolved Se were elevated before and after *A. anophagefferens* blooms but were significantly reduced during mid-bloom at about 0.05 nM. Validation of this observation was performed using enrichment experiments by spiking seawater during the different stages of the bloom of the pelagophyte. The results show positive impacts of Se enrichment only in seawater during mid-bloom, indicating Se limitation for the organisms at this stage. The results exemplify the role of Se in brown blooms and puts a premium in the conduct of complementary experiments to provide a holistic understanding of the interactions of environmental parameters with the ecological responses of critically important organisms.

4.5. Other Essentials (Mn, Co, Ni, Cd, Mo, V)

The crucial roles of other essential metals on algal physiology are recognized, but the current knowledge on their influence on HABs is quite scarce. In this section, we delve into the uses of other essential metals by HAB-causing species.

4.5.1. Manganese (Mn)

The major use for Mn is primarily in photosynthesis, respiration, and antioxidative defense mechanisms with MnSOD, a major reactive oxygen species-detoxifying enzyme. With these functions, Mn affects the growth rates, biomass production, and ultimately bloom dynamics of HAB species [316]. Mn enrichment experiments conducted by Rhodes et al. [231] reported increases in biomass of marine HAB species, namely *Ostreopsis siamensis*, *Karenia selliformis*, and *Prorocentrum lima*. Interestingly, despite the limited known metabolic functions of Mn (Table 1), a significant decrease in the toxin production of isodomoic acid and okadaic/diol esters of marine *Pseudo-nitzschia australis* and *P. lima*, respectively, has been reported [231]. Similar trends were also observed in freshwater *Microcystis aeruginosa*, where Mn depletion results in limited growth [255]. However, Lukač and Aegerter [254] reported that Mn does not significantly affect toxin yields, indicating a need for additional research in this area.

4.5.2. Cobalt (Co)

Similarly, studies regarding the role of Co in HABs are relatively limited and it was previously reported that the need for Co-containing cofactors is low in phytoplankton [193]. Early investigations focused solely on the effects of Co on the growth of a bloom-forming Prymnesiophyceae flagellate, *Chrysochromulina polylepis* [317,318]. The underlying biochemical basis remained largely unknown [162,193,319] until succeeding studies shed light on the metabolic role of Co and its potential influence on HAB formation. Co serves as

an integral component of cobalamin or vitamin B₁₂, an essential micronutrient for enzymes involved in N₂ fixation [320]. It also assists methionine synthase in DNA synthesis and methylmalonyl CoA, which is required for inorganic C assimilation [321]. Extensive research on various marine microalgae has revealed that many HAB species, including *Aureococcus anophagefferens*, *Prorocentrum minimum*, *Karenia mikimotoi*, *Chatonella marina*, and *Fibrocasa japonica*, among others, exhibit auxotrophy for vitamin B, particularly B₁₂, resulting in elevated vitamin B quotas [204]. These findings demonstrate the potential ecological significance of B vitamins, including B₁ and B₇, in regulating HABs. Moreover, while Co is required in trace amounts, its availability can influence the growth and proliferation of certain algal species [182]. Co enrichment experiments have shown increased cell densities in marine HAB species *Pseudo-nitzschia australis*, *Karenia selliformis*, *Ostreopsis siamensis*, and *Prorocentrum reticulatum* [231], with a general trend of decreasing toxin production, e.g., yessotoxins, gymnodimine, and palytoxins. However, Mitrovic et al. [234] observed no significant differences in growth and yessotoxin production in *P. reticulatum*, further suggesting that Co has species-specific influences on algal growth.

4.5.3. Nickel (Ni)

Ni has been considered as a common contaminant for aquatic ecosystems [322], and in fact, some algal bloom events were linked to Ni concentrations [153,323]. The known function of Ni is for nitrogen assimilation in the form of urease [324] and oxidative defense through the action of Ni-SOD [243,325,326]. Laboratory investigations revealed that Ni additions result in elevated growth of *Aureococcus anophagefferens* [214], consistent with the genomic study on the same alga [326]. About 82% of cellular Ni in *A. anophagefferens* was sequestered through surface adsorption resulting in internalization of Ni, directly affecting metabolism and cell division and thus potentially contributing to the persistence of brown tide development [214]. Other research on the influence of Ni on HABs demonstrates varying effects of Ni availability on the species under investigation. Ni addition starting from 3 µg L⁻¹ Ni affected the growth of freshwater *Mirocystis aeruginosa*, with complete inhibition observed at 24 µg L⁻¹ Ni [261]. Moreover, Ni exposure led to an increase in macromolecule production; activities of antioxidant biomarkers, e.g., catalase (CAT), glutathione peroxidase (GPx), superoxide dismutase (SOD); and toxic microcystin, which is in contrast with a previous report [254]. Nonetheless, these studies provide evidence for the link between Ni supply and algal bloom development.

4.5.4. Cadmium (Cd)

Cd is one of the few metals widely regarded as non-essential and toxic owing to health effects associated with long-term exposure to it. Earlier studies on diatoms [165,168,193] and other phytoplankton species [327,328] have otherwise shown that Cd may also promote algal growth via metal substitutions when bioavailability of essential Zn is limited or depleted. A couple of reported bloom events were associated with Cd contamination [153,219,256]. Dinoflagellate HAB species, including *Chatonella marina*, *Chatonella ovata*, *Gymnodinium catenatum*, and *Gymnodinium sanguineum*, were found to be the culprits of massive mollusks and fish kill events in Kun Kaak Bay, Mexico, that coincided with high sediment Cd concentrations reaching up to 4 µg g⁻¹ [219] from potential metal leaching [317,329]. Another HAB-forming dinoflagellate, *Lingulodinium polyedrum*, was found to be the dominant species in the HAB events in Todos Santos Bay, Mexico, coinciding with high average Cd concentration (0.37 ± 0.41 to 1.02 ± 0.99 nmol kg⁻¹ [232]. Tolerance to Cd levels has been reported in *A. anophagefferens* up to pCd values of 10.33 (defined as pCd = -log [Cd²⁺]) but further increases in Cd results in growth inhibition relative to the control: 21% ($p = 0.001$) and 67% ($p < 0.001$) at pCd 9.33 and 8.33, respectively [214]. Similar sensitivity to Cd was also observed in another marine dinoflagellate, *Alexandrium catenella*, in which drastic growth inhibition was observed starting from pCd 7.88 (30%) up to pCd 6.36 (100%), where growth is completely inhibited [207]. Cyst formation was observed at a pCd value of 7.88 and *A. catenella* released extracellular dissolved organic matter (DOM) as

a defense mechanism to Cd toxicity at pCd 6.36. Other phytoplankton species have been reported to employ similar strategies via release of chelating molecules to protect cells from metals [330–332]. Interestingly, in freshwater *M. aeruginosa*, Cd exhibited no apparent negative effects on growth [333] and microcystin production [254]. Moreover, increased floating rates and the buoyancy of *M. aeruginosa* at high Cd concentrations provide insights into its potential contribution to facilitate development of cyanobacterial blooms, highlighting the need for further research on the role of Cd in algal blooms [256].

4.5.5. Molybdenum (Mo) and Vanadium (V)

In phytoplankton metal physiology, both Mo and V are understudied. Nonetheless, growing concerns regarding contamination from Mo and V due to extensive industrial activities have sparked renewed interest in studying them in aquatic ecosystems [334–336]. Previous research has shown that Mo serves as a constituent of the nitrate reductase and nitrogenase enzymes, participating in nitrate assimilation and N₂ fixation [337]. Likewise, V has been identified as essential nutrient influencing photosynthesis [338–340], cell division [341], and nitrogenase and nitrate reductase activities [342], as well as bromoperoxidase enzymes containing V at the active site [163,164]. The existing knowledge base about Mo and V mostly comes from research on freshwater green algae, blue-green algae [343,344], and some diatoms [340] because the major Mo species, MoO₄^{2−}, is known to be generally less available in seawater than in freshwater [345].

Limited information is available concerning the involvement of Mo and V in HABs, although efforts to expand our current understanding have been made. Barros et al. [233] have explored the potential influence of the molybdate (MoO₄^{2−})-to-sulfate (SO₄^{2−}) ratio on redox metabolism and viability of marine dinoflagellate *Lingulodinium polyedrum*. Research revealed augmented xanthine oxidase (XO) and nitrate reductase (NR) activities, lipid peroxidation, protein carbonylation, as well as photosynthetic protein synthesis, as a response to elevated [Mo]:[sulfate] ratios. These observations suggest that increasing [Mo]:[sulfate] ratios impose gradual oxidative stress conditions on *L. polyedrum* cultures. Moreover, Facey et al. [255] explored the role of Mo on the growth and toxin production of freshwater *M. aeruginosa*; however, the reported results show no notable influence on growth and microcystin production. Meanwhile, studies on V in aquatic environments are mostly focused on redox geochemistry and mobility, providing limited evidence on the linkage between V and HABs [346]. A better understanding of redox metabolism in dinoflagellates, as well as physiological functions of Mo and V in both marine and freshwater HABs, could better inform on the roles of these metals in mitigating the impacts of HABs.

4.6. Non-Essentials (Pb, Hg, As, Sn, Ti, Zr)

Since HABs do not utilize non-essential metals, the major focus in encountering them is addressing the toxicity associated with these metals. The tolerance, survival, and adaptive mechanism of phytoplankton and HAB species are the aspects commonly investigated in the relationship of HABs and non-essential metals. Although the available data are considerably limited, this section will discuss HABs and their varying interactions with non-essential metals.

4.6.1. Lead (Pb)

Anthropogenic activities have been the primary reason for increased Pb contamination in both freshwater and oceanic ecosystems [347–349]. Pb is a nonessential element and toxicity has been documented for this metal. Photosynthetic systems, antioxidative activities, and changes in extracellular morphology are some of the primary responses of phytoplankton with regard to Pb stress [350]. The marine HAB species *Alexandrium catenella* was observed to have reduced protein expression, especially of those for photosynthetic functions (RUBISCO and Ferredoxin-NADP⁺ reductase) and oxidative stress management (superoxide dismutase), when exposed to Pb [208]. In contrast, ATP synthase was upregulated, indicating that this may serve as a survival mechanism to cope with

metal stress induced by Pb. For *Cochlodinium polykrikoides*, tolerance was observed at lower Pb concentrations, but total inhibition was demonstrated at higher concentrations [223]. In the freshwater HAB species *Microcystis aeruginosa*, high Pb concentrations with accompanying high pH conditions result in decreased cell division and growth inhibition [256]. Additionally, chlorophyll content and cell fluorescence in *M. aeruginosa* were also reported to decrease under elevated Pb concentrations [333]. However, the same study has shown tolerance to high Pb levels and a corresponding accumulation of intracellular Pb.

Sun et al. [296] described the mobilization of Pb from sediments during an algal bloom in the following steps: (1) algal blooms create anaerobic environments from their increased biomass; (2) the resulting reductive conditions cause the solubilization of Fe/Mn oxides, which induces a chemically-mediated release of Pb; (3) bloom-decay-derived dissolved organic matter complexes Pb effectively, decreasing dissolved Pb concentrations; (4) the lower Pb levels allow for algal growth and subsequent bloom; and eventually, (5) the collapse of the algal bloom creates anoxic conditions and the cycle repeats again. The effects of Pb towards the growth of HAB species and the development of blooms underscore its importance in understanding HAB dynamics. Underlying mechanisms governing the cycling of Pb in the context of algal blooms need to be further investigated. The adaptability to elevated Pb levels poses concerns of trophic transfer to higher organisms owing to phytoplankton serving as the base of the food chain and with the known biomagnification potential of Pb.

4.6.2. Mercury (Hg)

Mercury is a common pollutant and is most toxic in its organic form. In phytoplankton, Hg will bind to cytosolic ligands and distribute into the organelles [351], wherein it may affect photosynthesis [352–354] and increase reactive oxygen species inside the cell [355,356]. As a consequence of toxicity, phytoplankton has devised mechanisms to counter this toxicity, which include the conversion of ionic mercury to elemental mercury [357]. Even with this mechanism, several other factors may also affect the Hg composition during blooms. Unfortunately, increases in monomethyl mercury (MMHg) percentages were observed during an algal bloom in a high-altitude lake [358]. This increase in methylmercury may lead to cascading effects up the trophic ladder since this form can cross lipid bilayers and the blood-brain barrier. Transfer and bioaccumulation of methylmercury to organisms threaten organisms at the top of the food chain. Pickhardt et al. [359] demonstrated that increasing algal density reduces the amount of methylmercury found in phytoplankton by two- to threefold. MMHg levels may have been diluted due to the increasing number of organisms that uptake the metal. This denotes lesser Hg accumulation in fish in algal bloom environments as compared to algal bloom-free environments. The interaction between mercury and algal blooms remains relatively understudied, and future studies should fortify our understanding of the cascading effects of the two in food webs.

4.6.3. Arsenic (As)

Arsenic is a highly toxic carcinogenic metal found ubiquitously in rocks and sediments exposed to bodies of water [360]. It is known to be toxic to humans and other organisms and has no utilization in physiological functions [361,362]. Mechanisms of toxicity for As revolve around arsenate (V) and phosphorus being very biochemically similar [363–365]. Arsenate (V) interferes with energy metabolism with its substitution in the adenotriphosphate cycle. This was clearly exhibited by the HAB species *Chlamydomonas reinhardtii*, wherein As toxicity was observed to be characteristically similar to phosphate deficiency [361]. Mechanistic adaption involving As employed by phytoplankton centers around the conversion of As(V) to As(III) and monomethyl and dimethyl arsenic species [220,366,367]. As such, studies regarding As and algal blooms revolve mainly around As species transformation and correlation studies with phosphorus concentrations.

During bloom development, arsenate was rapidly reduced to arsenite and other methylated species [220]. The rate of reduction depended on pre-existing As concentrations,

dominant phytoplankton, season, and the degree of decline in phosphorus concentrations. Contrary to the onset of algal blooms, the decay stage of the event aggravates the release of As and other labile metals from sediments. Strong anoxic conditions [257], reduction of Fe and Mn oxides [290], and microbial action [368] were observed to cause an increase in As concentrations during algal bloom decay. Released Fe-sulfides from the decaying bloom facilitated As reduction, which was then mobilized to the aqueous phase [257,290]. Aside from the conversion of As(V) to As(III), a strain of *M. aeruginosa* isolated from a lake with naturally high As concentration was found to be resistant to As concentrations of 10^{-5} mol/L As(III) and 10^{-3} mol/L As(V) [271]. This observation was accompanied by increased total microcystin production under low As concentrations. The role of algal blooms in the cycling and transformation of As to its various forms remains relatively understudied. Furthermore, synergistic effects of toxic algal blooms and As poisoning may be on the horizon as adaptations to As toxicity may occur.

4.6.4. Tin (Sn), Titanium (Ti), and Zirconium (Zr)

Interests in the effects of other non-essential metals have recently been put in the limelight. The group IV metals tin, titanium, and zirconium are relatively understudied in terms of biological relevance, but these metals have interesting properties. The possibility of group IV metals to incur changes in phytoplankton has been exhibited in the case of germanium (Ge), which is able to modify the cell shape of silica-rich diatoms [369]. This modification may have been achieved by Ge mimicking the chemical properties of Si and replacing it in cellular structures in the phytoplankton. This ability to stimulate structural changes was also caused by Sn, Ti, and Zr in the freshwater diatom *Synedra acus* [370]. Aside from morphological changes these metals can induce, their inhibitory properties towards phytoplankton are also demonstrated. Zr salts were able to reduce phytoplankton populations through inactivation of phosphorous [371,372]. Chloride salts of Sn (II) and Sn(IV) exhibited toxicity towards *Synechocystis* [373]. Furthermore, titanium dioxide (TiO_2) nanoparticles have shown remarkable toxicity to natural phytoplankton assemblages [374]. Reductions in the maximal photosystem II quantum yields and induction of oxidative stress were observed upon introduction to TiO_2 [375]. Nano- TiO_2 particles were also described to induce changes in phytoplanktonic percent composition, denoting species-specific responses towards the nanoparticle [376]. Though studies focusing on these metals and algal blooms are lacking, increasing evidence of interactive effects merits further studies to be conducted on these metals.

5. Gaps and Recommendations

The current knowledge base on phytoplankton physiology primarily comes from research conducted on larger diatoms and cyanobacterial diazotrophs. Over the past decades, investigations have expanded to other phytoplankton functional types, including dinoflagellates, picoeukaryotes, green algae, non-diazotrophic cyanobacteria, and others, shedding some light on the roles of trace metals on the dynamics of HABs. However, variations in trace metal requirements, modes of nutrient uptake and assimilation, redox metabolisms, and toxin production call for further investigations on the role of trace metals and vitamins on phytoplankton growth, metabolic processes, bloom dynamics, and other ecosystem-level interactions. Studies describing the effects of trace elements towards HABs and their toxin production leave much to be desired. A general focus of current studies hinges on the toxicity of certain essential nutrients such as Cu and Zn when supply is in excess. Detailing the role of metals towards growth and toxin production under deficient conditions demonstrative of actual scenarios in coastal environments prone to HAB occurrences would provide new insights into the importance of metals in these processes.

The initiation and dynamics of phytoplankton blooms will be further complicated in the scenario of the future ocean with acidification and global warming looming to cause complex and interdependent responses in phytoplankton and their growth factors. Trace metal cycling and availability will be influenced since the solubility and reactivity

of metals are controlled by pH and temperature changes. Pinpointing specific responses of phytoplankton groups to these environmental changes will require carefully designed experiments that may use complementary and orthogonal studies for holistic and cohesive understanding that will permit inference of the projected ecological changes of algal blooms. Nowadays, omics strategies are more readily accessible and field- or laboratory-derived physiological and physicochemical information backed with genomics or transcriptomics data will be more valuable and provide more definitive insight into the underlying processes that we wish to bring to light. To address the paucity in data about the role of metals in phytoplankton growth, structure, and community succession, more research is needed, especially focusing on algal species of concern. In the context of HABs, further trace metal research should consider environmentally relevant amendments when conducting metal enrichment work and field-based studies should be guided by timing and frequency to capture information that is illustrative of ambient conditions. It is expected that expanding agriculture and aquaculture activities will continue to exert pressure and shape ecological niches in coastal environments. It is then imperative that studies incorporate these considerations when putting forward plans for monitoring bloom occurrences so that sampling designs will factor in spatial, temporal, and seasonal variabilities for more accurate data, especially when these will be inputted into predictive models. More importantly, data gathered on the interactive effects of trace metals and other nutrients on harmful algal blooms should be communicated to stakeholders so that translation into policies and sustainable practices will be implemented.

Author Contributions: Conceptualization, D.C.M., R.D.R. and I.B.R.; data curation, D.C.M. and R.D.R.; writing—original draft preparation, D.C.M., R.D.R. and I.B.R.; writing—review and editing, D.C.M., R.D.R. and I.B.R.; visualization, D.C.M. and R.D.R.; supervision, I.B.R. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: No new data was created or analyzed in this study. Data sharing is not applicable to this article.

Acknowledgments: We express our gratitude to the University of the Philippines System, the Marine Science Institute, Department of Science and Technology (DOST), Philippine Council for Agriculture Aquatic and Natural Resource Research and Development (DOST-PCAARD), and the RVA-Marine Microalgal Culture Collection (RVA-MMCC) for their support to our research group.

Conflicts of Interest: The authors declare no conflicts of interest.

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