

The Impact of Climate Change on The Bioavailability of Environmental Toxins and Their Toxicological Effects

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Abstract. Climate change has become one of the biggest challenges for the 21st century. Global warming, sea level rise, changes in weather conditions, and atmospheric contamination caused by climate change not only have impacts on nature but also present threats to human health. Climate change can influence the generations and distribution of some representative toxic compounds with specific examples, including heavy metals (arsenic and manganese), persistent organic pollutants (POPs), air pollutants, and biotoxins (domoic acid and β -N-methylamino-L-alanine). This review discusses how the effects of climate change drive the production and spread of toxic substances that enter the human body through different means as well as presents the biochemical mechanisms and experimental evidence of their toxicological effect on human health, which provides an insight on climate change allowing toxic substances to enter human body and calls on readers to understand and pay attention to climate change from a more comprehensive aspect

Keywords: Climate change, Global warming, Heavy metals, POPs, Air pollutants, biotoxins.

1. Introduction

Climate change is one of the most serious and most urgent challenges in the 21st century with potentially far-reaching consequences for both nature and humans. Climate change is originally a natural event that has been going on since the earth formed 4.5 billion years ago. However, human activities, such as burning fossil fuels, deforestation, and excessive agricultural practices, have brought climate change into an unprecedentedly concerning situation [1].

Human-induced climate change can be reflected by abnormal changes in the patterns of three areas: global warming, changes in precipitation patterns, and increases in frequency and intensity of extreme weather events [2]. Global warming is mainly caused by the increase in greenhouse gasses (CO₂, CH₄, NO₂). The atmospheric CO₂ concentration has increased from 280 parts per million (ppm) in the pre-industrial times to over 400 ppm currently, which is higher than at any point in at least the past 800,000 years [1]. From NOAA's observations, global methane emissions in 2021 (17 parts per billion) are 162% greater than pre-industrial levels [3]. Current global mean surface temperature has about 1°C above the pre-industrial level and is predicted to rise 2-4 °C more by 2100 [1]. Regarding the changes in precipitation patterns, generally, there is increased rainfall in higher latitudes and altitudes, including Alaska, northern Europe, northern Asia, Tibetan Plateau, and so on, and decreased rainfall in lower latitudes, including the Mediterranean region, southern Africa and so on [1]. Climate change also brings about increases in the frequency and intensity of extreme weather events (heatwaves, droughts, hurricanes, tropical storms or floods, etc). Climate-related disasters increased from 3656 in the period 1980-1999 to 6681 in the period 2000-2019 [4]. Attribution studies of 405 extreme weather events show that 70% of them were made more likely or more intense by human-induced climate change [5]. Moreover, these outcomes of human-induced climate change can interact with each other and impose further compounded effects. For example, global warming promotes the melt of methyl clathrate and thus leads to more methane released into the atmosphere, causing a greater greenhouse effect and further warming up the earth [6]. Therefore, if these problems cannot

be resolved in time, these problems will enter a vicious cycle and lead to more serious and more intense problems that are more difficult to reverse.

Climate change not only affects the natural environment, the distributions and lives of plants and animals, and the socio-economic activities of humans, but it also threatens the health of humans in various ways. One way is that climate change can alter the bioavailability of some environmental toxins, making them be exposed to humans more easily and then impose toxicological effects on human bodies [7]. The change in physical level manifested in climate change (for example, the temperature increase, the precipitation increases, and the pH decrease in acidified ocean) will lead to the changes on the chemical level, in this case, the properties, distribution, and the concentration of some environmental toxins. It will eventually impact the biological level when humans are exposed to these toxins with the increased bioavailability and suffer from the toxicological effects.

This review summarizes the pathways of how climate change impacts the bioavailability of four types of environmental toxins (heavy metal, persistent organic pollutant, air pollutant, and biotoxin) and introduces their toxicological effects on humans. This review aims to provide a clearer and broader link and explanation between climate change and the bioavailability of various environmental toxins and their toxicological effects on human health, so as to raise the reader's awareness of environmental protection from a novel perspective of toxicology.

2. Climate change and environmental toxins

Fig. 1 showed proposed pathways of how climate change affects human body. Climate change impacts heavy metals, such as arsenic and manganese. This review discusses how the rising sea level caused by the climate change increases the bioavailability of the heavy metals by expanding their reduction zone in the ocean, and their toxicological effects after human being exposed to them from drinking water. POPs can also be influenced by climate change. This review summarizes the pathway of climate change accelerating the remobilization and the increase in the environmental concentration of the POPs, and also their toxicological effects after human inhalation. In addition, air pollutants can be affected. With the case of ozone, this review analyzes how climate change promotes the generation of ozone and ozone precursor pollutants, followed by a review of the toxicological effects of lipid ozonation products and ozonation by-products (compounds formed after ozone is inhaled into human bodies). Moreover, neurotoxins, including domoic acid (DA) and β -N-methylamino-L-alanine are introduced. This review discusses the relationship between climate change, increase in CO₂ the bloom of some toxin-producing organisms, and increased concentration of biotoxins in the environment, as well as their toxicity after taking up by human through consuming marine organisms.

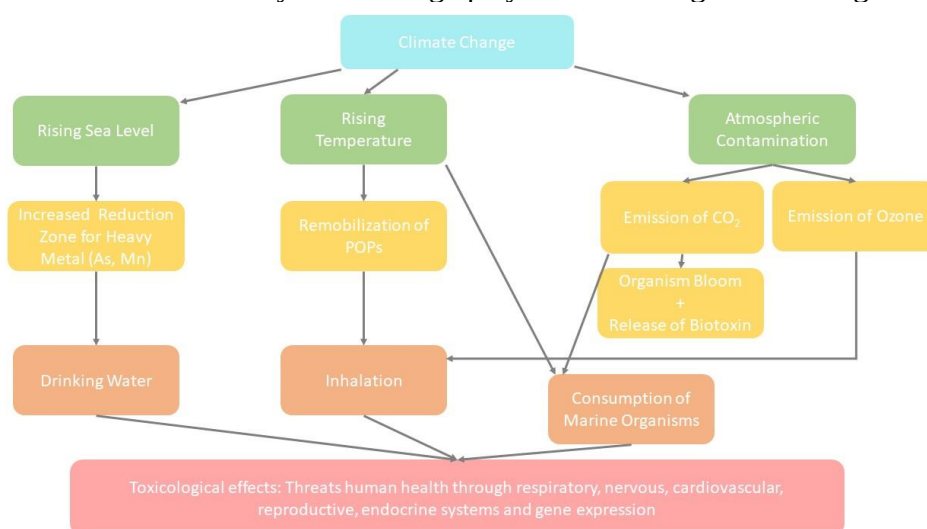


Figure 1. Climate change introduces toxicological effects to human body through different pathways.

3. Climate change and heavy metals

Changes in hydrology alter the redox state of soil and underground mineralogy, introduce salinity and reduction zones in areas where oxygenation or brackish water is retained for long periods of time, creating a threat of redox-sensitive toxic elements such as arsenic (As) and manganese (Mn) being released to soils (Table 1) [8].

3.1. Rising sea level provides new reductions zones

The reaction and migration of as in soil and sediment are closely related to environmental conditions such as pH and ionic competition, as well as other elements in soil such as Fe and Mn hydrogen oxide [8]. Scientists used an advanced biogeochemical microcosm (MC) system to create oxidative and reductive environment using arsenic-contaminated soil samples. Microwave acid digestion and other characterization of soil content discovered by inductively coupled pairing as well as other ion atomic emission spectrometry provide a range of data on coastal arsenic-contaminated soils exposed to seawater in biogeochemical microreactors under redox conditions [9].

3.2.1. Distribution of As.

The study found that in the case of seawater inundation, the introduction of reducing conditions may increase arsenic being released from soil by dissolving arsenic-containing mineral oxides. Rising sea levels can release arsenic into polluted coastal soils. Hypoxic conditions caused by sea level rising reduce surface-bound As (V) weakly-adsorbed As (III), thereby increasing As mobility in coastal soils [10]. Arsenic contamination in sediments and drinking water is a global concern, and arsenic is naturally present in drinking water in many countries. Arsenic is found in nearly 20% of public groundwater in the United States [11]. In Southeast Asia, millions of population are recurrently poisoned by arsenic contaminations in groundwater [8]. Inorganic arsenic is strongly associated with the induction of a range of human cancers (skin, lung, and bladder, as well as liver, prostate, and kidney cancers) [12]. Arsenic is present in drinking water in the form of arsenate (As(V)) or arsenite (As(III)) [13].

3.2.2. Toxicological impacts of As.

Arsenite hinders with energy metabolism by interacting with lipoic acid to inhibit pyruvate dehydrogenase (PDH) in the tricarboxylic acid cycle (TCA) cycle, while arsenate, like phosphate, inhibits oxidative phosphorylation, inhibits mitochondrial respiration and Energy-related NAD⁺ reduction during ATP synthesis [14]. Arsenic can cause oxidative stress in a variety of ways, such as activation of NADPD oxidase and nitric oxide synthase during the reduction of As(V) to As(III) leading to elevation of reactive nitrogen species, inhibition of PDH, and exhaustion of glutathione (GSH) reduction, etc.

Methylated metabolites of arsenic also tend to induce cancer in animals. Arsenic, one of the few metals that can be metabolized in the body, is methylated to produce mono (MMA) and dimethyl-arsenic compounds (DMA). Dimethyl-arsenic (DMA), the major metabolite of inorganic arsenic, was found to promote cancer and tumors in rats [15]. The main route of the introduction of inorganic arsenic into animals is through drinking water. Thus, the threat of the reactivation of As brought about by sea level rise to human toxicity cannot be underestimated.

3.2.3. Distribution of Mn.

Manganese (Mn) is the 4th most plentiful metal and is widely spread in the earth's soil and water resources. Due to its redox sensitivity, this metal is included in a wide variety of chemical processes. The anthropogenic supply of Mn to ocean biomes comes primarily from mining and steel production, with about 90% of Mn being used as deoxidizing and desulfurizing additives and alloying components [16]. Recent forecasts of Methylcyclopentadienyl manganese tricarbonyl (MMT) use suggested that a person may absorb a few percentage higher of manganese during the recent year. In tropical regions where shrimp farming is rapidly expanding, Mn is introduced to shrimp aquaculture

in the form of potassium permanganate (KMnO_4) disinfectant, resulting in an increase of manganese effluent discharged into ponds and coastal areas [17].

Mn turns into bioavailable Mn (II) when Mn in sediments is reduced under anoxic conditions. The reduction of Mn dioxide happens when the organic substances in the sediment decompose [18]. Mn solubility and bioavailability increase with decreasing oxygen pressure [19]. In anoxic conditions where the concentration of O_2 is relatively low, the amount of Mn (II) can grow by orders of magnitude. When Mn is filtered through soil, it is reduced to an even more soluble form Mn^{2+} , which can easily enter groundwater and surface water [20].

3.2.4. Toxicological impacts of Mn.

In Canada, high levels of Mn in drinking water resulted in an increase of manganese in hair samples from school-aged children. Increased Mn concentrations in hair are significantly linked with increased hyperactivity, weakened cognitive competence, and lower intelligence quotient among children [21]. Analysis of North Carolina's groundwater showed that increases in groundwater Mn level are associated with an increase in infant mortality per 1000 live births [22]. Despite differences in exposure levels between human and animal studies, Mn has been shown to be closely correlated to mitochondrial dysfunction, causing decreased myocardial contractility and induction of vasodilation. Decreased blood pressure is also discovered after acute exposure, but the exact mechanism of cardiotoxicity remains unknown [23].

4. Climate change and POPs

4.1. Shifted weather conditions alter the fate and behavior of POPs

Persistent organic pollutants (POPs) are substances of global concern because of their potential for long-distance transmission, persistence in the environment, and capacity to biomagnify and bioaccumulate in ecosystems. Climate change may impact persistent organic pollutants' environmental behavior by affecting the underlying processes of solvent transition and solvent consumption, as well as increasing pollutant degradation (Table 1) [24-28].

The volatility of persistent organic pollutants and their dissemination into the atmosphere through solvent conversion may increase as a result of global warming. POP deposition in aquatic and terrestrial ecosystems can be exacerbated by increased precipitation and melting snow and ice [26, 29]. Falling snow creates a solvent-switching condition, allowing pollutants to be quickly absorbed to the snow surface and then transferred to the ground. Solvent depletion can occur as snow melts, resulting in higher contaminant concentrations in the meltwater. The exchange rate of some persistent organic pollutants from air to water may also be accelerated by melting sea ice and the extension of open waterways [30]. POPs may be stored in glaciers for extended periods of time, and the melting of these ices can reflow the pollutants [31].

Climate change may also impact the organic carbon cycle in terrestrial and aquatic systems, thereby affecting the distribution of persistent organic pollutants [29, 32]. POPs are easily isolated from carbon-rich particles like Dissolved Organic Carbon (DOC) in water. Drought-induced reductions in water flow and increased evaporation as a result of warming can decrease water's capacity to bind contaminants and make them more easily accessible to aquatic organisms and even humans.

Increased POP concentrations and easier dissemination to water and aquatic biota may be facilitated by the temperature-induced acceleration of organic carbon metabolism in soils and sediments [29]. Warmer temperatures further boost the volatilization of POPs from the soil to the atmosphere, where they are photodegraded and migrate [24]. As permafrost melts due to rising temperatures, toxins are released, enabling them to escape into the atmosphere or run off into aquatic systems.

4.2. Toxicological impacts of POPs

Using microarray technology, researchers examined miRNA and transcriptome responses in the blood of healthy volunteers and discovered a total of 93 miRNAs whose levels were substantially linked with POP exposure [33]. Interactions with oncogenes such as *Myc*, *Ccnd1*, *Bcl2*, and *Vegfa* can be detected by combining miRNA and transcriptome profiles. POP exposure may alter cancer gene expression via influencing miRNAs and target genes linked with many kinds of cancers and implicated in related signaling pathways such as Wnt and P53.

Studies showed associations between occupational exposure to POPs and cardiovascular and endocrine disruptive health issues [34]. POPs have been related to poor neurobehavior and immunity, reduced Reproductive hormone secretion, diabetes, and more [35]. Some POPs operate as endocrine disruptors, imitating hormones by binding or inhibiting hormone receptors, according to another survey of POP exposure studies [36]. Studies have been conducted on combining the effects of intrauterine and lactation exposure to human-relevant POPs on the mammary gland, ovarian folliculogenesis, and liver function in CD-1 progeny female mice [37]. Female offspring that were perinatally exposed developed abnormal mammary glands and ovarian follicle maturation was inhibited. Hepatocyte enlargement was seen 30 weeks after weaning, probably leading to hepatotoxicity. Increased hepatic cytochrome P450 enzymatic activity indirectly suggested activation of nuclear receptors.

5. Climate change and air pollutants

5.1. Greenhouse gas emission causes rapid formation of ozone

Ozone is produced in the lower atmosphere where precursor pollutants react under sunlight. The ozone-forming reaction occurs faster with more sunlight and higher temperatures [38]. Global warming can accelerate the generation of ozone and ozone precursor pollutants. The two main precursor pollutants of ozone formation are nitrogen oxides (NO_x) (produced primarily through the combustion of fossil fuels) and volatile organic compounds (VOCs) (produced through the combustion of fuels and the evaporative storage of fuels). Emissions of anthropogenic and biological VOCs grow with increasing temperature. NO_x emissions also increase with rising temperature due to increased combustion of fossil fuels for power generation during heatwaves.

Atmospheric scientists at the University of Cambridge used the Chemical Climate Predicting UM_CAM to model the interaction between ozone and a range of other climate change factors [39]. Changes in circulation caused by climate change have an impact on the amount of O₃. The stratospheric-tropospheric exchange of ozone is accelerated by doubling CO₂, resulting in an increase in O₃ in the temperate troposphere and subsequent diffusion to the surface. Enhanced convection also accelerates the removal of ozone precursor pollutants from the boundary layer, boosting ozone production in the troposphere. Furthermore, as carbon dioxide levels rise, so do the nitrogen oxides from lightning, which enhances ozone generation as isoprene levels rises [39].

5.2. Toxicological impacts of ozone and its by-products

Ozone is so reactive that when it contacts the first layer of tissue at the lung/air interface, it is completely devoured [40]. As a result, biochemical changes caused by ozone inhalation must be conveyed to deeper tissue layers through lipid ozonation products (LOPs). Unsaturated fatty acids are found in the lipids of the lung intima and lung cell bilayers, and ozone combines with them to form ozone-specific compounds [41]. According to preliminary findings, a single LOP activates certain lipases, causing endogenous inflammatory mediators to release. Ozone exposure stimulates the synthesis, production, and release of many pro-inflammatory lipid mediators: Exposure of epithelial cells to ozone in vitro results in a dose-dependent increase in the activities of PLA₂, PLC, and PLD, which are phospholipases responsible for hydrolyzing phospholipids, leading to inflammation and pain [42]. The formation of ozonation by-products (OBP) is also a concern. Ozonated carbamazepine

(CBZ) is an antiepileptic drug often found in zebrafish embryos. Ozonation of CBZ induces its toxic effects in zebrafish embryonic larvae, primarily as cardiovascular toxicity, leading to malformations and reduced heart rate [43].

6. Climate change and biotoxins

6.1. Elevated temperature and CO₂ level expedite the growth of photosynthetic organisms

The increase in global temperature and atmospheric CO₂ level accelerates the rate of photosynthesis in photosynthetic organisms. This generates extra nutrients for them to reproduce in a larger number. In this way, more biotoxins such as DA and β -N-methylamino-L-alanine (BMAA) are produced into the environment by some photosynthetic biotoxin-producing organisms (Table 1).

6.2.1. Increased production of DA.

DA is an excitotoxic glutamate receptor agonist that can cause amnesic shellfish poisoning (ASP) and neurodegeneration [44]. The symptoms of ASP in humans include gastrointestinal distress, confusion, disorientation, seizures, permanent short-term memory loss, and death in the most severe cases [45]. DA is naturally produced in several types of algae, in which the toxigenic diatoms, represented by the genus *Pseudo-nitzschia*, threaten human health the most. By consuming the DA-producing algae, filter-feeding marine animals, such as clams, oysters, and crabs can accumulate DA in their bodies. Then, because of the bioaccumulation mechanism of the food chain, human beings may be exposed to DA if they eat those animals [44].

Climate change can lead to *Pseudo-nitzschia* bloom and increased DA production. The growth rate of *Pseudo-nitzschia* continues to be positive as the temperature increases from 12°C to 30°C. The research also shows that as the temperature increases, both the relative abundance of *Pseudo-nitzschia* spp and DA production will increase [46]. An applied DA risk assessment model for the US West Coast also reveals “a common relationship” that the greater the ocean temperature is, the more likely DA is to exceed the alert thresholds in the upwelling season, and the more toxic and/or extensive a DA event could become [47]. Besides global warming, an increase in atmospheric partial pressure of CO₂ (pCO₂), a factor that contributes to climate change, can also cause an enhanced growth in *Pseudo-nitzschia*. A meta-analysis in 2019 of *Pseudo-nitzschia* suggested that there is a significant increase in the growth rate of *Pseudo-nitzschia* with elevated pCO₂ (by 32%) [48]. Thus, climate change can lead to bloom in *Pseudo-nitzschia* and thus an increase of DA in seawater.

6.2.2. Toxicological impacts of DA.

DA is an excitatory neurotoxin, similar in structure to the excitatory amino acid's glutamate and kainite. These excitatory amino acids can activate the glutamate receptors which are mainly located in the postsynaptic membrane of neurons in the central nervous system, astrocytes, and oligodendrocytes. By mimicking the structure of those amino acids, DA can also bind to and activate ionotropic glutamate receptors (a type of glutamate receptors that control the flow of ions) *in vivo* and promote the subsequent responses. Therefore, exposure to excessive DA will cause a continuous activation of ionotropic glutamate receptors [49]. The activation of ionotropic glutamate receptors can activate voltage-dependent ion channels, and continuous activation of their receptors by DA will cause an excessive influx of extracellular Na⁺, K⁺, and Ca²⁺, and continuously elevated intracellular osmotic pressure will lead to damage to nerve tissue. Moreover, neurons are very sensitive to calcium ions overload caused by the excessive influx of Ca²⁺ [50]. Although Ca²⁺ acts as a second messenger and plays an important role in the maintenance of cellular function under normal physiological conditions, overload of Ca²⁺ may lead to various detrimental excitotoxicity effects, including the mitochondrial damage and dysfunction, production of reactive oxygen species (ROS), endoplasmic reticulum (ER) stress, cellular inflammation, and damage of cellular structures. These effects exert compounded damage on the cell and one effect may provoke or exacerbate the others, and ultimately lead to cell apoptosis and neurodegeneration in the context of the nervous system [51].

In the DA-induced chronic neurotoxicity model of mice, DA can reduce the expression of Complex I-V in mitochondria, cause the inhibition of electron transport chain function and energy depletion, lead to mitochondrial dysfunction, promote the release of cytochrome c, and eventually induces apoptosis. Besides, DA can significantly increase the level of ROS in hippocampal neurons in mice, causing oxidative stress to brain tissue, and finally causing cognitive damage in mice [52]. After microinjection of DA in the hippocampus of rats, rats exhibited long-term anterograde amnesia for spatial memory in the Morris water maze test [53]. DA can not only induce persistent epilepsy in rats but also promote aggressive behavior in rats [54]. Significant destruction of dopaminergic neurons is shown after long-term treatment of primary mesencephalic cell culture with DA [55]. Besides its toxicity on the nervous system, DA may also exert toxicological effects on other organs since most of the human organs have some level of glutamate receptor expression [56].

6.2.3. Increased production of BMAA.

BMAA is a neurotoxin produced in various types of cyanobacteria. It has been postulated to play a significant role in neurodegenerative diseases. Humans are exposed to BMAA when they inhale the aerosolized BMAA, drink water containing cyanobacterial blooms, or consume seafood living in and around areas containing blooms [57].

Climate change and global warming have been shown to correlate with the growth of cyanobacteria and higher production of BMAA. An experiment examining eight types of cyanobacteria at six different temperatures (20-35°C) shows that all the eight types grew well up to 35°C [58]. A large-scale and long-term study is carried out on the effects of climatic variables on the expansion of cyanobacterial blooms during the past 23 years in Taihu, China. The results showed that increased temperature directly affects cyanobacterial bloom events by advancing its onset time and extending its duration [59]. Moreover, many cyanobacteria can form gas vesicles that enable them to float near the water surface. These surface blooms can maintain a high rate of photosynthesis while shading out underlying, non-buoyant organisms, and thus outcompete other species [60].

6.2.4. Toxicological impacts of BMAA.

BMAA also acts as an excitotoxin in human bodies and has a similar toxicological mechanism to DA. BMAA reacts with CO₂ in the presence of bicarbonate or carbonate to form chemically stable β -carbamate, which has a similar structure to the ligands of glutamate receptors and can activate the glutamate receptors. Therefore, exposure to excessive BMAA would over-activate the glutamate receptors, changing the intracellular ion, especially Ca²⁺, concentration and eventually damaging the cells by excitotoxicity [61]. In addition to the excitotoxic mechanism, BMAA can be misincorporated into human proteins by replacing the serine, which can lead to protein misfolding and aggregation, ER stress, and apoptosis. It has also been found that BMAA can interfere with enzymes that are important for neurotoxin sequestration, neurodegeneration, and the detoxification of β -amyloid-linked cellular toxicity, including melanin, neuromelanin, and catalase [62].

BMAA can cause degeneration of cortical neurons in mice at physiological concentrations of bicarbonate [63]. Different concentrations of BMAA were perfused into the striatum of the mouse brain by microdialysis technology, and it was found that the perfusion volume of BMAA had a dose-response relationship with the amount of extracellular dopamine output, and rapid infusion of high doses of BMAA resulted in significant damage to dopamine terminals [64]. 10 μ L of 100 mM BMAA could induce neuronal damage or even partial neuronal death in the CA1 region of the mouse hippocampus [65]. BMAA in dissociated mixed spinal cord cultures can increase Ca²⁺ concentration in motor neuron cells and selectively promote the production of ROS in motor neurons and result in motor neuron damage at concentrations ($\sim$ 30 μ M) significantly lower than those previously found to induce widespread neuronal degeneration [66]. Rhesus macaques were fed high doses of BMAA (2100 mg·kg⁻¹·day⁻¹, experimental period 2-12 weeks), and it was found that the rhesus monkeys developed motor neuron dysfunction and exhibited Parkinson's disease lesions features include muscle atrophy in the extremities, degeneration or loss of cerebral cortex, and insufficient conduction capacity of the central motor pathway [67]. Using *Drosophila melanogaster* to study the toxic effects

of BMAA, it was found that daily intake of BMAA reduced the neurological function and average lifespan of *Drosophila* [68]. The brain tissue analysis of patients who died of ALS-PDC in Guam found that all samples contained protein-bound BMAA ($149\text{--}1190\ \mu\text{g}\cdot\text{g}^{-1}$), and 83% of the samples contained free BMAA ($3\text{--}10\ \mu\text{g}\cdot\text{g}^{-1}$). No form of BMAA was detected in human brain tissue from other causes of death, indicating that BMAA may be involved in the pathogenic process of amyotrophic lateral sclerosis-parkinsonism (ALS-PDC) [69].

Table 1. Effects of Toxic Substances Stimulated by Climate Change.

Chemical Name	Toxicity	References
Inorganic arsenic	Induces skin, lung, and bladder cancers, as well as human liver, prostate, and kidney cancers	[12]
Arsenite	Interacts with lipoic acid to inhibit pyruvate dehydrogenase (PDH) in the tricarboxylic acid cycle (TCA) cycle to interfere with cellular energy metabolism	[14]
Arsenate	Inhibits oxidative phosphorylation and energy-related NAD^+ reduction during mitochondrial respiration and ATP synthesis	[14]
Dimethyl-arsenic compounds	Promote cancer and tumor	[15]
Manganese	Associated with hyperactivity, weakened cognitive competence, and lower intelligence quotient; associated with increased infant mortality; affects mitochondrial function; causes decreased myocardial contractility and vasodilation; causes acute reduction in blood pressure	[21-23]
Persistent organic pollutants (POPs)	Alters cancer gene expression by affecting miRNAs and target genes associated with a variety of cancers; associated with cardiovascular and endocrine disrupting health problems; acts as endocrine disruptors, mimicking hormones by binding or inhibiting hormone receptors; causes mammary gland dysplasia and Inhibited ovarian maturation; causes enlarged liver cells, which may lead to hepatotoxicity, etc.	[33, 34, 36, 37]
Lipid ozonation products (LOPs)	Activates lipase and stimulates the synthesis and production of many pro-inflammatory lipid mediators, leading to the release of endogenous inflammatory mediators	[41,42]
Ozonation by-products (OBP)	Cardiovascular toxicity, resulting in cardiovascular-related malformations and reduced heart rate	[43]
Domoic acid (DA)	Amnesic shellfish poisoning (ASP), excitotoxicity, oxidative stress, apoptosis, cognitive damage, potential damage other than the nervous system	[44, 51, 52, 56]
β -N-methylamino-L-alanine (BMAA)	Neurodegeneration, excitotoxicity, misincorporation into human proteins, interfering with important enzymes, suppressing cell cycle in non-neuronal cells	[57, 61, 62]

7. Conclusion

Impacts of climate change have always been focused on the environment and the biosphere. This review mainly focuses four different aspects: sea level rise provides reducing conditions for heavy metals; warming temperature leads to regeneration of POPs; atmospheric pollution leads to increased ozone content; changes in marine environment enable algae blooms. Toxicity related to climate change mainly enter the human body by breathing, water drinking and consuming marine organisms, and threaten human health from different aspects such as the respiratory system, nervous system, reproductive system and endocrine system: POPs regenerated from melted glacier and warmed soil,

as well as the volatile organic compounds and reactive oxygen species released from fuel combustion enter the respiratory system; sea level rise allows more chemical elements to be in the anaerobic environment and convert them to more toxic forms, which enter human drinking water; algae with neurotoxins also obtained better growth conditions under higher temperature and higher CO₂-contained conditions, eaten and digested by marine organisms then further consumed by human. Climate change is closely related to human health, and the threat it brings cannot be underestimated. It is expected that the academic communities can make more connections between climate change and its threat to human health, and also call on readers to understand and pay attention to climate change from more aspects, and carry out behaviors such as resource conservation and green travel in daily life in order to respond to environmental advocates.

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