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Selenium's Utility in Mercury Toxicity: A Mini-Review

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Abstract

Purpose: This review of the literature intends to provide readers an understanding of the prophylactic and antidotal usefulness of selenium (Se) for mercury (Hg) toxicity. We will provide an explanation of Hg and Se interactions for potential remediation options to contaminated ecosystems. **Design/methodology/approach:** In this mini-review, we discuss mechanistic aspects between Hg and Se, the implication for health outcomes, and its usefulness in the ecological recovery of Hg contaminated areas. **Findings:** Mercury has a strong affinity for Se, resulting in Se-dependent enzymes and proteins' deactivation with devastating consequences to the host. It is likely that Hg's toxicity results in Se deficiency. Selenium compounds can have prophylactic or antidotal effects to prevent or reverse the adverse toxicity action of Hg exposure. Current research indicates that the chemical interactions between Hg and Se are unique. The Hg capturing capacity of Se is a million times higher than sulfur compounds and results in inactive complexes. **Practical implications:** Future work can target engineering methods for technologies that can reduce the toxicity of Hg in the environment. **Originality/value:** The unique interactions between the elements are that Hg can compromise Se dependent enzymes; however, pharmacologic doses of Se can prevent or modulate the toxic effects of Hg. **Paper type**: Literature review.

Keywords

Mercury, Selenium, Toxicity, Selenoproteins, Human Health, Oxidative Stress

1. Introduction

1.1. Mercury

Environmental mercury (Hg) has the reputation of being a poison, and exposure to this element or derivatives of Hg either by ingestion or inhalation has been

documented to result in adverse health effects. Both natural and anthropogenic sources result in Hg emissions with adverse environmental and human health issues. Human activities have increased Hg concentrations in the Earth's atmosphere by three-fold since the 1800s [1] [2] [3]. Once Hg enters the environment, it can be transformed by microbial organisms to a more bioavailable form, methyl Hg (CH_3Hg) [4], which is more readily absorbed by organisms and bioaccumulates. A buildup of Hg in food, such as; fish, can become health issues for larger animals and humans.

1.2. Selenium

Selenium (Se) at high concentrations can be a poison, too [5] [6] [7]; however, it is essential for life at low levels. In areas where Se is found in the soil, plants can absorb large concentrations, and animals that feed on such plants can result in Se toxicities. Acute Se toxicity caused by ingestion of Se leads to gastrointestinal and neurological disturbances, myocardial infarction, renal failure, acute respiratory, and distress syndrome. Since the 1970's we have known that Se is a cofactor for enzymes, which detoxify hydroperoxides and as a trace element required for the health of animals and humans [8]. There are interactions between mercury and selenium. These interactions are highlighted by the inhibition of mercury's toxic effects via selenium as well as mercury inducing its adverse health effects by disabling and inhibiting selenium dependent enzymes and proteins [8] [9] [10] [11]. It is the purpose of this review to summarize this information regarding Se and Hg interactions, giving particular emphasis on how scientists and regulatory agencies can utilize such information on dealing with ecological and human health exposure to Hg.

2. Health Concerns for Hg and Se

2.1. Mercury Toxicity

Exposure to Hg has been linked to many pathological conditions and is recently associated with various disorders. This is disconcerting since Hg is pervasive in our environment and different consumer products ranging from dental amalgam, seafood, vaccines, and energy-saving light bulbs. Within our exposure to Hg, there are different chemical forms Hg, including elemental Hg (metallic, Hg°), inorganic, and organic Hg [12]. Elemental Hg can be found in thermostats, thermometers, dental amalgams, and has been added to latex paint, and under some situations, enters the atmosphere in a vaporized state [12] [13] [14]. Mercury (Hg°) can penetrate across the blood-brain barrier where it can be oxidized to ionic Hg^{2+} intracellularly [12] [13] [14] and likely retained in the brain cells for years [15] [16] [17]. Inorganic Hg or Hg salts have been found as the formulations of cosmetic products, laxatives, teething powders, antiseptics, and diuretics. Organic Hg is considered as the greatest menacing form and the common form of Hg exposure, e.g., CH_3Hg [4]. Organic Hg has been found in various sources, e.g., fish, poultry, insecticides, fungicides, pesticides, and was

commonly found in thimerosal-containing vaccines.

2.2. Selenium Toxicity

Selenium salts are toxic in massive amounts [5] [6]. Selenium requirements in plants vary by species, with some plants requiring relatively large quantities and others requiring none. Excess Se excretes in the breath as a volatile compound [5]. Selenosis (chronic selenium toxicity) is commonly associated with nail structure changes, loss of nails and hair. Upon further ingestion, lesions of the skin and the nervous system occur [6]. Other symptoms include; nausea, weakness, and diarrhea. Selenium salts are toxic in large amounts, but trace amounts are required for cellular function in many organisms, including all animals. In the case of an excessively high dose, excess excretes in the form of urine. Also, high consumption of Se results in high blood pressure and cancers such as melanoma, oropharyngeal, urinary, and lymphoid cancer [7].

2.3. Selenium Essentiality

Schwarz and Foltz [18] are accredited for the discovery of the essentiality of Se. They showed that dietary Se traces prevented liver necrosis in laboratory rats fed a diet deficient in vitamin E and sulfur amino acid. Subsequently, several investigators demonstrated that Se is a nutritionally essential element for various animal species and resulted in the widespread use of Se supplementation in animal feeds [19] [20]. Selenium was shown to be unconditionally essential for rats and chickens adequate in vitamin E in 1969 [20] and that the type of disease was found to be species dependent. Rats developed liver necrosis, while mice developed multiple necrotic degenerations of skeletal muscle, heart, kidney, liver, and pancreas. Reproductive failure occurs in males of both rodent species. Swine developed a cardiac condition, lambs developed muscular dystrophy, and turkeys developed a gizzard myopathy. Cattle develop a myopathy affecting skeletal and heart muscle. The minimum dietary Se requirements useful in preventing deficiency diseases in species were extraordinarily consistent across species, illustrating that common molecular regulatory mechanisms are shared among species. Most Americans meet the daily requirement for Se in adults (55 μg/day); however, specific populations in Europe, Asia, and parts of Africa have intakes much less than 55 μg/day, and Se deficiency is related to disease conditions. In parts of China, deficient intakes (<25 μg/da) may contribute to a type of juvenile cardiomyopathy (Keshan disease) that is avertible by Se supplementation [21]. In 1973 investigators at the University of Wisconsin illustrated that the enzyme glutathione peroxidase was a selenoprotein [22], confirmed by several groups after that [23] [24] [25] [26].

The amount of Se required to prevent deficiencies ranges from 15 - 70 μg/day. The current recommended dietary daily allowance for Se is about 55 μg/day for healthy adults [27]. Selenomethionine and selenocysteine are the selenium analogs of methionine and cysteine, respectively. Many plants incorporate Se in place of sulfur as selenomethionine [28]. However, in higher animals, seleno-

methionine cannot be synthesized from inorganic Se. In general, enzymes in the plant world or animals will not differentiate between selenomethionine or methionine. Dietary selenomethionine originating from plants and animals fed selenomethionine mixes with the methionine pool and is incorporated into protein needs, unrelated to selenium status [28].

However, selenocysteine can be converted within the animal into selenide, and selenide is the form of Se used to synthesize selenoproteins. Se can enter directly into regulated Se metabolism for incorporation into selenocysteine and selenoproteins in the inorganic Se form. In turn, Selenoproteins are incorporated into enzymes as main component parts of the enzymes, which facilitate lowering of activation energy for reactions in several metabolic pathways, including thyroid hormone metabolism, antioxidant enzyme systems, immune functions [28]. The inorganic forms of Se are more accessible to the body. In contrast, the organic forms need first to be broken down before Se can be utilized for selenoproteins in the body.

Overall there are two body pools illustrated in **Figure 1**: 1) for entry for dietary Se for animals; the unregulated (selenomethionine) dietary forms of Se including the low-molecular-weight and protein forms of Se and 2) the well-regulated selenocysteine inorganic selenium.

The significant difference between these pools is that selenocysteine pools are homeostatically regulated by Se status, and the selenomethionine pool is not. The selenomethionine pool changes and is proportional to selenomethionine's dietary intake because selenomethionine cannot be synthesized from Se in animals [28]. Therefore, the synthesis of proteins that contain methionine will not differentiate between selenomethionine or methionine. To animals, the Se in these selenomethionine proteins is unavailable until the protein turns over. The selenocysteine pool consists of the Se in selenoproteins and low-molecular-weight inorganic forms of Se [28]. Mammalian selenoproteins always contain Se as selenocysteine. This pool responds to the dietary status of Se and results in the synthesis

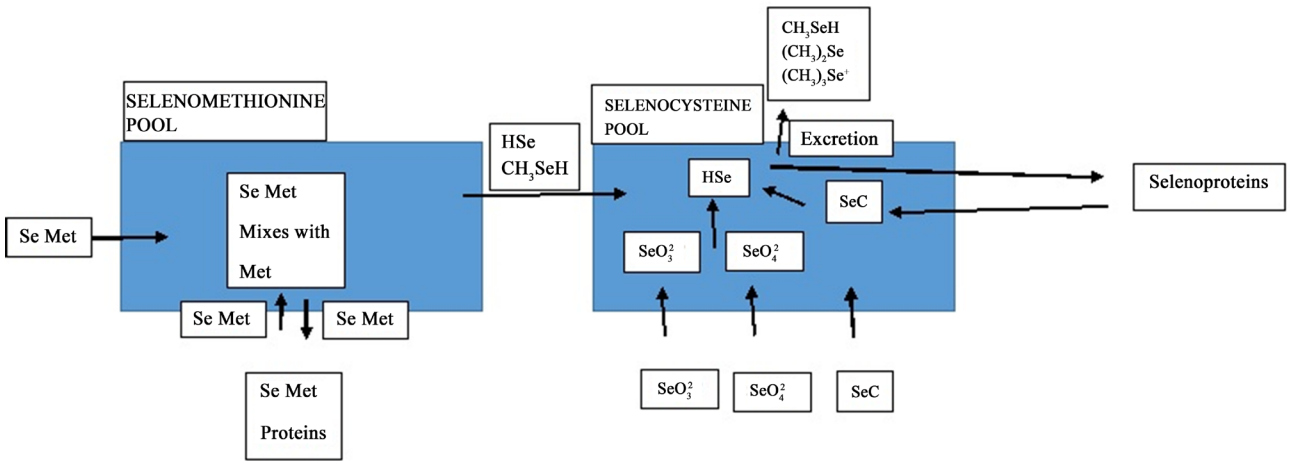

Figure 1. Selenium body pools: Selenomethionine (Se Met) pool; mixes readily with methionine (Met)and Selenocysteine (Sec); selenite (SeO_3^{2-}), selenite (SeO_4^{2-}), hydrogen selenide (HSe), methyl selenide(CH_3SeH), dimethyl selenide (($CH_3)_2Se$, and trimethyl selenide (($CH_3)_3Se^+$).

of selenoprotein. The relationship between the two pools of Se is only in the direction of catabolism of selenomethionine to release selenide by the transsulfuration pathway [29] or methyl selenol through the decarboxylase pathway resulting in low molecular weight species that become part of the selenocysteine pool. The presence of Se metabolites facilitates methylation. The methylation is carried out by enzymes such as methyltransferase. Because of the reaction, dimethyl selenide, monomethyl selenide and trimethyl selenide metabolites materialize in the bloodstream. To perform the methylation, methyltransferase uses the methyl donor S-adenosyl methionine. The continual donation of the methyl group from S-adenosyl methionine consumes the molecule by depriving it of its methyl groups, a primary constituent to its structure. S-adenosyl methionine is considered to be a universal methyl donor. It functions to facilitate the transformation of homocysteine back into methionine. After that, adding more methionine to the pool and changing the concentration of the available S-adenosylmethionine since methionine is a principal constituent of the S-adenosylmethionine molecule.

A novel metabolic pathway is invoked to convert dietary forms of Se into the selenocysteine moiety found in selenoproteins involving the selenocysteine pool. Selenate or selenite must be reduced using glutathione (selenoenzyme thioredoxin reductase may catalyze this reaction). The reduction can occur in intestinal cells, erythrocytes, or other tissues. Synthesis of selenocysteine occurs during protein synthesis and involves several unusual intermediates, and requires at least five gene products. Each selenoprotein mRNA must contain two specific mRNA elements plus a unique selenocysteine s insertion sequence (SECIS) element for Se to incorporate. As illustrated in **Figure 2**, selenocysteine's synthesis starts with selenide and the formation of selenophosphate, which is the activated form of Se used in the synthesis of selenoprotein. The reaction is catalyzed by selenophosphate synthetase using ATP. Intact selenocysteine or selenomethionine is not used for synthesis; instead, the amino acid serine provides the carbon skeleton for selenocysteine.

In all selenocysteine-containing organisms, the synthetic cycle of selenocysteine

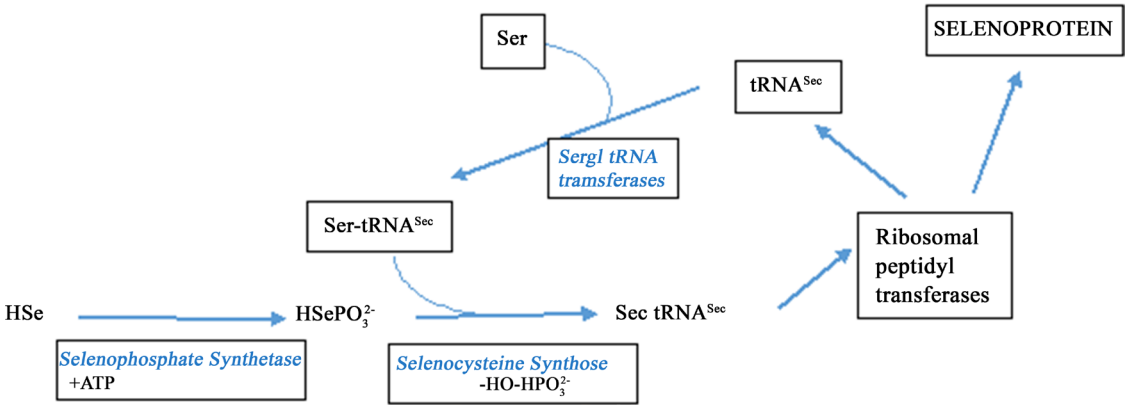

Figure 2. Selenocysteine synthesis. Serine (Ser), hydrogen selenide (HSe), Selenophosphate ($HSePO_3^{2-}$).

begins with an essential "error:" seryl-tRNA synthetase (SerRS) "erroneously" charges selenocysteine tRNA ($tRNA^{Sec}$) with serine, thus yielding seryl-$tRNA^{Sec}$. The mischarged Ser-$tRNA^{Sec}$ is not edited and is released into a solution to serve as an intermediate for the subsequent enzymatic reactions. The ability of SerRS to aminoacrylate two tRNAs with completely different anticodon sequences is unusual. It is even more perplexing that SerRS can act on both $tRNA^{Ser}$ and $tRNA^{Sec}$ with significant efficiency, considering that the two tRNAs adopt completely distinct folds. Selenocysteine synthase replaces the serine –OH with –SeH from selenophosphate for form Sec-$tRNA^{Sec}$. Selenocysteine is degraded by a Se-specific enzyme, selenocysteine lyase, which releases elemental Se. This Se is then reduced to selenide by glutathione or other thiols [28]. As illustrated in **Figure 2**, Sec is synthesized co-translationally from serine (Ser) and selenide (HSe) while esterified to $tRNA^{SEC}_{UCA}$ by the indicated enzymes.

Selenoenzymes are of vital importance in maintaining the balance of oxidation and reduction inside the cells. These enzymes contain very tightly bound forms of Se. They are metalloenzymes since they have trace metal elements in their molecular structures. The human genome encodes for about 25 of the (seleno-enzyme). A partial list of established selenoenzymes can be found tabulated by Combs [28]. They are the secondary after the metalloenzyme superoxide dismutase, which contains the metals copper and zinc. Selenium dependent (Se)-dependent enzymes (selenoenzymes) protect brain tissues against oxidative damage and perform other vital functions, but their synthesis requires a steady supply of Se [29]. The metalloenzymes of Se reduce the number of free radicals inside the cells. Free radical products can damage lipids and proteins inside cells and prevent them from performing their normal functions. Glutathione peroxidase is one of the selenoenzymes that offers the most protection from damaging free radicals. Glutathione peroxidase detoxifies hydroperoxides and works in concert with antioxidants that protect the animal's cells from damage due to the presence of free radicals [22] [23] [24] [25] [26].

2.4. Novel Seleno Amino Acid, Selenocysteine

The bulk of characterized selenoproteins are enzymes, most of which are involved in redox reactions. Their Sec residue is essential for the catalytic activity by taking part in the catalysis. That at least some selenoproteins are of major importance for mammalian life was unequivocally demonstrated by the mouse knockout of the selenocysteine-tRNA gene (necessary for Sec incorporation and thereby selenoprotein synthesis), which show early embryonic lethality [10]. Thus far, 25 human genes encode for selenoproteins, with several of these still having an unknown function. Selenoproteins have been found in all kingdoms of life, but individual organisms, like yeast or higher plants, lack selenoproteins. Remarkably, individual selenoproteins are generally different between different life domains, *i.e.*, bacteria, archaea, and eukaryotes. Separate branches of organisms within these kingdoms of life have developed different selenoproteins [10] [30].

3. Selenium Protective Effects against Mercury Toxicity

Evidence demonstrating the prophylactic and antidotal usefulness of Se in Hg toxicity has been known for over 50 years, way before understanding the chemical mechanism of such interactions. The first recorded incident was when an injection of selenite into rats treated with mercury chloride prevented Hg toxicity [10] [30]. Subsequently, other reports became available, showing the positive tissue relationship between Se and Hg in protecting animals and humans from high Hg areas. An equimolar ratio of the two elements was first reported in livers of marine mammals [30], followed by the observation that Idrija Hg miners had the highest accumulating and retention of both elements. Regardless of the very high Hg concentrations, the morphologic damage was low when both factors were found in an equimolar ratio. Investigators have emphasized that there are two modes of interactions between Se and Hg [3] [11], Se co accumulation through the formation of nontoxic Hg-Se complexes and Se coexcretion Hg. It is essential in understanding Se protection against Hg toxicity to appreciate that critical target sites for Hg are Se-dependent enzymes and proteins [3] [9] [10] [17] [31].

Chemistry between Se and Hg Interactions

Early reports speculated that Hg becomes associated with lipid, particularly the CH_3Hg form; however, in tissues, Hg can be bound to thiols or sulfhydryl with $K_a = 10^{39}$ [9] [11] [32]. Although the interaction between thiol and sulfhydryl compounds and Hg was an attractive Hg toxicity mechanism, it was ironic that such compounds range ~10,000 times greater than the 1 - 25 μM blood Hg level associated with Hg toxicity. However, the interaction between Hg and Se is estimated to be ~1 million-fold higher than for sulfur [9] [11] ($K_a = 10^{45}$). Thiol molecules likely function as vehicles that conduct CH_3Hg onto selenoproteins or Se compounds. Such conclusions are consistent with the recent images generated using the GausView software program depicting a high binding affinity of Hg to Se [33] [34] [35] [36]. The much larger electron cloud of Se in comparison with Hg results in a robust molecular dipole. The action stables the molecule, which potentially contributes to the remarkably high binding affinities between these elements.

Se's ability to interact with Hg likely explains Hg toxicity to initiate Se deficiency and concurrent oxidative stress [33] [34]. In a recent report [35], it was shown that mercury selenide (HgSe) nanoparticles in the liver and brain of long-finned pilot whales are attached to Se-rich structures and possibly act as a nucleation point for the formation of large Se-Hg clusters, which can grow with age to over five μm in size. The detoxification mechanism is fully developed from the early period of the animals, with particulate Hg found in juvenile tissues. As a consequence of CH_3Hg detoxification, Se-methionine, the selenium pool in the system, is depleted to maintain essential levels of Se-cysteine. These results suggest evidence of so far unreported depletion of the bioavailable Se

pool, a plausible driving mechanism of demonstrated neurotoxic effects of CH_3Hg in the organism affected by its high dietary intake. Also, it indicates the possible mode of action Se can play in the remediation of environmental issues involving Hg deposition and ways we might mitigate Hg contamination. The Hg capturing capacity of Se is a million times higher than the sulfur compounds. It is interesting that Se was used as filters and scrubber to capture Hg in metallurgical plants to combat toxic metal pollution [10] [36] [37] [38].

A recent study showed gram-negative bacteria performing the same function within the long-finned pilot whale within the brain and liver. That process was a formation of immobile SeHg compounds. The Se tied up the Hg preventing it from traveling anywhere outside of the cells in the brain and liver tissues. This article revealed that this process is also completed by the gram-negative bacteria *P. fluorescens* [39]. This single-celled organism performs the same function as the multicellular organs of the whale. The intracellular Se rendered the Hg immobile. This process readily occurs in the soil and sediment; however, it remains determined whether it happens in water. Within the water, dissolved Hg and Se levels are low, but this process likely occurs. These non-reactive and non-toxic complexes of Hg and Se provide hope for the use of Se as a remediation agent. The authors suggest a way of reducing the amounts of Hg in an ecosystem [39]. However, there is still much more research to be done since it only takes a small overdose of Se to endanger aquatic organisms. Therefore, carefully coordinated and controlled doses of optimally minimal amounts of Se would be necessary to reduce harm to aquatic ecosystems effectively. This requirement for immense caution represents the need for the development of new nanotechnologies. In the modern time, we have the technology to produce microscopic size particles of Se. This has led to the application of Se in nanoparticle (SeNP) forms. Out of the many applications of SeNPs reported in the literature, the use of varieties of nano-Se sorbents for capturing different forms of Hg was reported [40]. SeNPs capture sorbents are 300 times per unit mass more effective than other commercial sorbents. Such technology can be useful in the remediation and mitigation of Hg deposition in the environment or for new methods or detection or analysis [41] [42].

Current research has identified the possibility of synthesizing Se sulfide [40] that demonstrates the advancement recently made in the field of Se chemistry. Selenium can be delivered in such minute quantities and is a considerable step towards augmenting the legal aspects related to Hg remediation. The authors noted that scientists are discovering ways of synthesis using yeast for manufacturing chemical species [40]. Over the past year, the understanding related to the Se contained within yeast has rapidly advanced. A recent study describes the potential for yeast in Se supplementation in its primordial stages. Se-yeast's most abundant species was found to be SeMet, but there are over 60 types of Se-dependent yeast species reported [40]. The common method of characterizing and comparing Se-yeast was quantifying the total SeMet content, and the

speciation analysis traditionally involves the determination of low-molecular-mass selenospecies [41].

4. Ecosystem Remediation of Hg

The awareness of remediating areas that have become overburdened with Hg with Se is not new [42]. Several studies suggest this could be a realistic means of remediating decades of pollution that resulted from industrialization. Proper remediation will require very carefully coordinated doses of Se that are calibrated to be ecosystem specific, recognizing that there are no antidotes to Se overdose. Mercury became known as a problem starting in the 1970s. Soon after, it was discovered that Hg emitted from fossil fuel combustion could enter into aquatic ecosystems. A study utilized enclosures along with radioisotopes to measure the levels of Hg and Se in the sheltered Bay of Clay Lakee finding that Se and Hg become stored in the sediment [43]. In the following study [44] [45] illustrated how Se is beneficial as an antidote in water bodies that are more heavily contaminated, which explains the importance of the proper dosage being used and provides evidence for the effectiveness of the treatment.

A study in Sweden in 1991 showed that by the addition of Se selenite to eleven lakes, mercury levels were reduced [45] [46]. Adding the selenite in this way is known as the Boliden SRM-method. The fish studied were pike and perch. In their findings, the subgroup representing more heavily Hg contaminated fish shows a marked reduction in all individual perch samples of the different lakes. After one year of treatment, the average Hg concentration was reduced from 0.19 to 0.1 $mg{\cdot}kg^{-1}$, 48% [44]. Coupled with this reduction in the concentration of mercury in perch was an increase in Se's concentration. There was a rise in Se concentration from 0.29 to values between 5.3 and 7.0 $mg{\cdot}kg^{-1}$.

The Se was added to the lakes after the lakes were already treated with lime, where calcium carbonate is added to raise the lake's pH. The liming process with calcium carbonate reduces the Hg content of the perch, and it was shown to lower Hg levels by 30%. Selenium can minimize Hg concentrations by 60% - 85%. The Se gets added to the water by placing it into a skeleton that holds the mineral block. In the lakes in which there was poor circulation, the selenite under the ice during the winter caused a gradient to form around where the blocks are placed. The farther away from the blocks, the measuring is done, the lower the levels of Se. Such intervention is an effective way to add Se because it prevents Se's levels from becoming too high within the lake's food chain. Selenium was able to reduce the levels of Hg without the liming taking place beforehand. The findings show that the amount of Se and the addition's timing needs to be specific to the conditions of the lake that is being treated. The study indicates that Se is beneficial in treating levels with markedly higher levels of mercury contamination. While, in some circumstances, liming is an acceptable remediation method in the more severely contaminated lake, Se is required to cause a major change in the Hg concentrations [44]. There need to be studies done on

other fish, and it can't be assumed that other species will react in the same way. Se compounds' capability to decrease the toxicity of Hg has been established in many species of mammals, birds, and fish investigated [45] [46]. Although there are skeptics [47] [48], proponents understand Se's potential to mitigate Hg contamination [10] [17] [38] [42] [44]. Knowledge of selenium's influence on mercury's effect in aquatic ecosystems and Hg exposure, bioaccumulation, and toxicity is considerable and directly requires increased attention.

5. Future Research and Conclusion

To perform accurate environmental and epidemiological Hg exposure risk assessments, we recommend that future studies will need to simultaneously assess the amounts and forms of Se that are also present. With further research, a full understanding of selenium's health and disease's role may become a reality. It could be the foundation for the treatment of Hg and perhaps other heavy metal intoxications and the remediation and mitigation of environmental issues. As noted, Hg is a global issue and technological methods to mitigate Hg are long overdue. Although beyond the scope of this review, many health disorders are potentially rooted in the alteration of Se status [28], which may be rooted in heavy metals' ability to inactivate Se dependent proteins. Finding ways to address such disorders through potential pharmaceutical or pharmacologic Se analog may be beneficial. Additional knowledge of Hg and Se's molecular interactions can lead to effective engineering technology for the environmental remediation of Hg and other heavy metal contaminations [49] [50].

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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