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REVISION OF RECIPROCAL ACTION OF MERCURY AND SELENIUM

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Abstract
Diverse forms of mercury (Hg) have various effects on animals and humans because of a variety of routes of administration. Inorganic mercury (iHg) binds to thiol groups of proteins and enzymes in one's body or is methylated by microorganisms. Organic form of Hg, contrary to the iHg, is more stable but may be demethylated to Hg^{2+} in the tissue of intestinal flora. Selenium (Se) also occurs in a variety of chemical forms in one's body but both of these elements behave very differently from one another. Mercury binding to selenide or Se-containing ligands is a primary molecular mechanism that reduces toxicity of Hg. Complexes formed in such a way are irreversible, and thus, biologically inactive. Se deficiency in a human body may impair normal synthesis of selenoproteins and its expression because expression of mRNA may be potentially regulated by the Se status. This paper provides a comprehensive review concerning Hg–Se reciprocal action as a potential mechanism of protective action of Se against Hg toxicity as well as a potential detoxification mechanism. Although interactions between Hg–Se have been presented in numerous studies concerning animals and humans, we have focused mainly on animal models so as to understand molecular mechanisms responsible for antagonism better. The review also investigates what conclusions have been drawn by researchers with respect to the chemical species of Se and Hg (and their relationship) in biological systems as well as genetic variations and expression and/or activity of selenoproteins related to the thioredoxin (thioredoxin Trx/TrxR) system and glutathione metabolism. Int J Occup Med Environ Health 2018;31(5)

Key words:
Gene expression, Polymorphism, Mercury, Selenium, Antagonism, Interaction

INTRODUCTION

Since effects of the mercury–selenium (Hg–Se) interaction seem to be complex, more and more scientists are interested in the issue of potential Hg detoxification mechanism in the presence of Se. The undertaken issue will allow to disseminate knowledge concerning the influence of Se levels, its speciation forms and expression of selenoproteins on avoidance of adverse effects of Hg. However, in order to explain the mechanisms of interaction of Hg–Se in animals and humans, one should become thoroughly familiar with toxicokinetics of Hg which is diverse for the variety of its chemical forms.

There are differences in the kinetics and metabolism depending on Hg compounds, which exert impact on the animal as well as human body and interactions between various factors that cause biochemical changes in many metabolic reactions leading to respiratory [1], nervous system [2–4] and immune system disorders [5]. Its toxicity is also manifested in damaged kidneys [6,7] and heart diseases [8,9]. Exposure to Hg reveals significant metabolic al-

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terations associated with the damage to the cell membrane and thus, decreasing or even blocking the biochemical function of proteins and other molecules of major biological significance (e.g., the glutathione system (GSH), glutathione peroxidase (GPx), thioredoxin reductase (TrxR)). Metallic mercury (Hg^0) is usually rapidly oxidized in the red blood cells by catalase (CAT) enzyme and hydrogen peroxide to bivalent ionic (Hg^{2+} mercuric) and partly penetrates other tissues. The resulting Hg^{2+} is biologically active and has a very high affinity with sulfhydryl (thiol; -SH) groups of e.g., cysteine (Cys), homocysteine (Hcys) and N-acetylcysteine (NAC) proteins.

Mercury and the sulfur (S) present in thiol groups form stable complexes, which leads to toxic effect of Hg at the molecular level. Since S and Se present in the same group of Mendeleev's periodic table, they are characterized by similar chemical properties. Selenium forms complexes with Hg and these complexes have been confirmed in numerous studies [10–13]. Irreversible and nonspecific binding to the protein causes vast changes in the protein conformation leading to its inhibition or denaturation. Since mercuric ion has weak ability to penetrate blood–brain barrier (BBB) back, it accumulates in brain and thus, impairs metabolism of the nervous system and gets from placenta to the fetus. It is associated with oxidation of Hg^0 in the brain to Hg^{2+}, where it accumulates. Chronic occupational exposure to Hg^0 influences permeability of lysosomal membranes, which leads to urinary excretion of low molecular weight proteins (e.g., β_2-microglobulin (β_2-M), retinol binding protein (RBP) and lysosomal enzymes, such as: β-galactosidase (β-GAL), N-acetyl-β-D-glucosaminidase (NAG), and its isoenzyme (NAG-B), β-glucuronidase (β-Gr) [14,15].

Bernard et al. [16] have shown that RBP, next to NAG, is one of the most sensitive markers of renal damage. Renal tubules damage is caused mainly by the interaction of Hg^{2+} with enzymes responsible for protection of a cell against redox balance disorders. In kidneys, mainly Hg^{2+} has affinity with metallothioneins (MTs), thus exposure to Hg^0 affects induction of synthesis of MTs in kidneys. Metallothioneins as specific proteins, rich in cysteine with high affinity to metals, play a protective role against neurotoxic effect of Hg^0 as well as against nephrotoxic effect of Hg^{2+}, enabling its transportation and excretion. Metallic mercury effortlessly passes through the placental membrane and BBB. Organomercury (e.g., methylmercury (MeHg)) compounds are lipophilic, they also pass blood-brain, as well as placental barriers easily, which results in impairment of the nervous system metabolism. Because of MeHg, which is a highly specific and irreversible inhibitor of Se-dependent enzymes, animals as well as humans require selenoenzymes to protect their organisms against oxidative damage [17].

Occupational as well as environmental exposure to Hg is the factor which induces upsetting the balance between creation of reactive oxygen species (ROS) and biological capacity of their detoxification. The redox imbalance may lead to enormous implications in antioxidant activity (stimulates formation of free radicals and ROS) and energy metabolism. Studies carried out so far have indicated the role of Hg in the induction of oxidative system [18–21]. Chronic toxic effect of Hg induces excessive generation of free radicals, which when reacting with components of the cell affect the redox potential. Reactive oxygen species impair structure of biological membranes of cells, among others, by lipid peroxidation, protein oxidation or DNA damage through modification of nitrogenous bases, or they induce cell apoptosis, the result of which is acceleration of neurodegenerative diseases, cardiovascular diseases and cancers.

Cebulska-Wasilewska et al. [22] claim that occupational exposure to Hg does not cause direct genotoxicity but causes significant deficiency in DNA repair. There is also data that indicates that 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) appearing in urine suggests oxida-

tive DNA damage. The specific system of this damage repair involves a removal of oxidatively modified nucleoside (guanosine) and its excretion from the body [23,24]. The analysis of concentrations of 8-oxodG in urine may provide information about cell defense mechanism in response to Hg-induced oxidative stress and free radicals. Li et al. [5] indicated that in the case of local people with long-term Hg exposure living in mining areas of Wanshan (China), after supplementation with Se (100 μg of organic Se daily in Se-enriched yeast), an increase in urinary Hg excretion and a decrease in oxidative stress-related biomarkers including 8-hydroxy-2-deoxyguanosine (8-OHdG) were observed.

Popular interest in Se as a primary antioxidant, immunological factor and simultaneously a metalloid inactivating toxic effects of Hg is large. It is mainly involved in metabolic pathways associated with regulation of the redox potential [25–27] but it may be toxic depending on its concentration and chemical forms [12]. Inorganic form of Se (iSe) occurs as salts and easily passes the placental barrier and BBB. Since selenite (Se^{4+}) has a higher affinity with tissue than selenate (Se^{6+}), it may form complexes with proteins. Inorganic form of Se compounds are converted into organic selenocomplexes and these complexes, especially in the second oxidation state, constitute the most available form of Se for humans. The major biological form of Se is selenocysteine, the 21st proteinogenic amino acid, which is related to its presence in the active center of selenoenzymes (especially GPx as the main enzymatic system which participates in the defense against free radicals Hg-induced and TrxR, which coordinates Hg-induced redox reactions maintaining the proper cellular function) and Se-dependent proteins like selenoprotein P (SeP), the best known selenoprotein in plasma, which protects organism against Hg toxicity. Its selenol groups (-SeH) present in the multiple selenocysteine residues form complexes with Hg, and thus contribute to its detoxification [28,29].

METHODS

Literature referred to in this review was identified via search of electronic databases, such as: PubMed, Scopus, Science Direct and Google Scholar and textbooks in the field of toxicology. The following search key words (or combinations of them) were applied: Hg, MeHg, Se, speciation, Hg–Se interaction, Hg–Se antagonism. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were used [30].

During literature search, 1888 citations were detected and 102 of them were selected for the review. All articles were defined according to the following categories of inclusion (data from published studies, literature published 1967–2017, the English language, animal studies, general human population, Se:Hg molar ratios in organisms, Hg and Se levels in biological samples, the impact of diverse chemical forms of Se on biological/health effects of various chemical forms of Hg) and exclusion criteria (the non-English language, data from unpublished studies, methodological issues, special population groups, i.e., infants, children, pregnant women, case-control studies, clinical outcomes, others interaction e.g., synergism). In the end, we chose the one, which included reciprocal action between the 2 elements, and the related effects on the organism, organs and the tissues.

RESULTS

Possible mechanisms of Hg–Se interaction

Majority of the studies available in the literature and concerning the mechanisms of the Hg–Se interaction as well as the potential detoxification processes use animal models. In addition, antagonistic influence of Se on bioaccumulation of Hg in experimental animals is well known, however, interaction mechanism between these elements in a human body has still remained unexplained [31,32]. Considering interspecies differences in the toxicity of Hg, it is very difficult to unambiguously explain this interaction in a human body. Currently, Hg–Se interaction and its bio-

logical responses in organisms related to their antagonistic reciprocal action still raises a large interest [13,33–35]. In science, it is crucial to understand protective mechanisms against Hg toxicity. There are several known possible pathways of Hg–Se interaction.

Formation of Hg–Se as well as MeHg–Se compounds

The above mentioned toxic effect of Hg at the molecular level is primarily diminished due to the formation of biologically inactive complexes with proteins containing Se, mainly with SeP [13,28]. There is evidence that plasma Se forms complexes with inorganic mercury (iHg), which then combine with SeP [11,13], which in turn prevents accumulation of Hg in the kidney [36]. Moreover, a bis-selenite-methylmercuric, selenocysteinemethylmercury complexes, a cluster of [(Hg–Se)*n*]*m*–SeP and onofrite ($HgSe_xS_{1-}x; 0 < x \leq 1$) biomineral, are responsible for the antagonism Hg–Se in biological systems at the molecular level [12]. Onofrite compound in a form of nanoclusters is created via glutathione. It is dependent on the pH and reversibly soluble, thanks to which it plays the largest part in distribution of Hg.

Selenium-aided demethylation of MeHg

This type of a possible pathway of the reciprocal action has been observed mainly in the liver and kidney in marine mammals and seabirds [37,38], where the highest concentration of iHg could be observed. Accumulation of iHg in these organs after exposure to MeHg may suggest a demethylation process. Additionally, it seems that, the demethylation takes place after a critical threshold value of MeHg has been reached. Palmisano et al. [39] calculated that threshold concentration of MeHg in the liver of a dolphin amounted to about 100 μg/g wet weight. Martoja and Berry [38] in their study identified a tiemannite (mineral in a form of mercuric selenide) in the liver of cetaceans as a probable product of demethylation. This stable and inert complex explains the protective effect of Se on Hg.

The latest studies have been performed with regard to the pathway of interaction between Hg–Se based on the influence of selenoneine (SeN, Se-containing compound) intake (mainly from fish) on MeHg accumulation and resulting toxicity. Nevertheless, this mechanism still remains unclear. Selenoneine has a strong antioxidant potential in the redox cycle due to its unique structure of Se atom in the imidazole ring (similar structure to ergothioneine). Yamashita et al. [40,41] showed that, SeN discovered in tuna may remove free radicals which are initiated by MeHg. The potential detofixication mechanism consists in forming a complex between SeN with MeHg, which then may be incorporated into endosomes and lysosomes. This molecular mechanism is mediated by a selenoneine-specific transporter, organic cations/carnitine transporter-1 (OCTN1). The latest study describes the demethylation process of Hg in marine fish (black seabream) after Se treatment. Wang et al. [42] showed in their study that not liver but the intestine was the major site for Hg–Se interaction. Authors claimed that Se affected elimination of the generated iHg, but not the distribution of MeHg.

Redistribution of Hg (in the presence of Se)

Redistribution of Hg among various organs, which often takes place from more sensitive to the less critical ones. Transport of Hg to specific organs and its redistribution depend on binding of Hg to low molecular weight thiols (sulfur-containing biomolecules: MTs, GSH and albumin), that are diffusible and thus, that easily pass through cell membranes. Some studies concern the transport mechanism of Hg in the body based on the molecular mimicry. Bridges and Zalups [43] define the mechanism of molecular and/or ionic mimicry as the formation of complexes (mainly organo-metal) similar to endogenous biomolecules. Similarity may be structural and/or functional. This way low molecular weight thiols bound to Hg ions may pass and entry into each cell via the mechanism of molecular mimicry [44,45]. Three known conju-

gates are similar to each other in terms of their chemical structure: the amino acid cystine and the Cys S-conjugate of iHg (Cys-S-Hg-S-Cys), the amino acid methionine and the cysteine S-conjugate of MeHg (CH_3Hg-S-Cys) and the homocystine and homocysteine S-conjugate of iHg (Hcys-S-Hg-S-Hcys) [43,45,46].

A hypothesis assumes that, Se causes the release of bound iHg to low molecular weight thiols and their diversion to high molecular weight proteins in organs [10,36,47]. Yamamoto [36] showed that, in the presence of Se, Hg bound into a high molecular weight complex with selenoprotein P, which seemed to prevent Hg uptake by the kidneys and therefore, Hg content in the kidneys of mice was low. García-Sevillano et al. [48] observed a protective effect of Se on Hg toxicity in blood plasma of mice. The effect results in a decrease of intensity of Se-protein in plasma with Hg exposure and correlative increases of Hg-albumin that transports Hg to kidney for excretion. Chen et al. [10] have found that, uptake and binding of Hg to MT in blood of rats, is then affected by Se which alters Hg distribution to high molecular weight proteins in the liver, testis and kidneys. However, Se-pretreated rats had an elevated Hg concentration in their blood and testis but significantly diminished Hg level in the kidneys. It shows a possible path of detoxification of Hg in the presence of Se.

Selenium prevention of oxidative stress and of free radicals induced by Hg

Prevention by means of increasing the Se-dependent enzymes such as: GPx [49] and TrxR [50]. The studies have indicated that Hg and its compounds may inhibit GPx activity [25,51–53]. Starting from animal models, a number of studies indicate that Se antagonizes Hg-induced toxicity related to the oxidative stress markers and activity of selenoproteins depending on the Se status. Su et al. [35] describe that mercury chloride ($HgCl_2$) significantly decreases ($p < 0.05$) the activity of GSH and superoxide dismutase (SOD) and at the same time increases level of the malondialdehyde (MDA) in the liver of rats, the product of lipid peroxidation. After equimolar co-administration of Se and Hg, the MDA level was significantly decreased and SOD activity was increased ($p < 0.05$). After Hg administration the content of SOD in kidney significantly decreased ($p < 0.05$), in contrast to GSH and MDA.

In another study, Grotto et al. [54] showed the possible antigenotoxic effect of Se in rats. After chronic exposure to low levels of MeHg, it revealed GPx activity and DNA lesions in rats. Moreover, a significant and negative correlation was found ($r = –0.559$, $p < 0.05$) between GPx activity and DNA damage. Additionally, the authors claimed that Se in concentrations of 2 and 6 mg/l from drinking water reduced DNA injuries caused by MeHg exposure, by about 35% and 40%, respectively. Methylmercury is toxic and induces pathological changes in the nervous system. A group of researchers of Mori et al. [55] showed a decreased GSH level and GPx activity due to oral administration of an organic form of Hg, contrary to the SOD activity in mitochondria isolated from cerebellum and cerebrum of rats.

According to the research by Zemolin et al. [56] after MeHg administration, the activity of the antioxidant enzymes glutathione S-transferase (GST), CAT, SOD and glutathione reductase (GR) was increased in the cerebellum of mice. The electron microscopy analysis delivered useful information of mitochondrial ultrastructure in cerebral cortex. Micrographs showed excessive alterations (curved-shaped, elongated or an increase in their volume) and reduction in their number (up to 60% of reduction) after MeHg-treated mice as compared to controls as well as organoselenium compound (diphenyl diselenide $(PhSe)_2$) co-administration [57,58]. De Freitas et al. [25] confirmed a decrease in MeHg-induced cerebral oxidative stress by $(PhSe)_2$. Diphenyl diselenide in dose 1 mg/kg/day and 0.4 mg/kg/day decreased MeHg toxicity via its reduction to selenol/selenolate ($PhSeH/PhSe^-$). Then this form

of PhSeH/$PhSe^-$ could either directly block the pro-oxidative effects of MeHg due to its thiol-peroxidase activity or form a stable complex with MeHg that was more easily excreted, simultaneously decreasing Hg body burden. What is interesting, iSe compound sodium selenite (Na_2SeO_3) did not protect from MeHg-induced oxidative stress [3].

Hg–Se interactions in animals

Toxicokinetics of Hg has been well described in octopus [59], fish [60,61], birds [62], mice [3,5,36,48,63,64], rats [6,35,44,47,54,65,66], rabbits [7,49], poultry [67], dolphins [68] and so forth. Over 50 years ago, numerous investigations attempted to describe Hg–Se interaction in animals. Parizek and Ostadalova [69] and Parizek et al. [70] described studies that found inhibitive effects of Se on the toxicity of Hg in rats. A series of experiments showed different percentage of surviving rats after injection of salt of iHg in a dose of 0.02 mmole $HgCl_2$/kg body weight and after injection of the salt of iHg in the same dose and injection of Na_2SeO_3 in a dose of 0.03 mmole/kg body weight 1 h later. The percentages of surviving rats were: 100% (iHg) and 97.5% (Hg–Se) on the second day, and 3.3% (iHg) and 97.5% (Hg–Se) on the seventh day. Subsequent experiments in rats [65,71] claimed that Se prevented Hg-induced intestinal necrosis. As a consequence, Se decreased mortality.

Many researchers investigated the Hg–Se interaction to be the most effective when these elements (mainly in the form of Na_2SeO_3 and $HgCl_2$) were co-administrated in equimolar ratio [47,65,69]. Authors have claimed that, only a correct chemical form of Hg and Se and their concentrations may determine whether a potential protective effect appears. Considering Hg–Se interaction, Hg is not harmful to human health if the molar ratio of Se:Hg meets the defined criteria. Selenium will exert its protective action against Hg toxicity when the molar ratio approaches or exceeds 1. When Se:Hg molar ratio is below 1 more toxic effect is visible. What is more, the co-exposure of Se and Hg antagonistically diminishes each other's toxic effects (being in agreement with outcomes of Peterson et al. [72], Li et al. [5]). This statement may show that toxic effects of Hg are mitigated by Se but only when Se:Hg molar ratios is ≥ 1.

Liao et al. [60] showed opposing results in medaka fish, who claimed that after co-administration of MeHg:Se in molar ratio about 1, the interaction between MeHg:Se gave a limited protection against toxicity of both elements. According to Burger et al. [73] the Se:Hg molar ratio in saltwater fish decreased along with the size of the fish species, decreased with the Hg levels, and within a fish species. Comparing the interspecific and intraspecific variation in Se:Hg molar ratios, the authors claimed that in the interspecific variation the mean Se:Hg ratio was negatively correlated with the mean Hg levels (the mean total fish length was not found significantly correlated). The intraspecific differences showed that fish occurring in the North Pacific (dolly varden) had the ratio that was positively correlated with its length and weight and the halibut had the ratio that was negatively correlated with its length and positively correlated with its weight. Selenium does not show protective effects against Hg toxicity, when the increased fish size is tantamount to a decreased molar ratio. The Hg:Se molar ratio in nearly all marine fish was less than 1, in marine mammals it was 16:1 [74].

Beijer and Jernelöv [74] showed that increased Hg retention caused by Se occurred in the marine environment. It may cause the incremental increase in concentration of Hg and/or Se at each level of a food chain, namely biomagnifications and thus, the higher burden in organism. This might counteract the positive effect of a decreased intoxication. Branco et al. [75] claimed that co-administration of Se and Hg and thus mutual Hg–Se interaction in exposed fish may protect organism (juvenile zebra-seabream) against Hg-induced toxicity but this protection is tissue-specific and it depends on the examined form

of Hg and the target organ. Moreover, an accumulation of Hg was considerably lower when exposure to MeHg and exposure to Se were simultaneous.

Fang [76] showed different efficiency of Se compounds in Hg toxicity in rats. Iwata et al. [77] noticed the redistribution of Hg in the presence of Se, only when administering Se^{4+} and MeHg to rats was concurrent. Iwata and co-authors showed that Se^{4+} decreased the amount of MeHg in organs such as: liver, kidneys, brain, heart, and in blood after a week of exposure, in comparison with the high initial concentration of MeHg. Observations of other authors [10,49] of the above studies led to the conclusion that there was a reduction of Hg concentration in kidneys and liver and increase of it in other tissues e.g., muscles. Jureša et al. [78] found that accumulation of Hg decreased in kidneys and increased in liver after concurrent administration of $HgCl_2$ and Na_2SeO_3. Diminished level of excretion of Hg in urine (Hg-U) is due to the presence of Se^{4+}. Lailson-Brito et al. [27] showed a high and positive correlation ($p < 0.05$) between hepatic molar concentrations of Hg and Se, which was confirmed by the Se-mediated MeHg detoxification process in dolphins.

Bjerregaard et al. [79,80] showed that Se adjusted the biokinetics of Hg through increasing Hg retention in some aquatic mammals but decreasing MeHg retention in fish. The authors claimed that Se which occurred naturally in marine food chains (the lower trophic level) could play a key role as a main modifier of MeHg accumulation at these levels, thereby also potentially affects biomagnification of MeHg toward the higher trophic levels in the aquatic food chains. Naganuma and Imura [49,81] have explored Hg–Se *in vitro* interaction in rabbits. Their studies have shown that the elements may form a bis(methylmercuric)selenide complex in rabbit blood as a product of MeHg and Se^{4+}. In plasma and erythrocytes most Hg^{2+} and Se^{4+} were found in high-molecular weight substance(s), their molar ratio was 1:1 and they hardly passed erythrocytes membrane. The Hg and Se incorporated to these substances were found in stroma-free hemolysate but not in plasma.

By creating biologically inactive complexes (Hg–Se complex) it increases the co-excretion [34]. We can describe 2 potential biological effects of Hg and Se exposure:

1. In the case of a specific concentration of Hg and increasing concentration of Se, first Hg toxicity is reduced and then Se deficiency is alleviated and that eventually leads to Se toxicity.
2. In the case of a specific concentration of Se and increasing concentration of Hg, first toxicity of Se decreases, then Se deficiency occurs until Hg toxicity finally takes place [12].

Moreover, the authors notice that optimal conditions for marine mammals (Se:Hg molar ratio of 1:1) occur in the Se deficiency regions, as Se is bound to Hg and thus, is not bioavailable. Organic forms of Se, like selenomethionine (SeMet) and selenocysteine (SeCys) were more effective than inorganic forms (Se^{4+} and Se^{6+}), which is inverse of the Sharma and Davis [82] results in goldfish. Similar results to those of Sharma were confirmed by Magos et al. [6] and 30 years later by Bjerregaard et al. [79]. Magos revealed that Se^{4+} diminished renotoxicity of iHg. Moreover, the authors claimed that biological Se had different effect from Se^{4+}. Formation of Hg–Se complexes decreased in the following order: Se^{4+} > SeMet > biological Se. Fang [76] stated that after co-administration in equimolar ratio the efficiency of Se on Hg elimination in kidney decreased in the following order: SeMet (the most effective) > SeCys > Se^{6+} > Se^{4+} (the least effective). In the study of Bjerregaard et al. [79] pre-administration of dietary Se^{4+}, SeMet and SeCys to freshwater fish (goldfish and zebrafish) increased elimination of MeHg, in contrast to iHg. Moreover, higher Se concentration diminished retention of MeHg in a dose dependent manner. In conclusion, Bjerregaard has claimed that Se concentration in aquatic food chain may affect Hg contamination along the food chain. Selenite as well as organic selenium forms (SeCys and SeMet) increase elimination of Hg from shrimps.

Selenate does not induce a more readily elimination [80]. Above interactions are related to Se and Hg concentration and their forms, which is summarized in the Table 1.

Hg–Se interactions in humans

The holistic overview of Hg–Se relationships, where Se plays direct and/or indirect (through mainly selenoproteins) role is a well-known topic among many scientists. Data on the occurrence of correlation between metabolism of Hg and expression of selenoproteins in the occupationally (elemental Hg vapor) and environmentally (organic form of Hg) exposed people is still limited [33,89–91]. Studies on humans concerning dysfunction of cellular redox system, disruption of the glutathione system and system-related enzymes glutathione-S-transferase (GST), TrxR and glutamate cysteine ligase (GCL) by exposure to Hg are inadequate.

Kobal et al. [89] investigated the relationship between occupational exposure to Hg^0 and GSH system: erythrocyte GSH level, enzymatic activity of GPx and activities of CAT and GR. Although there were no statistically significant differences between the mean GPx activity, levels of total GSH, oxidized disulphide glutathione (GSSG) and GSH/GSSG ratio between the studied miners and the control group. The mean concentration of reduced GSH was significantly higher in the miners (13.64±3.71 mmol/g Hb) in comparison with the retired miners (9.64±1.45 mmol/g Hb) as well as with the control group (11.68±2.66 mmol/g Hb), ($p < 0.05$). Moreover, the retired miners had the lowest ($p < 0.05$) level of the mean total GSH. The mean GR and CAT activity in erythrocytes in the miners was significantly higher ($p < 0.05$) than in the retired miners and in the control group. In the end, Kobal showed a positive correlation between GSSG and present Hg-U excretion ($r = 0.41$, $p = 0.001$) in the retired miners.

The relationships between Hg^0 exposure and activities of SOD and GPx in erythrocytes of the workers from a chloroalkali plant were examined by Bulat et al. [92]. Mercury-exposed individuals had significantly lower activities of GPx and SOD when compared to the control group (GPx: 9.05±7.52 IU/g Hb, $p < 0.001$, SOD: 1280.7±132.3 IU/g Hb, $p < 0.006$ and GPx: 15.54±4.85 IU/g Hb, $p < 0.001$ and SOD: 1377.9± 207.5 IU/g Hb, $p < 0.006$). Similar results occurred in the study by Samir and Aref [93], where dental personnel had GPx and SOD activity in blood significantly decreased ($p < 0.001$) in comparison with the control group. Additionally, these authors showed an inverse significant association between Hg-U and both GPx and SOD activity in blood ($r = –0.668$, $p < 0.001$ and $r = –0.670$, $p < 0.001$, respectively). What is more, dental staff had significantly higher ($p < 0.001$) concentrations of albumin and α1 microglobulin in urine (the biomarkers of early renal effects), which means that occupational exposure to Hg^0 diminished activity of antioxidant enzymes and that their effect may influence a possible mechanism of renal disorders.

The study of Chen et al. [33] is another confirmation that Se is reversing of oxidative stress including Hg-induced inhibition of the enzymes of GSH metabolism. The occupationally Hg^0-exposed people who worked in mining, in Guizhou (China), contrary to the control group, had a statistically significantly increased ($p < 0.05$) concentration of MDA and SeP in serum as well as activity of GPx in serum. Along with the increase, the authors observed an increase of Se concentration in serum (Se-S) and a decreased production of ROS. A strong positive correlation between concentrations of Se in urine (Se-U) and Hg-U ($R = 0.625$, $p < 0.001$) but not between Se-S and Hg in serum (Hg-S) as well as a higher concentration of Se-S were also investigated in the study by Chen et al. [33] in the case of workers compared to the control group.

Additionally, a significantly higher ($p < 0.05$) concentration of Hg in SeP in serum occurred among the Hg^0-exposed subjects compared to the control group, where the SeP-containing fraction bound more Hg. The molar

Table 1. Impact of diverse chemical forms of selenium on biological and health effects of diverse chemical forms of mercury

Chemical form of selenium	Mercuric chloride ($HgCl_2$)	Methylmercury (MeHg)
Sodium selenite (Se (IV)) Na_2SeO_3	Se^{4+} protects kidney from Hg toxicity; Se^{4+} greatly diminishes mortality of rats treated with Hg [69] after co-administration the content of Hg in kidney decreases as compared to the concentration in the liver (rats) [76] pretreatment with Se^{4+} causes decreased Hg in the kidney (rats) [10] Hg and Se^{4+} incorporated to high-molecular weight substances in stroma-free hemolysate but not in plasma (rabbits) [49] Se^{4+} inhibits Hg-induced decrease in the activities of the enzymes of the GSH metabolism pathway in the kidney (rats) [83] at molar ratio 1:1 most Hg and Se^{4+} delivered into plasma and erythrocytes were next found in high-molecular weight substance(s) (rabbit) [81] after co-administration of Se^{4+} and Hg, Hg contents in liver were higher than in those after administration of Hg alone; Hg contents in kidney decreased distinctly over a 1–120 h period, and it was Se^{4+} dose-dependent (mice) [36] Se^{4+} protects against Hg-induced nephrotoxicity; Se^{4+} decreases renal desorption of Hg (rats) [6] protective effects of Se^{4+} against Hg toxicity in renal dolphin cell; moreover, co-administration of elements was essential for the protective effects of Se^{4+} against the Hg toxicity (dolphin renal cells, Sp1K cells) [68] equimolar ratio Se:Hg causes retention in kidney (rats) [84]	Se^{4+} reduced dietary MeHg toxicity (tuna) [71] after co-administration the content of Hg in brain, heart, liver, kidneys and in blood was decreased after a week of exposure (rats) [77] after co- and post-administration Se^{4+} increased Hg in brain, in contrast to the blood (rats) [85] MeHg forms a bis(methylmercury) selenide complex in blood (rabbits) [86] after co-administration Se^{4+} and Hg have been shown to diminish enzyme activities in kidney and liver (mice) [87] the ratio of GPx activity to the concentration of Se^{4+} was decreased in MeHg-treated groups, regardless of the dietary level of Se^{4+} (mice) [64] co-administration of Se^{4+} and vitamin E during treatment with MeHg significantly increased the number of post-natal survivors (rats) [65] after co-administration, Se^{4+} and methylmercury chloride (MMC) in equimolar ratio protected from Hg in the liver, in contrast in gill (medaka) [60] co-administration of Se^{4+} reduced Hg in brain (mice) [3] pre-administration of Se^{4+} to the food increased elimination of MeHg but not of the iHg, independently of any specific organ (goldfish and zebrafish) [44] co-administration of Se^{4+} decreased by a half the accumulation of MeHg but not of the iHg (juvenile zebra-seabream) [74]
Sodium selenate (Se (VI)) Na_2SeO_4		MeHg inhibited selenoenzymes activities; the high molar ratio was associated with toxicity (rats) [88] co-administration of Se^{6+} diminished DNA damage induced by MeHg (rats) [54] Se^{6+} may counteract MeHg neurotoxicity (mice) [3] Se^{6+}, in contrast to Se^{4+} and organic Se, does not eliminate organic forms of Hg (shrimps) [80]

Table 1. Impact of diverse chemical forms of selenium on biological and health effects of diverse chemical forms of mercury – cont.

Chemical form of selenium	Mercuric chloride ($HgCl_2$)	Methylmercury (MeHg)
Diphenyl diselenide $(PhSe)_2$		$(PhSe)_2$ decreases MeHg-induced cerebral, hepatic and renal oxidative stress as well as Hg deposition (mice) [25] treatment with $(PhSe)_2$ neutralized the inhibitory effect of MeHg on mitochondrial activities and elevated oxidative stress parameters (mice) [57] subcutaneous $(PhSe)_2$ co-treatment provided a defense against mitochondrial alterations caused by MeHg (mice) [58]
Seleno-methionine SeMet	SeMet decreases Hg content in kidney in the first 48 h, but less than Se^{4+}; only Se^{4+} diminishes Hg content in kidney at the end of this period [6] Se decreases Hg content in kidney but increases it in blood and liver (rats) [35]	Se diminishes Hg in kidney, in contrast to Hg in liver (mice) [63] co-administration of Se decreases porphyrins excretion (rats) [66] after pre- and co-administration, Se reduces mortality (offspring of rats) [65] pre-administration of SeMet and SeCys into the food increases elimination of MeHg (goldfish and zebrafish) [79]

Hg – mercury; Se – selenium; GSH – glutathione system; GPx – glutathione peroxidase; Se^{4+} – selenite; iHg – inorganic mercury; Se^{6+} – selenate; SeMet – selenomethionine; SeCys – selenocysteine.

ratio Se:Hg in SeP was significantly lower ($p < 0.05$) in the exposed group 7.8±3.1 as compared to the control group 535±216. All these results indicate a strong Hg–Se reciprocal action leading to the induction of antioxidant defense mechanisms. An increased synthesis of SeP induced by a high level of Se caused a mechanism that prevented accumulation of Hg in the body due to its bounding with SeP in blood.

In people from Brasilian Amazon environmentally exposed to Hg, a negative linear correlation ($p < 0.05$) between the activity of GPx, concentration of GSH and activity of CAT in blood samples and concentration of Hg in the whole blood (Hg-B) [19] was observed.

Impact of genetic susceptibility on mercury metabolism

Since a configuration of genetic information of the human body determines the situation in which some of the genes are expressed, while other genes stay inactive, eukaryotic gene expression may be controlled and modulated/regulated from transcriptional initiation, to RNA processing and to the posttranslational modification of proteins. In a response to a disturbance of the environment caused by Hg exposure, the gene expression levels directly relate to suitable protein levels, thus, proteins activity and their function may be altered by Hg. More and more scientists are trying to understand the toxicologically relevant interaction between Hg and Se with an emphasis on pathway from gene expression to molecular processes. Humans have individual sensitivity to Hg and their inter-individual variability may indicate the influence of genetic regulatory mechanisms (Gundacker et al. [94]).

Numerous studies have reported that genetic polymorphism: glutathione S-transferase (*GST*), metallothionein (*MT*) and selenoprotein P (*SEPP1*) may be associated with the metabolism of Hg [90,94–96]. Glutathione S-transferase belongs to the family of polymorphism enzymes with the predisposition to accumulation and elimi-

nation of Hg in the urine or its retention may be indirectly dependent on GST in cytosol. Glutathione S-transferase is a group of phase II enzymes involved in the biotransformation of coupling heavy metal ions with reduced GSH. Studies have shown ethnic differences in minor allele frequencies (MAFs) within the GST. Deletion polymorphism for *GSTT1* gene (41% MAF for Caucasian population according to HapMap base) is associated with the absence of the gene-encoded enzyme but not only *GSTT1* deletion polymorphism but also nonsynonymous polymorphism of *GSTP1* gene (rs1695 Ise105Val) play a role in Hg metabolism [97].

Minor allele frequencies of the above mentioned polymorphism similar to that of Caucasian populations (HapMap base) amounted to 13%. Genetic polymorphisms in the selected genes may determine the inter-individual differences in sensitivity response to the environmental and occupational exposure to MeHg and Hg^0 (gene-environment interactions). Schläwicke-Engström et al. [98] presented the results suggesting the modifying effects of polymorphism of *GSTP1* and gene encoding of gammaglutamylcysteine ligase (*GCLM*) on metabolism and retention of MeHg in environmental exposure in Swedish population. Authors have examined that *GSTP1* polymorphism may exhibit a higher concentration Hg in erythrocytes. Gundacker et al. [94] showed the concentration of Hg-B for genotype *GSTT1+* was negatively correlated with *GSTM1+* among a group of students from Austrian population.

It is also known, that selenoproteins (i.e., SeP and GPx) may affect toxicokinetics of Hg and alter metabolism of Hg. Chen et al. [33] showed that miners in Guizhou (China) with occupational exposure to Hg presented increased expression of *SEPP1* gene. This may suggest ability to bind Hg by selenocysteine. Polymorphism in the *SEPP1* gene (rs7579) is associated with a change of cytosine (C) to thymine (T) in the 3'UTR untranslated region. TT homozygotes may lead to an increase in Hg-binding ability [99].

Goodrich et al. [90] showed inter-individual variability among dentists from Michigan. T allele modified an association between sources of exposure to Hg and concentration of Hg-U. In the case of a higher exposure to Hg, the CT or TT genotype, in genotype-by-amalgam interactions, was characterized by a higher urinary excretion of Hg than the CC homozygotes. The authors also claim that genetic polymorphisms in selenoproteins and glutathione-related genes may influence excretion of Hg-U (polymorphisms significantly associated – *GSTT1* deletion) and hair or Hg retention (*GSTP1*-105, *GSTP1*-114, *GSS* 5') or both (*SEPP1* 3' UTR) following exposures to Hg^0 (dental amalgams) and MeHg (fish consumption). Moreover, the study of Goodrich et al. [90] have indicated that a higher expression of *SEPP1* in dentists with genopyte T (CT or TT) may influence Hg binding and following distribution to various tissues.

Metallothioneins are specific proteins which contain cysteine groups, to which Hg preferably binds. Since they play a protective role against nephrotoxic effects of Hg, they allow its transport and excretion. Exposure to Hg affects induction of MTs synthesis in the kidneys. The study of Thornalley and Vasak [100] reveals that MTs may be involved in the response to increasing oxidative stress. Therefore, genetic polymorphisms in MT genes may affect the inter-individual differences in Hg exposure-biomarker levels [101]. People with the *MT1M* (rs2270836) AA genotype or the *MT2A* (rs10636) CC genotype are characterized by lower concentration Hg-U in comparison with GG homozygote levels. In addition, Wang et al. [101] show that genetic polymorphism in *MT2A* and *MT1A* have also a modifying effect on the levels of early renal dysfunction biomarkers. Homozygote variant AA genotype for *MT1A* (rs11076161) showed the highest activity of NAG and concentration of β_2M in urine. These MTs were selected with polymorphism in 3' UTR: *MT2A* G > C (rs10636) (30% for MAF according to Entrez SNP base) and *MT1M* G > A (rs2270836) (15% for MAF).

Without a doubt, we cannot forget about the individual susceptibility to the toxic effects of Hg, either. It should be noted that Hg affects all types of tissues and may affect many organs but the response of the organ/organism (including age, sex, ethnicity) to Hg depends on the individual genetic susceptibility to Hg metabolism [94,102] and the workable detoxification process in a human body. Numerous studies have reported that genetic variations such as: *GST*, *MT* and *SEPP1* may be associated with metabolism of Hg [90,94–96,101]. It is considered that the predisposition to accumulation and elimination of Hg in the urine or its retention may be indirectly dependent on the proteins and other molecules of major biological significance.

CONCLUSIONS

Summing up, this paper has reviewed interactions between Se and Hg in animals and humans. The majority of studies carried out using animal models show that concurrent administration of Hg and Se in diverse chemical forms at supraphysiological concentrations reduces toxicity of Hg in the case of acute as well as chronic exposure. Treatment with high concentrations of Hg and Se provides short-term and observable effects, where such an interaction most probably counteracts the adverse effects (neurotoxic and renotoxic) of exposure to Hg. However, human studies on Hg–Se reciprocal actions are not consistent. It is suggested that the Hg–Se–protein complex plays a role in restraining toxicity of iHg as well as MeHg by binding Hg to prevent it from reaching target tissues. Selenium plays its biological function through selenoproteins, in the case of which the highly reactive selenol group may bind to Hg as well as through antioxidative properties that cause a direct reduction of ROS levels triggered by Hg.

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