Chapter 34
Selenium Antagonism with Mercury and Arsenic: From Chemistry to Population Health and Demography

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Abstract Selenium (Se) has been shown to act as a functional antagonist to mercury (Hg) and arsenic (As). Se may influence Hg and As toxicity by modulating redox homeostasis and inflammation. At the same time, the clinical significance of such interactions is questionable. Despite extensive experimental data, human studies on the interaction between these trace elements, as well as on the influence of such interaction on human health are limited. Current data are reviewed on how Hg and Se interplay impacts on cardiovascular diseases, neurotoxicity, neurodegeneration, diabetes and obesity. Studies also demonstrate that the interaction between

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Se and As significantly affects the development of certain cardiovascular diseases and cancer. This notion is further supported by the results of our analysis of 63,118 adults and 13,734 children from different regions of Russia indicating that the hair Se/Hg ratio is characterized by a tighter association with demographical indices (birth rate, mortality, life span, total morbidity) and morbidity than Hg or Se individually. It is proposed that modulation of the Se/As and Se/Hg ratios in humans may help to improve population health and demography.

Keywords Arsenic • Cancer • Demography • Interaction • Mercury • Morbidity • Mortality • Neurotoxicity • Toxicity

34.1 Introduction

Selenium (Se) is an essential trace element involved in regulation and function of metabolic systems in humans through its role as a component of selenoproteins [1]. Consequently, its deficiency is associated with numerous pathologic states. However, excessive intake of Se may also have adverse health effects [2]. Hg and As are key inorganic pollutants having a significant impact on human health [3, 4]. Various studies suggested antagonism between Hg, As, and Se, as well as clinical implications of such interactions [5, 6]. Despite extensive experimental data on this topic, results from human studies are less clear. Herein, we briefly discuss the main crossroads between biological effects of As, Hg, and Se and review the influence of this interaction on human health.

34.2 Oxidative Crossroad Between Se, As and Hg

Se may be viewed as both an antioxidant and pro-oxidant nutrient that produces its effects through action of Se compounds (supranutritional levels) [7] and its role in selenoenzymes such as glutathione peroxidases (GPx), thioredoxin reductases (TrxR) [8], methionine sulfoxide reductase and other selenoproteins [9, 10]. Se deficiency is associated with oxidative stress in organisms due to deficiency of selenoproteins, although this effect is partially alleviated by induction of detoxification programs, most notably the nuclear factor (erythroid-derived 2)-like 2 (NFE2L2 or Nrf2) response. It was shown that a Se-poor diet resulted in induction of phase II detoxification and antioxidant enzymes [11]. At the same time, the levels of Se above nutritional requirements may lead to a pro-oxidant effect of this element, also activating the Nrf2 response. For example, certain Se compounds like selenite (SeO_3^{2-}), selenocysteine, and diphenylselenide take part in generation of superoxide [12]. Thus, in the case of Se-induced oxidative stress, the activity of antioxidant selenoproteins is increased as a compensatory mechanism to alleviate Se toxicity [13].

In contrast to complex chemical biology of Se, Hg is characterized by a significant pro-oxidant effect due to its high affinity for –SH groups of low molecular weight thiols and proteins, and presumably this element also targets selenocysteine residues in selenoproteins, including GPx and TrxR [14]. In turn, As-induced oxidative stress is mediated through the direct pro-oxidant effect of arsenite (AsO_3^{3-}) [4] and induction of NADPH oxidase [15]. However, our previous data indicate that arsenate (Na_3AsO_4) treatment in pregnant mice dams simultaneously affected Se status and oxidative stress parameters in the liver of the offspring [16].

Numerous studies indicate that Se shows a protective effect against Hg- [17] and As-induced [18] oxidative stress. Taking into account the pro-oxidant effect of certain Se compounds [12], a possibility of potentiation of Hg and As pro-oxidant action by Se should be kept in mind [19].

34.3 Inflammatory Crossroads Between Se, As and Hg

Hg is a potent activator of nuclear factor kB (NF-kB) [20] and mitogen activated protein kinase (MAPK) [21] signaling pathways involved in regulation of an inflammatory response [22]. Experimental studies demonstrated a significant Hg-induced stimulation of tumor necrosis factor α (TNFα), TNF receptor-1, interleukin (IL)-1β, IL-2, IL-17, IL-4, IL-6, IL-8, interferon-γ (IFN-γ) expression or production [23]. However, depending on the dose and form of Hg, it may also exert immunotoxic effects resulting in immunosuppression and autoimmunity [24].

Various As compounds have also been characterized as activators of certain pathways like NF-kB, activator protein 1 (AP-1) and MAPK [25]. Clinical studies indicated a significant association between As exposure and proinflammatory cytokine levels in lymphocytes [26] and maternal and cord blood [27]. However, some studies indicate a significant anti-inflammatory activity of As trioxide (As_2O_3) in allergen-induced inflammation [28] through inhibition of NF-kB-mediated gene transcription [29].

In contrast, Se when present in physiological concentrations acts as a potent anti-inflammatory nutrient mediating its action via down-regulation of NF-kB and lipoxygenase/cyclooxygenase pathways [30]. Conversely, high Se may activate NF-kB in immune cells leading to increased production of IL-2 and IFN-γ [31].

Modulation of Hg- or As-induced inflammatory response by Se may also serve as a potential mechanism of antagonism between these trace elements. Interesting results were obtained by Jin and coauthors who demonstrated that Se pre-treatment in various doses may differentially modulate an inflammatory response to methylmercury (MeHg) administration [32]. Se administration also has been shown to modulate immunotoxic effects of Hg in mice [33]. Previous studies indicated that Se in combination with other biologically active compounds may prevent As-mediated alteration of NF-kB and TNF-α expression [34, 35]. Selenomethionine pretreatment in sufficient and excessive levels (0.2 ppm and 2 ppm, respectively) also provided protective properties against As-induced immunotoxicity by increasing secretion of IL-4, IL-12 and IFN-γ [36].

34.4 Clinical Outcome of Hg–Se Interaction: Cardiovascular Diseases

The influence of interaction between Se and Hg on the incidence of cardiovascular diseases (CVD) has not been extensively characterized [37]. A recent study indicated a significant decrease in the Se/Hg ratio in scalp hair, serum, and urine in myocardial infarction [38] and hypertensive patients [39]. Our investigation also demonstrated a significant positive association between Hg/Se and body mass index, triglycerides, and serum atherogenic index values all being risk factors of CVD. The observed association was stronger for Hg/Se than for hair Hg or Se concentrations [40]. In turn, blood concentrations of Hg and Se were differentially associated with paraoxonase 1 activity in Inuit adults from Nunavik [41]. It is also notable that human subjects of this ethnicity were characterized by a significant statistical interaction between Hg/Se ratio and F_2-isoprostanes and isofurans [42] being used as cardiovascular risk markers [43]. In addition, the inverse association between dietary polyunsaturated fatty acids intake and the incidence of hypertension was more expressed at low Hg and high Se toenail levels [44].

An investigation of the role of Hg in hypertension in Inuit adults demonstrated that, in both systolic and diastolic blood pressure models, low Se decreased the regression coefficient [45]. However, examination of two prospective cohorts of US men and women failed to reveal any significant influence of the Hg-Se interaction on the incidence of hypertension [46]. Park and colleagues also demonstrated that serum Se did not efficiently modify the association between Hg markers and hypertension [47]. The absence of significant modification of the relationship between Hg and coronary heart disease by toenail Se levels was also demonstrated [48]. Despite the fact that the trend was insignificant, the highest Hg level was associated with a higher risk of coronary heart disease than those with the lowest one in the highest toenail Se category [48]. Finally, a significant association between the increased Hg/Se ratio and 15-year mortality in men was demonstrated [49]. However, a recent study indicated that the association between daily ambient concentrations of Hg and Se is not characterized by a significant relationship with daily cardiovascular mortality [50].

34.5 Clinical Outcome of the Hg–Se Interaction: Neurotoxicity and Neurodegeneration

It has been proposed that the main health effect of the Se-Hg interaction is its influence on the central nervous system [51]. However, human data to support this claim are insufficient and in part contradictory. In particular, umbilical cord blood Se did not significantly affect an association between prenatal exposure to MeHg and neurobehavioral deficits in memory function of Faroese children of school age [52, 53]. An investigation of the influence of seafood contaminants from the maternal diet during pregnancy on neonatal neurologic function indicated only a slightly improved

association of Hg/Se ratio with a variable outcome [54]. Therefore, the role of maternal Se intake in prevention of developmental MeHg neurotoxicity in humans is questionable [55].

An investigation involving adult lamp factory workers exposed to Hg indicated a significant protective effect of Se and/or vitamin E supplementation resulting in reduced cases of anxiety-insomnia, improved short-term memory, perceptual ability, short-term visual memory and trail-making [56]. It has been also noted that subjects suffering from depression are characterized by increased blood Hg/Se ratios [57].

Recent studies have demonstrated the association between Hg exposure and the incidence of autism [58]. However, the possible protective potential of Se in autism patients due to its antagonism with Hg is unclear. It has been demonstrated that children with autism are characterized by a significantly increased hair and nail Hg content in parallel with decreased Se levels. Moreover, the observed changes were especially marked in children with low functioning autism [59]. In contrast, we observed a significant increase in hair Se associated with lower Hg content in autistic and mentally retarded children. However, no such relationship was observed in serum and urine [60].

Recent studies indicated a significant role of Hg in the development of neurodegenerative diseases [61]. Despite the protective role of certain selenoproteins in neurodegeneration, data on the influence of Se are inconsistent [62]. Neurodegenerative diseases are characterized by differential patterns of Se and Hg. In particular, Alzheimer's disease (AD), but not multiple sclerosis patients, were characterized by a significant decrease of blood Se with a nearly threefold decrease in the Se/Hg ratio in comparison to control groups [63].

Similarly, the value of plasma Hg/Se ratio in amyotrophic lateral sclerosis patients from Hokkaido exceeded the control values by a factor of more than 4 [64]. This observation was partially confirmed by Roos et al. [65], who demonstrated a decrease in plasma Se/Hg ratio accompanied by the elevation of this index in cerebrospinal fluid of ALS patients. Thus, AD was associated with an increased plasma Hg/Se ratio, whereas CSF values were not related to the disease state [66]. Examination of motor neuron disease patients did not reveal a significant difference in blood Hg/Se in comparison to the respective control values [67]. In contrast, a recent study on the population of Brazilian Amazon residents exposed to Hg through fish consumption revealed that Se biomarkers were significantly associated with better motor function, especially when controlling for blood Hg levels [68].

The changes in brain trace elements levels in patients suffering from neurodegenerative diseases were rather distinct. In particular, no significant alteration in the Hg/Se ratio in the pituitary gland was detected in AD patients [69]. Analysis of different brain regions revealed a significant, almost threefold decrease of the Hg/Se ratio in hippocampus of multiple sclerosis patients, whereas no significant differences were observed in subjects with AD [70]. In contrast, a significant increase in Hg/Se values in various brain subcellular fractions was also revealed in AD [71].

34.6 Clinical Outcome of the Hg–Se Interaction: Diabetes and Obesity

A significant association between Hg and Se and type 2 diabetes mellitus has been detected [72–74]. In particular, diabetic patients were characterized by a significant increase in serum Hg levels and Hg/Se ratio in comparison to the healthy controls [72]. However, an earlier study involving diabetic patients and subjects with impaired glucose tolerance or impaired fasting glucose did not detect any significant changes in plasma Hg and Se when compared to control values [73]. An 18-year follow-up study of 3875 Americans revealed a significant positive association between toenail Hg and diabetes that was improved after adjustment for toenail Se [74]. At the same time, a later prospective cohort study did not confirm this observation [75].

34.7 Clinical Outcome of the As–Se Interaction: Cancer

Potential mechanisms of the As and Se interaction regarding carcinogenesis may involve modification of angiogenesis [76], modulation of DNA repair processes [77], and DNA methylation [78]. Despite the presence of multiple indications of the carcinogenic effect of As [79] and the role of Se in cancer [80], the interactive effect of As and Se on the incidence of cancer is insufficiently studied [81]. A recent study indicated that hair and blood samples from As-exposed females with skin cancer are characterized by significantly elevated As and lower Se levels [82]. Moreover, a significantly higher risk of As-related premalignant skin lesions in persons with low blood Se levels was demonstrated [83]. However, data obtained from a Health Effects of Arsenic Longitudinal Study indicated that Se intake was not significantly associated with As-induced hyperkeratosis [84]. A possible mechanism of the association between low Se status and As-associated skin lesions may involve impaired As methylation that increases metalloid toxicity [85]. Antagonistic relationships between Se and As were also confirmed by the intervention trial in Inner Mongolia, where Se supplementation significantly improved As-induced skin lesions being characteristic for arsenism [86]. The results of this study are in agreement with the reported efficiency of Se treatment of endemic arsenism [87, 88]. A later study in general confirmed this observation [89]. However, the effect of Se treatment on skin lesion status was not significant. It has been also shown that long-term Se supplementation may change the patterns of gene expression in subjects with premalignant As-induced skin lesions [90].

Finally, our earlier investigation [91] of 184 control and cancer patients from an As-polluted area in Plast city (South Ural region, Russia) characterized by the highest oncology-related morbidity in Russia demonstrated a nearly two and threefold increase in the hair As/Se ratio in lung and skin cancer patients as compared to the respective control values. However, no significant changes in the As/Se ratio were observed in gastrointestinal, breast and ovary cancer patients.

34.8 Clinical Outcome of the As–Se Interaction: Cardiovascular Diseases

Previous studies made clear that As exposure is associated with multiple CVD forms, including coronary heart disease, stroke and peripheral artery disease [92]. However, the role of the interaction between As and Se was widely demonstrated only in the latter. Lin and Yang provided the first indication of increased As/Se ratio in biological samples from Blackfoot disease patients [93]. Later investigations of Blackfoot disease patients have also demonstrated a significant increase in As concentration associated with low Se levels in hair [94], blood [95], urine [96, 97] and bone [98]. Moreover, these changes became more marked at later stages of the disease [94, 96]. Interestingly, As content in arterial tissue from Blackfoot disease patients was sixfold higher than in the control volunteers, whereas Se was not altered significantly [99].

34.9 Se-Hg Interaction and Population Health and Demography in Russia

Generally, previous research provides sufficient evidence that the interaction between Se and As, and especially between Se and Hg, may have a significant impact on public health. At the same time, the interactions between these elements may also impact the quality of life and demographic indices.

During a cross-sectional observation involving 63,118 adults and 13,734 children from different regions of Russia [100], scalp hair concentrations of Hg and Se were assessed using inductively-coupled plasma mass spectrometry. The obtained values of hair Hg, Se and the Se/Hg ratio and the statistical data on demographical indices and morbidity from the leading causes for every region were used for correlation analyses using Spearman's rank correlation coefficient.

The data indicated that, in the adult population, hair Hg content inversely correlates with birth rate, whereas Se levels are significantly positively associated with life span and negatively correlate with mortality (Table 34.1). At the same time, the hair Se/Hg ratio is interrelated with all the above mentioned parameters (birth rate, mortality, life span and total morbidity) and characterized by higher correlation coefficients. It is also notable that total morbidity directly correlated with the hair Se/Hg ratio, but not with Se or Hg alone.

Further analysis also indicated a significant association between Hg and Se, and especially their interaction (Se/Hg ratio) with the most incident diseases of the adult population in Russia. The hair Se/Hg ratio was found to be significantly inversely associated with the incidence of tumors, type 2 diabetes, acute myocardial infarction, cerebrovascular diseases, stomach and duodenal ulcers, skin and subcutaneous tissue diseases, musculoskeletal disorders and arthrosis. The correlation coefficients were higher than those for individual hair Se and Hg levels.

Table 34.1 Correlation between hair Hg, Se content, Se/Hg ratio and parameters of morbidity and demography in adult population from 83 regions of Russia

	Hg		Se		Se/Hg	
Parameter	r	p	r	p	r	p
Birth rate	–0.260	0.018*	0.059	0.602	0.382	<0.001*
Mortality	0.147	0.188	–0.253	0.022*	–0.415	<0.001*
Life span	–0.170	0.128	0.447	<0.001*	0.501	<0.001*
Total morbidity	0.125	0.263	–0.113	0.312	–0.258	0.019*
Tumors	0.247	0.025*	–0.032	0.775	–0.333	0.002*
Type 1 diabetes	–0.030	0.790	0.131	0.240	0.038	0.734
Type 2 diabetes	0.278	0.011*	–0.066	0.556	–0.330	0.002*
Obesity	–0.082	0.466	0.013	0.910	0.011	0.923
Hypertension	–0.050	0.653	–0.141	0.205	–0.133	0.232
Coronary heart disease	0.088	0.431	0.056	0.595	–0.094	0.404
Acute myocardial infarction	0.322	0.003*	0.008	0.941	–0.340	0.002*
Recurrent myocardial infarction	0.275	0.012*	0.078	0.485	–0.216	0.052
Cerebrovascular diseases	0.227	0.041*	–0.124	0.267	–0.312	0.004*
Stomach and duodenal ulcers	0.105	0.350	–0.131	0.241	–0.236	0.033*
Liver diseases	–0.012	0.915	0.146	0.190	0.022	0.845
Skin diseases	0.200	0.072	–0.234	0.035*	–0.380	<0.001*
Musculoskeletal disorders	0.237	0.032*	–0.270	0.014*	–0.431	<0.001*
Congenital abnormalities	–0.048	0.668	–0.126	0.260	–0.091	0.416

r—correlation coefficients; p—individual p value for a certain interaction; *—correlation is significant at $p<0.05$

Generally, the same trends were observed in children (Table 34.2). In particular, hair Se/Hg was inversely associated with total morbidity, the incidence of tumors, type 1 diabetes, obesity, skin and subcutaneous tissue diseases, atopic dermatitis, and musculoskeletal disorders. The significance of such association was higher than that for hair Se or Hg alone. Similar associations were found in follow-up investigations of certain Russian territories such as Russian North that is characterized by challenging life conditions, increased morbidity and mortality, and short lifespan [101].

Our data indicate that the interaction between Hg and Se may not only affect biological systems in an organism but also may influence public health and even demographic indices. Further studies aimed to assess the association between As and Se and demography on the territory of Russia are currently being carried out.

Table 34.2 Correlation between hair Hg, Se content, Se/Hg ratio and morbidity in a children's population from 59 regions of Russia

	Hg		Se		Se/Hg	
Parameter	r	p	r	p	r	p
Total morbidity	0.231	0.079	–0.389	0.002*	–0.638	<0.001*
Infectious and parasitic diseases	0.400	0.002*	–0.012	0.930	–0.354	0.006*
Tumors	0.064	0.632	–0.156	0.237	–0.336	0.009*
Type 1 diabetes	–0.030	0.823	–0.342	0.008*	–0.402	0.002*
Type 2 diabetes	0.213	0.105	0.007	0.957	–0.080	0.549
Obesity	0.130	0.326	–0.313	0.016*	–0.487	<0.001*
Stomach and duodenal ulcers	0.018	0.894	–0.040	0.765	–0.121	0.362
Gallbladder and bile ducts diseases	0.193	0.144	–0.057	0.669	–0.192	0.146
Skin diseases	0.211	0.108	–0.293	0.024*	–0.506	<0.001*
Atopic dermatitis	0.145	0.273	–0.248	0.058	–0.414	0.001*
Musculoskeletal diseases	–0.091	0.491	–0.311	0.016*	–0.358	0.005*
Congenital abnormalities	0.229	0.080	0.036	0.785	–0.210	0.111

r—correlation coefficients; p—individual p value for a certain interaction; *—correlation is significant at $p<0.05$

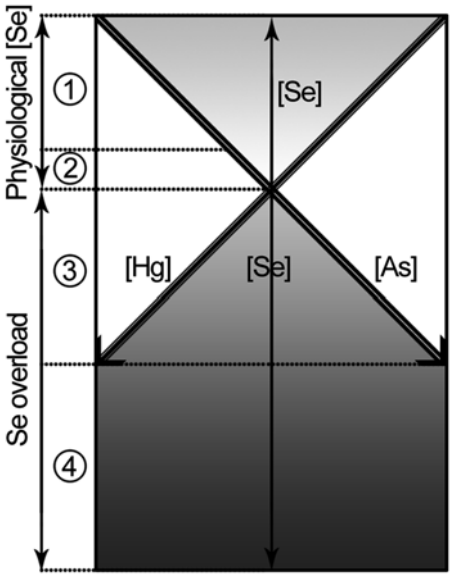

Fig. 34.1 Possible effects of interaction between Se, As, and Hg in humans. Density of *grey color* is proportional to Se burden. (*1*) At physiological concentrations Se is capable of preventing Hg- and As-induced toxicity (especially at the molar ratio of 1:1); (*2*) Se deficiency along with increasing Hg and As concentrations results in clinical manifestations of Hg and As toxicity; (*3*) An increase in Se concentrations in biological fluids over a physiological maximum (Se overload) in the presence of Hg and As hypothetically results in synergistic toxic effects; and (*4*) In the presence or absence of heavy metals, excessive Se levels in the organism may exert toxic effects

34.10 Perspectives

Additional studies are required to assess the influence of the interaction between Se and As or Hg on human public health both in clinical and epidemiological studies. Taking into account a possibility of both antagonistic and synergistic toxic effects of these trace elements (Fig. 34.1), future studies should estimate their levels and ratios in humans that are associated with healthy conditions and adverse health status. Simultaneous speciation analysis for investigation of Se, Hg and As metabolism in health and disease is of particular interest. Such information may be used in biomonitoring, risk assessment and/or treatment of chronic As and Hg poisoning. In particular, it will help estimate whether Se supplementation may assist in alleviating or aggravating heavy metal toxicity in each individual case. Finally, modulation of the ratio between Se, As and Hg in the human population may help to improve population health and demography.

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