Biological responses related to agonistic, antagonistic and synergistic interactions of chemical species

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The species specific essential/toxic character of the elements encouraged the development of analytical strategies for chemical speciation over the last twenty years and actually, there are a great number of them with very good performance. However, biological systems are exposed to a complex environment in which the elements species can interact in a synergistic/antagonistic fashion. Thus, the metabolism of trace elements can not be considered in isolation. On the other hand, the biological systems are dynamic and for this reason, the study of the trafficking of elements species between organs, tissues or cell compartments is mandatory to decipher the biochemical processes of the interactions in which they are involved. Although, liquid chromatography-inductively coupled plasma-based 'metallomics' methods in combination with organic mass spectrometry can provide much needed insight, new analytical strategies are mandatory to really understand the role of elements species in biological systems and the mechanisms of their interactions. In the present paper, the interactions of the most studied elements (Se, Hg and As) are discussed as well as other important interactions between different elements.

Keywords: speciation, metals, agonists, synergist, antagonist, trafficking, multispeciation, mass spectrometry, ICP-MS

Contents

Abbreviations used

APS-ATP sulfurylase/adenyl sulphate reductase

APSe-5´-adenylylselenate

CE-Capillary Electrophoresis

DMA-Dimethylarsinate

ESI-Electrospray ionization

GPx-Glutathione peroxidase

HPLC-High performance liquid chromatography

IC-Ion Chromatography

ICP-AES- Inductively coupled plasma with atomic emission spectroscopy

ICP-MS-Inductively Coupled Plasma Mass Spectrometry

MS-Mass Spectrometry

MALDI-Matrix Assisted Laser Desorption Ionization

$MeHg^{+}$-Methylmercury

MA-Methylarsonate

$PheHg^{+}$-Phenylmercury

SeBet-Selenobetaine

SeMet-Selenomethionine

SeProt-Selenoproteins

TlAc-Thallium acetate

Aims and scope

Over the last 20 years, chemical speciation studies have generated very important information and powerful analytical methods related to health, environmental issues or food quality control. Nowadays, a deeper knowledge about the chemical species in biological systems is mandatory and the new scenery is a real challenge for the analytical chemist. The metallome was defined by Williams as the distribution of elements, concentration at equilibrium of free metallic ions or free elements in a cellular compartment, cell or organism [1]. The metallome refers to the identity and/or quantity of metals/metalloids and their species [2-5]. The complexity of biological molecules increases considerably against those considered in classical speciation studies (i.e. inorganic arsenic, methylarsonate, methylmercury, Cr^{6+} and other species) and the most important difficulties for the analytical chemist are the absence of standards for identification, the labile character of the metal/metalloid-organic molecule or the typical concentrations of elements in the range of sub-ng g^{-1}.

In science is important to understand "what happens" inside the cell which requires new analytical tools to obtain "massive" information of all molecular processes and reactions that take place into that cell in a given instant. For this purpose, genomics is very useful since reveals the characteristics of the information contained in the cellular core that determines the cell function and behaviour. In addition, proteomics studies give also important information since proteins are the workers that convert this potential information on current, so they are the functional expression of the genome. However, some important questions remain unsolved: which proteins are expressed? In which quantity? In which form? Moreover, post-translational modifications, as phosphorylation and glycosylation of proteins determine their function and it is well-known that a lot of environmental factors or multigenic processes (i.e. aging and disease) can not be explained only with a genomics basis.

On the other hand, an important fact is that approximately one third of proteins need the presence of metals as cofactors to develop their function [2, 6-7]. These metals are responsible of catalytic properties or structure of proteins and the presence in molecules is determined in many cases by the genome [6]. In addition, to understand the behaviour of a cell, tissue or living organism low molecular mass molecules should be considered since they represent the last action mechanism of the organisms. Therefore, while genomics

informs us about how an organism can potentially work and proteomics about how it can do it, metabolomics explains how the organism actually works. Since there are also a lot of metabolites that contains metals, the important information given by metallo-metabolomics should be integrated with the other -omics [8-9].

Nowadays, huge information about the biological function of elements is available in the literature, and numerous analytical methods have been developed for this purpose providing a wide application field. However, most of the methods are focused on only one element or very well-defined species family linked to an element, and some elements or their species can counteract the action of others through cooperation or availability mechanisms [10]. A good example of this is the antagonistic effect of selenium on mercury toxicity that was first reported in 1967 in an experiment with rats treated with mercury chloride and selenite [11]. Since the living organisms are usually exposed to a complex environment in which different elements and their species are present together, these types of interactions complicate even more the panorama and analytical methods for multispeciation considering their biological, synergistic and inhibitory effects are claimed. Thus, the metabolism of trace elements can not be considered in isolation.

The most studied interactions of elements species have been those related to Se, Hg and As and the present paper is mainly focused on them. However, other important elements interactions less considered in the literature are also discussed.

Agonistic actions of elements

As it is well known, the use of metal ions by all living organisms depends of their relative abundance, availability and singular chemistries. These factors have served as driving force for life evolution on Earth, as Thiele et al assert [12]. Another important factor is the lability of the metal-biomolecule link that promotes the rapid assembly and disassembly of the metal cores as well as rapid association and dissociation of substrates. In this way, metal ions as Cr^{3+} and Co^{3+}, well known in inorganic chemistry for their kinetic inertness, are rarely utilized in biological systems, and metalloproteins consists of kinetically labile and thermodynamically stable units [13].

Among the twenty one elements recognized as essentials for all the living organisms, eleven are metals (Na, K, Mg, Ca, Mo, Mn, Fe, Co, Ni, Cu and Zn), six non-metals (H, C, N, O, P, S) and two halogens (Cl and I). Essential ultratrace elements (dietary requirement in µg/day) include: Si, V, Cr, Se, Br, Sn and F. Some elements have also biological concern due to their use as drugs or probes such as Y, Cr, Tc, Co, Pt, Ag, Au, Cd and Hg. An example is the use of cis-platinum for the treatment of cancer [13-15]. As established by Shroeder, trace elements can be classified in two groups, first one including those elements that participate in biochemical reactions (essential trace elements) and other which includes elements with other functions. The last group can be divided into those that do not cause damage to living beings at the concentrations commonly found in the environment, and those with deleterious effects. In this sense, there are elements with probed essential functions (F, Si, Cr, Mn, Fe, Co, Ni, Cu, Zn, Se, Mo and I) that produce nutrition deficiencies in humans (F, Cr, Fe, Cu, Zn, Se and I) or animals (Si, Mn, Co, Ni and Mo) and other elements with suspected essential function but unknown action mechanisms (V, As, B, Br, Cd, Li, Pb and Sn). Finally, other elements such as Hg do not exhibit known essential functions. The classification of essential elements is not absolute because some elements historically considered as toxic are now considered as essential, as the case of selenium, chromium [15-16] or tungsten that has also been recently added to the list of metals found in biology [13]. In addition, there are elements with a double essential/toxic character depending on their concentration and/or chemical form that in turn depends on their chemical properties (i.e. selenium or chromium).

The ligands in bioinorganic chemistry are commonly amino-acid side chains or constituents of nucleic acids. The coordination depends critically upon the three-dimensional folding of proteins and tertiary structures of nucleic acids [13]. However, metals can be also bond to prosthetic groups of metalloproteins (i.e. iron-protoporphyrin IX, magnesium-chlorophyll), bleomycin, siderophores, coenzymes (i.e. cobalamin-Co), and methylcobalamin. This last can transfer a CH_3^- ion to Hg, Pb, and Sn salts in aqueous solution, a biomethylation reaction that probably contributes to the toxicity of these elements. Finally, metals can be bond to complex assemblies such as cell membranes, viruses and intracellular compartments (i.e. ribosome, the mitochondrion and endoplasmatic reticulum) [13]. In this way, some elements such as Cu, Zn, Cd, Hg and Ag, coordinate by proteins through a sulphur atom and others through nitrogen or oxygen atoms as Mo, Mn, Fe, Co, Ni, Cu and Zn. Metabolites of As, Se and I, have a metalloid-

carbon covalent bond. Other elements as Al, Ni and Fe coordinate by small organic ligands. Mg, V, Fe, Co and Ni coordinate by tetrapyrol ligands; Ca, Sr, Ba, La and Pb form complexes with polysaccharides and finally, Pt, Ru, Cr and Ni coordinate by nucleic acids and their constituents [17]. In selenoproteins (i.e. glutathione peroxidase, selenoprotein P), selenium is strongly bond to the organic moiety since selenocysteine is genetically encoded in these selenoproteins and thus it is an integral protein constituent [18].

Table 1 shows the most important antagonistic and synergistic interactions of elements species that are discussed in the following sections.

Antagonistic interactions

Arsenic and selenium

Beneficial actions of arsenic species

The first evidence of the arsenic-selenium antagonism was in 1938 when drinking water containing arsenite completely protected rats against the otherwise lethal liver damage caused by seleniferous wheat or selenite [19]. Sodium arsenite and sodium arsenate, when used as sources of arsenic, were equally effective in preventing the toxic action of selenium in albino rats fed with seleniferous wheat (sodium selenite and selenium-cysteine). However, AsS_2 and AsS_3 were ineffective in this experiment [20]. The organic arsenicals have also shown protective action against selenosis, at least partially. This is the case of antisyphilitic drugs, neoarsphenamine, sulfarsphenamine, arsanilic acid and 3-nitro-4hydroxiphenylarsonic acid [21-22].

Arsenite has also been found effective in preventing selenite induced cataracts (75 % of protection) in rats [23]. Moreover, arsenic compounds also induce clinical remission in patients with acute promyelocytic leukemia [24], dermatological disease [25], and may have potential for treatment of other cancers [26-29]. In relation with cancer, the first proof of the As/Se interaction was in mice [30] and rats [31] when As^{III} antagonized the carcinogenic effect of Se^{IV}. Later, studies with human malignant melanoma cells demonstrate that arsenite-induced apoptosis is prevented by selenite [32].

The protective effect of arsenic has been observed/suggested in rats [19-20, 23, 33-34], dogs [35], cattle [36], mice [37], hogs [38], steers [39], mallards [40] and poultry [41-43]. Several studies apparently suggest that the same interaction can occur in humans [44-49].

Selenium against arsenic toxicity

Although the narrow range between deficiency and toxicity of selenium, it is a necessary element to animal life and possesses cancer chemopreventive properties [50]. On the other hand, it is known that arsenic exposure has been associated with a greater production of free radicals and increased oxidative stress that may be reduced by the action of selenoproteins [51]. Some authors conclude that higher selenium dietary intake in humans may reduce the risk of arsenic-related skin lesions [52-54] but selenium recommended daily intake may not be adequate in the presence of physiologic stressors, such as chronic arsenic exposure from drinking water [52].

In experiments carried out with cell lines, it has been demonstrated that arsenic suppresses necrosis induced by selenite in human leukemia cells [55], and selenate and selenite (at nontoxic levels) reduced, but did not eliminate, the acute cytotoxicities of arsenate and, into a lesser extent, of arsenite in fish cells (fibroblastic and epithelioid) [56]. In a recent study with human kidney cells, it has been observed that selenomethionine (SeMet) significantly reduces the cytotoxic effect of inorganic arsenic while inorganic selenium did not. In addition, it has been demonstrated that the presence of SeMet with As^{III} enhances the appearance of phosphorylated proteins, although it can not yet be concluded that these are part of a molecular mechanism for reduced cytotoxicity [57].

Global hypomethylation of DNA is thought to constitute an early event in some cancers and occurs in response to arsenic exposure and/or selenium deficiency, in both in vivo and animal models. In a study with humans, selenium was found to be inversely associated with genomic leukocyte DNA methylation and may influence blood and urinary As concentrations as well as relative proportions of As metabolites in blood [58].

In plants, several experiments conclude that selenite co-exposure prevents against arsenate toxicity. In this way, the detection of Se^{II}-PC_2 complex and Se-cysteinylserine glutathione in *Thunbergia alata*, suggested that the increased toxicity symptoms might have been a

result of the competition of Se^{II} with As^{III} for sulfhydryl groups that are crucial for arsenite detoxification in plant cells [59].

Selenium and mercury

Selenium against mercury toxicity

The antagonistic interaction between mercury and selenium was first reported in 1967 in an experiment with rats treated with mercury chloride and selenite [11]. After that, other experiments confirm again this finding in tuna fish [60] and other animals. Thus, in general, the simultaneous administration of selenite counteracts the negative impacts of the exposure to inorganic mercury, particularly in relation with neurotoxicity, fetotoxicity [61-65] and cardiovascular diseases [66]. However, some authors suggest further studies to deep insight this potential interplay in cardiovascular diseases, especially in relation with fish consumption [67]. Also, quails fed with methylmercury ($MeHg^+$) containing diet survived longer when tuna with high levels of selenium was co-administrated [60]. In humans, selenite and SeMet-dependent protection against mercury induced apoptosis and growth inhibition in human cells has been observed [68]. However, other studies reveals that inorganic selenium is ineffective in preventing most of the $MeHg^+$ induced brain biochemical alterations and that it is also toxic alone [63].

The selenium to mercury molar ratio is very important as described later in the present paper and in this way; it has been observed that Hg in molar excess over Se was a stronger inducer of metallothionein levels in trout [69].

As previously stated, selenium can also counteract the toxicity of methylmercury [70]. In an utero study on mice with $MeHg^+$ and Se, the group that was given the lowest amount of Se and the highest dose of $MeHg^+$ was mostly adversely affected in neurobehavioural outcome [71]. In rodents, antioxidant nutrients as Se and vitamin E in the diet may alter reproductive and developmental toxicity induced by $MeHg^+$ [72]. Selenium has also been shown to reduce mercury bioavailability and trophic transfer in aquatic ecosystems [73].

A great number of studies have been carried out related to the protective influence of the selenocompounds against $MeHg^+$ toxicity, especially selenomethionine (SeMet) [74-76].

Also, exposition of $MeHg^+$ in rats resulted in a significant increase of urinary porphyrins and a decrease in motor activity that was counteracted by SeMet [75].

Selenium and sulphur

Sulphur against selenium toxicity

Selenium and sulphur atoms are chemically very similar and in several organisms, selenate can be metabolized in some degree by enzymes that reduce sulphate [77]. In 1941, Horn and Jones [78] reported the extraction from *Astragalus pectinatus* of a crystalline amino acid complex containing sulphur and selenium that was assigned to a mixture of cystathionine and its selenium analogue. There are several enzymatic processes that do not distinguish selenium from sulphur and therefore may be important in selenium toxicity [79]. In adition, sulphate and other sulphur metabolites as sulphur amino acids can antagonize selenate toxicity in a competitive fashion in green plants [80], *Desulphovibrio desulfuricans* [81,82], yeast [83] and so on. Analysis of *Chlorella vulgaris* cells for selenium indicated that sulphate prevents the absorption of its selenium analogue and that they compete during the absorption process into the cell. Similar relations have been found between L-methionine and its analogue selenium-methionine [77].

Organoselenium compounds are in general, less stable and more reactive than the corresponding sulphur analogues that can be related to the toxicity of selenium when it is incorporated in the place of sulphur in cellular constituents. Studies carried out in algae suggest that when exposed to sub-lethal, but higher than trace concentrations of Se, the algal cells tend to substitute Se for part of their sulphur. Thus, under overloading conditions, Se appears to use the sulphur enzymatic system, while under normal levels, Se specific enzyme systems seem to be in operation, at least in bacterial systems [79].

In the Se-hyperaccumulator plant *A. bisulcatus*, similar trends were found for oxidized and reduced Se and S species but the proportions of them were very different, and although sulphate and selenate reduction were correlated, the results suggests important differences between S and Se biochemistries [84].

Therefore, although Se and S are in the same chemical period, the biological properties of these elements are different in part due to the differences in their oxidation-reduction

properties. In this way, in animals, Se tends to undergo reduction *in vivo* in contrast to sulphur compounds which are required in reduced form (i.e. amino acids). Another important difference is the acid strength of their hydrides, and at physiological pH the selenohydryl group of selenocysteine is in the anionic form while the sulfhydryl group is protonated [85].

Synergistic interactions

Arsenic and selenium

Selenobetaine in the chloride form [$(CH_3)_2Se^+CH_2COOH$] and its methyl ester are extensively metabolized in rat to mono-, di- and trymethylated selenides. Coadministration of selenobetaine with arsenite in rats enhances the tumor-suppressive effect of selenobetaine, although arsenic by its self was totally ineffective. This fact can be related to the inhibition of certain steps of selenium methylation by arsenic suggesting that partially methylated forms of selenium may be directly involved in the anticarcinogenic action of selenium [86].

In cells, selenite, rather than its methylated metabolites, is responsible for the inhibition of arsenite methylation in cultured rat hepatocytes and may stimulate the observed increases in cellular toxicity of inorganic arsenic [87].

Selenium and mercury

Selenium and mercury are also less toxic to animals when administrated simultaneously than individually since selenium may counteract the membrane-destabilizing characteristics of methylmercury and may retard its binding to the cells [88].

In terms of their concentration in the grown medium of carcinoma cells, selenite and methylmercury hydroxide are of equal efficacy in inhibiting DNA synthesis. However, if replication is expressed as a function of the amounts of toxicant bond per cell, sodium selenite is more toxic but selenite is taken up by cells more slowly than methylmercury. In addition, more selenium is needed in the growth medium to bring about the same membrane damage. Best mutual protection appears to exist when selenite and

methylmercury are present in equimolar ratios or when there is a slight excess of selenite [88].

Other interactions

Taking into account the literature, selenium, mercury and arsenic are the most interesting element in relation with its antagonistic and synergistic actions with other elements. However, there are other important interactions between elements species that are less studied. For example, selenium and zinc counteract the toxic effect of cadmium. This interaction has been studied in cultured cells (**Se/Cd**) [89] and rat kidney (**Se/Cd**, **Zn/Cd**) [90]. In addition to Se and Zn, Ca and P seem to be also related to Cd toxicity (**Ca/Cd**, **P/Cd**), especially in connection with nephropathy and osteodystrophy [91].

On the other hand, it has been issued that cadmium and other elements, ameliorated the frequency of selenium-induced cataracts [23] and that tungsten, bismuth, germanium and antimony (as the trichloride administrated in the diet but not as sodium antimoniate) showed partial effect against selenium toxicity (**W/Se**, **Bi/Se**, **Ge/Se**, **Sb/Se**) [21, 33, 92].

Selenium also interacts with nickel and experiments carried out with Winstar rats conclude that the deleterious effects of $NiCl_2$ on the reproduction is antagonized by Na_2SeO_3 (**Se/Ni**) [93]. Interactions between Cd, Cu and Pb in soil urease and dehydrogenase activities have also been described [94]. Important antagonistic interactions between Cu and Zn have been described in relation with health (**Cu/Zn**) [95]. On the other hand, Zn appears to be an antagonist against arsenic-induced abnormal blood lipids in rats (**Zn/As**) [96] and an interesting interaction has been described between molybdenum and copper in diabetes mellitus (**Mo/Cu**) [97].

As previously described in the present paper, there are also many cases of trace elements substitution like sulphur by selenium (**Se/S**). This is the case of tungsten for molybdenum (**W/Mo**) and cadmium for zinc (**Cd/Zn**) in some enzyme families [98,99], and copper for iron (**Cu/Fe**) as an oxygen carrier in some arthropods and molluscs [100]. Undoubtedly, the most surprising interaction recently reported in Science is that related to a bacterium that can grow with arsenic instead of phosphorous suggesting that arsenic can be present in macromolecules as proteins or nucleic acids (**As/P**) [101]. This paper describes

evidences about the presence of arsenate in macromolecules that normally contain phosphate, mainly nucleic acids and proteins. A technical comment later published in the same journal, pointed out that although the previous work is a splendid example for capacity of life to cope with extreme conditions, do not reveal that life can emerge based on other elements different from the canonical [102]. The first study has generated today significant commentary, often as anonymous electronic communications. There are other examples of arsenate substituting by phosphate in the literature [103-104].

These interactions among other described in the literature are summarized in Table 2.

Traffic of chemical species and mechanisms

The study of the trafficking of elements between organs or tissues is mandatory to really understand the effects of the interactions. Table 3 shows several examples of the traffic of chemical species in living organisms. This topic has been issued by several authors but usually only for one element and not for an interaction [105-108].

As/Se

Several experiments in rats demonstrated that arsenic markedly increased the excretion of selenium into the gastrointestinal tract when both arsenite and selenite were injected at subacute dosages, and there were almost corresponding decreases in the amounts of selenium retained in the liver. Also, selenite stimulated the gastrointestinal excretion of arsenic in experiments similar to those in which arsenic stimulated the gastrointestinal excretion of selenium [34]. In this way, selenium deficiency can decrease excretion of inorganic and organic arsenic in animal models [109], and may induce the accumulation of As in mice liver [110]. On the other hand, selenium sufficiency increases excretion of arsenic in pregnant women [111] and mice [109].

In relation with the mechanisms of the As/Se interaction, in 2000, seleno-bis(S-glutathionyl) arsinium ion ($(GS)_2AsSe^-$) was identified by X-ray in the bile of rabbits injected with aqueous selenite and arsenite solutions. This fact can explain that in mammals lethal dose of selenium can be overcome by otherwise lethal dose of arsenic [112].

The investigations about the mechanism of this interaction suggest that the biochemical interaction between As^{III} and Se^{IV} occurs in blood and liver [113]. In addition, the interaction between As^{V} and Se^{IV} is related to the As^{III}-Se^{IV} interaction and the injection of rats with As^{V} and Se^{IV} twice a week for 4 weeks resulted in the formation of a precipitate in the kidney lysosomes, which was characterized as As_2Se [114].

Hg/Se

Mechanisms of the interaction

Until now, several mechanisms have been proposed to explain the interaction between these elements, namely:

(i) Selenium provokes the redistribution of mercury to less sensible organs

(ii) Competition for the same cleavages

(iii) Formation of Hg-Se complexes

(iv) Conversion by selenium of highly toxic Hg species in less toxic forms

(v) Selenium prevents the oxidative stress caused by Hg

It is believed that a 1:1 Hg-Se compound of low biological availability and activity is formed inside the cells, and cell damage is quite low even in the presence of very high Hg concentrations if both elements are mostly in equimolecular ratio. This has been stated in studies with marine mammals [115] and humans exposed to high levels of inorganic mercury [116]. In 1978, experiments with marine organisms suggest a direct Hg-Se linkage and the 1:1 molar ratio of mercury and selenium increment holds true in several species [115] including humans [116]. A tissue with Se:Hg molar ratio higher to 1 is suggested as a threshold for the protective action against Hg toxicity [117]. Different selenium to mercury molar ratios have been observed in some feeding organisms for marine mammals (16:1) [118], tuna fish (15:1 and 3:2 depending of the mercury levels) [119], mink fed (mercury-contaminated fresh water fish, 0.13:1) [120], sardine (2:1) [121], swordfish (17:1) [121], marbled sole [122], and so on. The conclusion derived is that the 1:1 ratio in marine mammals is established within themselves [118]. In addition, in an experiment with mink, low and decreasing Se/Hg ratios with the time of exposure have

been observed in liver and kidney suggesting that it might reflect the low selenium intake in the diet [118].

The possibility that HgSe formation is responsible for the 1:1 molar ratio is supported by experiments which showed two facts: (i) enzimatically digested liver and plasma fractions with a 1:1 molar ratio release mercury and selenium in insoluble forms [123] and (ii) binding to the same plasma protein is preceded with the conversion of selenite to H_2Se in red blood cells [124].

Selenium can also affect the activities of enzymes cleaving the carbon-mercury bond in organic mercury compounds. In this way, experiments with rats show an enhancement of PMA cleavage enzymes in liver when sodium selenite is supplemented in drinking water [125]. It has also been observed that MeHg exposure exerts an inhibitory effect on paronaxe 1 activity that can be counteracted by selenium in humans [126]. Other hypotheses are that: (i) selenium can promote a redistribution of Hg from more sensitive organs (kidney, central nervous system) to less sensitive ones (muscle), that there is competition of Se for the same receptors; (ii) complexes as tiemannite [127] or Se-Hg-S [128] are formed and, (iii) $MeHg^+$ conversion into less toxic forms is promoted and oxidative damage prevented [129]. In addition, Yang et al. proposed the involvement of Se in the demethylation of $MeHg^+$ in the liver to form inorganic and less toxic Hg compounds [130] and later, other authors proposed the same mechanism in octopus [131].

The formation of Hg-Se complexes are commented in detail in the next section.

Biochemical interactions

The ability of different selenium compounds and selenium incorporated in vivo into liver tissue (biological selenium) to form a Hg-Se compound is different and increases in the following order: biological Se < selenomethionine < selenite; thus the protective effect of the selenium compounds against mercury toxicity might follows the same order [132]. Mercury ions can react with thiols (-SH) and selenols (-SeH) that constitute a part of cysteine and selenocysteine and as a consequence they can be incorporated to proteins, prosthetic groups of enzymes and peptides. Mercury ions can also react with selenides (Se^{2-}), and with hydrogen selenide they can form complexes together with glutathione

which can be finally bond to selenoprotein P [133]. This complex ($GSH_5(HgSe)_{100}$) is formed in erythrocytes, then transferred to plasma, and finally bond to selenoprotein P [113, 134].

Similar complexes can be formed in other cells with active selenium metabolism or during degradation of metal bond proteins and metallo(selenoproteins) in lysosomes (biomineralization processes), representing the last step of detoxification [135]. A direct interaction between $MeHg^+$ and the selenol group of GPx (Glutathione peroxidase) has also been reported [64, 136], but to explain the reduced activity of the enzyme after $MeHg^+$ exposure another molecular mechanism has been proposed, based in the fact that cultured cells showed that $MeHg^+$ induced a "selenium-deficient-like" condition, which affects GPx1 synthesis thought a posttranscriptional effect [137].

Mercury vapour shows a similar behaviour to $MeHg^+$ in relation with the facility to penetrate cell membranes where it is oxidized in the biological active form (Hg^{2+}) by catalase. Such in situ generated ions can react with endogenously generated highly reactive Se metabolites, like HSe^-, and consequently a part of the selenium is unavailable for selenoprotein synthesis [133]. Mercury can also provoke the increase of free radicals that induce lipid, protein and DNA oxidation [138-140]

Trafficking

Selenite given simultaneously and in equimolar doses with $HgCl_2$ decreases the content of mercury in kidneys and increases it in other tissues [141], as liver or blood [142], alters the plasma binding of mercury, and both mercury and selenium, become attached to the same protein fraction in 1:1 molar ratio [143]. Exposure of rodents to low doses of $MeHg^+$ induces the accumulation of Hg in target organs [144-146]. In this way, Hg levels after co-exposure to SeMet have been measured in the brain, kidney and liver of fish, aquatic birds, rodents and primates but a number of inconsistencies have been found [147-149].

On the other hand, an increased retention of mercury caused by selenium has been observed in marine mammals that might counteract the positive effect of the decreased intoxification by selenium [118]. The addition of sodium selenite in the feed of chickens induces a decrease in organic mercury bioaccumulation but not in the case of $MeHg^+$

[150]. However, it seems that a threshold concentration of selenium in fish body parts must be reached before a clear protective role of selenium against mercury assimilation becomes noticeable [151]. Also, concurrent exposure to methylmercury chloride and selenite showed the increased selenium accumulation in medaka fish [152]. The influence of mercury on endogenous selenium after lifelong or acute exposure of mercury vapour (Hg^0) has also been studied in man and animals [133]. Besides the well-known Se co-accumulation through formation of Hg-Se complexes, a noticeable Se co(excretion) has been observed in rats (at least at the beginning of exposure) and also, there were higher accumulation rates of Hg in rats with lower basal selenium levels [133]. Since the antagonistic interaction of mercury and selenium is dependent on their species, when Se and Hg are administrated concurrently in the fish diets, different selenium species including selenite, selenate, seleno-DL-cysteine and selenomethionine affect Hg accumulation in different ways [153].

Se/S

The biotransformation of selenate to selenite by two-electron reduction can be performed al least in three different ways: (i) by substituting selenate into the sulphate reduction pathway (reduction by ATP sulfurylase/adenyl sulphate (APS) reductase) [154-155], (ii) by substituting selenate into the nitrate uptake pathway (microbial nitrate reductases can reduce selenate) [156], or (iii) by a specific selenate reductase. In non-hyperaccumulating plants, it seems that selenate reduction occurs by the first indicated path-way and that this is the rate-limiting step in selenate transformation [154, 157-159]. In Se-hyperaccumulating *A. bisulcatus* [157, 160] and *Escherichia coli* [161] selenate reduction is preceded by the activation of selenate by ATP sulfurylase to form 5´-adenylylselenate (APSe) and after, APSe can be nonezymatically reduced by gluthathione. In plants [162] and *E. coli* [161], reduction of selenite to selenide appears to occur nonenzymatically, that may explain why selenite is more readily assimilated by plants to organic forms than is selenate [163-164].

In plants, toxicity is due to substitution of S by Se in cysteine and methionine amino acids with alteration of the tertiary structure and catalytic activity of proteins, and with inhibition of enzymes involved in chlorophyll biosynthesis. The reaction between Se and thiol groups induces losses of efficiency in plants defence systems and increases the

549 reactive oxygen species. In *Senecio scandens*, while selenite induces oxidative stress,
550 selenate does not affect significantly [165].
551
552 In mammals, studies carried out in sheep reveals that more selenium, received as SeMet in
553 the diet, is incorporated into wool and plasma protein when dietary sulphur is limiting
554 [166]. In humans, studies suggest that the replacement of sulphur by selenium in
555 established cancer chemopreventive agents results in more effective chemopreventive
556 analogs [167].
557

558 Analytical strategies and techniques for multi-element
559 biological studies

560
561 Although nowadays there are very powerful analytical techniques and sample preparation
562 procedures for elements speciation and metallomics, biological systems require multi-
563 elemental analytical strategies that make possible the characterization of processes
564 involving interactions, trafficking and multispeciation of key elements. Thus, to deep
565 insight the interactions of elements in biological samples, analytical methods for
566 multispeciation are claimed and the determination of the species from different elements
567 in isolated analysis of a biological sample have several disadvantages, namely: (i) time
568 consumption, (ii) complexity, (iii) cumbersome manipulations of samples, that are usually
569 small in terms of volume or quantity, (iv) loss of information, and so on.
570
571 In relation with the detection, the problem is minor because a number of techniques allow
572 multielemental detection (i.e. inductively coupled plasma with mass spectrometry-ICP-MS
573 or atomic emission spectroscopy-ICP-AES) or the recognition of the isotopic pattern of an
574 element in the molecule (organic mass spectrometry-MS). The difficult task in
575 multispeciation is the chromatographic separation (when used) and sample preparation for
576 the suitable determination of chemical species with different charges and polarities. In this
577 way, mercury species are positively charged, except complexes formed with anionic
578 ligands while selenium species are anions, cations or zwitterions. Therefore, the use of a
579 chromatographic stationary phase combined with a careful selection of the mobile phase is
580 very tricky, but mandatory. In addition, and in contrast to conventional proteomic
581 approaches, sample preparation plays a much more critical role during the determination
582 of metalloproteins in biological tissues due to trace metal contamination issues and the

possibility to compromise the integrity of the metal-protein bond of the metalloproteins of interest. General considerations about drawbacks and solutions related to this kind of analysis have been exhaustively reviewed [5, 168-174].

Undoubtedly, ICP-MS is a valuable technique in this field since it allows: (i) multiisotopic analysis (including non-metals such as S, P, Se), (ii) detection capability, (iii) high sensitivity, (iv) tolerance to matrix and (v) large linearity range. However, the combination with organic mass spectrometry is mandatory for elements speciation in biochemical issues, especially electrospray ionization (ESI) or matrix assisted laser desorption (MALDI). The ESI-MS is better than MALDI-MS for tandem mass spectrometry and on-line couplings with separation techniques (HPLC, CE) while MALDI-MS is recommended for low complex matrices. The main differences between them are that ESI-MS is sensitive to concentration and that both covalent and non-covalent bonds are preserved while MALDI-MS is mass sensitive and only covalent bonds are preserved. Several very interesting reviews and papers consider the use of organic mass spectrometry [175], inorganic mass spectrometry [7, 176,177] and isotopic dilution techniques [178-181] in bioinorganic analytical chemistry.

Several attempts have been made for multispeciation of biological samples and others, using extraction plus chromatographic separation. Simultaneous extraction of arsenic and selenium compounds have been performed with Protease XIV and α-amylase with a later detection by ion chromatography (IC) and ICP-MS [182]; mercury and arsenic multispeciation have been carried out by using two on-line coupled atomic fluorescence detectors or ICP-MS after UV irradiation, cold vapour and hydride generation [183-184]; mercury and selenium species in urine samples have been simultaneously analyzed using reversed-phase HPLC-ICP-MS [185] and by means of a column switching system coupled to ICP-MS that allows also the separation of chiral species [186]. However, the analytical methods developed for multispeciation generally require very experimented analysts and they are limited to a number of species of only two elements. Therefore, a compromise between analytical procedures is usually required for multispeciation which represents nowadays a very difficult task.

Concluding remarks

Until now, only a little is known about the interactions of elements species. Even the essential/toxic character of some elements species remains unclear in some cases and much other new elements species will be discovered in the near future. On the other hand, the species specific essential/toxic character makes very difficult to understand some interactions between elements that are together in a biological system. Also, a lot of information related to the antagonistic or synergistic actions of elements species is available in the literature but some of them are contradictory and in other cases, the conclusions are poorly probed at the experimental level. In addition, taking into account the complexity of biological systems, some important effects of elements interactions might be caused by the interplay of more than two elements that is usually reported. Moreover, the study of the traffic of elements between organs or tissues is mandatory to really understand the effects of the interactions. This topic has been issued by several authors but usually only for element by element and not for a multi-element interaction. Finally, the study of the interactions of elements species in biological systems requires a joint known of biology, chemistry, medicine, biochemistry, molecular biology, nutrition, toxicology, microbiology and genetics that highly complicated the scenery. What is true is that the advances in analytical techniques are claimed in this field.

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References

[1] Williams RJP (2001) Coord Chem Rev 216-217:583-595

[2] Lobinski R, Sabine Becker J, Haraguchi H, Sarkar B (2010) Pure Appl Chem 82:493-504

[3] Szpunar J (2004) Anal Bioanal Chem 378:54-56

[4] Koppenaal DW, Hieftje GM (2007) J Anal At Spectrom 22:855-855

[5] Mounicou S, Szpunar J, Lobinski R (2009) Chemical Society Reviews 38(4):1119-1138

[6] Tainer JA, Roberts VA, Getzoff ED (1991) Curr Opin Biotechnol 2:582-591

[7] Bettmer J, Montes Bayón M, Ruiz Encinar, Fernández Sánchez ML, Fernández de la Campa MR, Sanz Medel A (2009) J Proteomics 72:989-1005

[8] Rensing C, Ghosh M, Rosen BP (1999) J Bacteriol 181:5891-5897

[9] Szpunar J (2005) Analyst 130:442-465

[10] Hill CH, Matrone G (1970) Federation Proceedings 29:1474-1481

[11] Parizek J, Ostadalova I (1967) Experientia 23:142-143

[12] Thiele DJ, Gitlin JD (2008) Nature chemical biology 4(3):145-147

[13] Lippard SJ, Berg JM (1994) Principles of Bioinorganic Chemistry. Mill Valley, California.

[14] Cowan, J.A. (1997). Inorganic Biochemistry. An Introduction, 2nd edition, New York, Willey-VCH.

[15] Escanero JF (1998). In: Cocho JA, Escanero JF, González de Buitrago JM (eds) Elementos Traza: Aspectos Bioquímicos, Analíticos y Clínicos. Barcelona, Sociedad Española de Bioquímica Clínica y Patología Molecular.

[16] Shroeder HA, Nason AP (1971) Clin Chem 17:461-474

[17] Schaumlöffel D, Lobinski R (2005) Int J Mass Spectrom 242:217-223

[18] Berry MJ, Banu L, Chen YY, Mandel SJ, Kieffer JD, Harney JW, Larsen PR (1991) Nature 353(6341):273-276

[19] Moxon AL (1938) Science 88:447-457

[20] DuBois KP, Moxon AL, Olson OE (1940) J Nutr 19:477-482

[21] Moxon AL, Jensen CW, Paynter CR (1947) Proc S Dak Acad Sci 26:21

[22] Hendrick C, Klug HL, Olson OE (1953) J Nutr 51:131-137.

[23] Shearer TR, Anderson RS, Britton JL (1983) Invest Ophthalmol Vis Sci 24:417-423

[24] Shen ZX, Chen GQ, Ni JH, Li XS, Xiong SM, Qiu QY, Zhu J, Tang W, Sun GL, Yang KQ, Chen Y, Zhou L, Fang ZW, Wang YT, Ma J, Zhang P, Zhang TD, Chen SJ, Chen Z, Wang ZY (1997) Blood 89:3354-3360

[25] Bobe P, Chelbi-Alix MK (2008) Md Sci 24:967-971

[26] Perkins C, Kim CN, Fang GF, Bhalla KN (2000) Blood 95:1014-1022

[27] Zhang TC, Cao EH, Li JF, Ma W, Qin JF (1999) Eur J Cancer 35:1258-1263

[28] Ogra I, Bondersson L, Jonsson C (2000) Biochem Biophys Res Commun 277:179-185

[29] Park WH, Seol JG, Kim ES (2000) Cancer Res 60:3065-3071

[30] Schrauzer GN, White DA, McGuinness JE, Xchneider CJ, Bell LJ (1978) Bioinorg Chem 9:245-253

[31] Ip C, Ganther HE (1988) Carcinogenesis 9:1481-1484

[32] Wang ZF, Guo X (2011) Biol Trace Elem Res 140:7-17

681 [33] Moxon AL, DuBois KP (1939) J Nutr 18:477- 482

682 [34] Levander OA, Baumann CA (1966) Toxicol Appl Pharmacol 9:98-105.

683 [35] Rhian M, Moxon AL (1943) J Pharm Exp Therap 78:249-264.

684 [36] Olson OE (1960) Feed Age 10:49-50.

685 [37] Biswas S, Talukder G, Sharma A (1999) Mutat Res 441:155-160

686 [38] Moxon AL (1941) Proc South Kadota Acad Sci 21:34-36

687 [39] Moxon AL, Rhian M, Anderson HD, Olson OE (1944) J Animal Sci 3:299-309

688 [40] Stanley Jr TR, Spann JW, Smith GJ, Rosscoe R (1994) Arch Environ Contam Toxicol 26:444-451

689 [41] Thapar NT, Guenthner E, Carlson CW, Olson OE (1969) Poultry Sci 48:1987-1993

690 [42] Moxon AL, Wilson WO (1944) Poultry Sci 22:149-151.

691 [43] Krista LM, Carlson CW, Olson OE (1961) Poultry Sci 40:1365-1367

692 [44] Wuyi W, Linsheng Y, Shaofan H, Jianán T, Hairong L (2001) Curr Sci 81:1215-1218

693 [45] Yang L, Wang W, Hou S, Peterson PJ, Williams WP (2002) Environ Geochem Health 24:359-374

694 [46] Wang CT, Chang WT, Huang CW, Chou SS, Lin CT, Liau SJ, Wang RT (1994) Eur J Clin Chem Clin Biochem
695 32:107-111

696 [47] Wang CT (1996) Eur J Clin Chem Clin Biochem 34:493-497

697 [48] Horng CJ, Lin SR (1997) Talanta 45:75-83

698 [49] Wang CT, Chang WT, Huang KC, Wang RT (1997) Anal Sci 13:497-500

699 [50] Brown KM, Arthur JR (2001) Public Health Nutrition 4:593-599

700 [51] Shi H, Shi X, Liu KJ (2004) Moll Cell Biochem 255:67-78

701 [52] Chen Y, Hall M, Graziano JH, Slavkovich V, van Geen A, Parvez F, Ahsan H, (2007) Cancer Epidemiol
702 Biomarkers Prev 16:207-213

703 [53] Spallholz JE, Mallory BL, Rhaman MM (2004) Sci Total Environ 323:21-32

704 [54] Verret WJ, Chen Y, Ahmed A, Islam T, Parvez F, Kibriya MG, Graziano JH, Ahsan HJ (2005) Occup Environ
705 Med 47:1026-1035

706 [55] Zeng H, Biol (2001) Trace Elem 83:1-15

707 [56] Babich H, Martin AN, Borefreund E (1989) Toxicol Lett 45:157-164

708 [57] Alp O, Zhang Y, Merino EJ, Caruso JA (2011) Metallomics 3:482-490

709 [58] Pilsner JR, Hall MN, Liu X, Ahsan H, Llievski V, Slavkovich V, Levy D, Factor-Litvak P, Graziano JH, Gamble
710 MV (2011) Environ Health Perspect 119:113-118

711 [59] Bluemlein K, Klimm E, Raab A, Feldmann J (2009) Environ Chem 6:486–494

712 [60] Ganther HE, Goudie C, Kopecky MJ, Wagner P, Oh SH, Hoekstra WG (1972) Science 172:1122-1124

713 [61] Raymond LJ, Ralston NVC (2004) Seychelles Med Dent J 7:56-60

714 [62] Choi AL, Budtz-Jorgensen E, Jorgensen PJ, Steuerwald U, Debes F, Weihe P, Grandjean P (2008) Environ. Res.
715 107:45-52

716 [63] Glaser V, Nazari EM, Müller YMR, Feksa L, Wannmacher CMD, Rocha JBT, Bem AFD, Farina M, Latini A
717 (2010) Inter J Develop Neurosci 28:631-637

718 [64] Farina M, Rocha JBT, Aschner M (2011) Life Sci 89:555-563

719 [65] Yin Z, Lee E, Ni M, Jiang H, Milatovic D, Rongzhu L, Farina M, Rocha JBT, Aschner M (2011) Neurotoxicol
720 32:291-299

721 [66] Yoshizawa K, Rimm EB, Morris JS, Spate VL, Hsieh CC, Spiegelman D, Stampfer, MJ, Willet WC (2002) N Engl
722 J Med 347:1755-1760

723 [67] Park K, Mozaffarian D (2010) Curr Atheroscler Rep 12:414-422

724 [68] Frisk P, Wester K, Yaqob A, Lindh U (2003) Biol Trace Elem Res 92:105-114

725 [69] Sormo E, Ciesielki TM, Overjordet IB, Lierhagen S, Eggen GS, Berg T, Jenssen BM, (2011) Environ Sci Technol
726 45:6561-6566

727 [70] Imura N, Naganuma A (1991) In: Suzuki T (ed) Advances in mercury toxicology. Plenum, New York

728 [71] Watanave C, Yin K, Kasanuma Y, Satoh H (1999) Neurotoxicol Teratol 21:83-88

729 [72] Beyrouty P, Chan HM, (2006) Neurotoxicol Teratol 28:49-58

730 [73] Kehrig H do A, Seixas TG, Palermo EA, Baeta AP, Castelo-Branco CW, Malm O, Moreira I (2009) Environ Sci
731 Pollut Res 16(1):10-24

732 [74] Weber DN, Connaughton V.P, Dellinger JA, Klemer D, Udvadia A, Carvan III MJ (2008) Physiol Behav 93:250-
733 260

734 [75] Dos Santos APM, Mateus ML, Carvalho CML, Batoréu MCC, (2007) Toxicol Lett 169:121-128

735 [76] Wen-Xiong W, Wong RSK, Wang J, Yu-Fong Y (2004) Aquat Toxicol 68:39-50

736 [77] Shrift A (1954) Amer J Bot 41:223-230

737 [78] Horn JM, Jones DB (1941) J Biol Chem 139:649-660

738 [79] Stadtman TC (1980) Ann Rev Biochem 49:93-110

739 [80] Hurd-Karrer AM (1938) Amer J Bot 25:666-675

740 [81] PostGate J (1949) Nature 164:670-671

741 [82] PostGate J (1952) J Gen Microbiol 6:128-142

742 [83] Fels IG, Cheldelin VH (1949) Arch Biochem 22:402-405

743 [84] Pickering IJ, Wright C, Bubner B, Ellis D, Persans MW, Yu EY, George GN, Prince RC, Salt DE (2003) Plant
744 Physiol 131:1460-1467

745 [85] Channa Reddy C, Massaro EJ (1983) Funsam Appl Toxicol 3:431-436

746 [86] Ip C, Ganther HE (1990) Cancer Res 50:1206-1211

747 [87] Walton FS, Waters SB, Jolley SL (2003) Toxicol 16:261-265

748 [88] Gruenwedel DW (1984) Adv Exper Medicine and Biol 177:229-240

749 [89] Frisk P, Yaqob A, Lindh U (2002) Sci Total Envirom 296:189-197

750 [90] Messaoudi I, El Heni J, Hammouda F, Said K, Kerkeni A (2009) Biol Trace Elem Res 130:152-161

751 [91] Sonne-Hansen C, Dietz R, Leifsson PS, Hyldstrup L, Riget EF (2002) Sci Total Environ 295:167-181

752 [92] Moxon A, Rhian M (1943) Physiol Rev 23:305-337

753 [93] Kaela R, Kakela A, Hyvarinen H (1999) Comparat Biochem Physiol Part C 123:27-37

754 [94] Chaperon S, Sauvé S (2008) Ecotoxicol Environ Safety 70:1-9

755 [95] Bremner I, Beattie JH (1995) Proceedings of the Nutrition Society 54:489-499

756 [96] Fang LY, Wei JZ, Yang J, Liu ZY, Li JY (2006) Chinese J Epidemiol 25:9-11

757 [97] Rodríguez-Flores C, Preciado-Puga M, Wrobel K, Garay-Sevilla MAE, Wrobel K (2011) Diabetes Res Clin Pract
758 91(3):333-341.

759 [98] Hille R (2002) Trends Biochem Sci 27:360-367

760 [99] Lane T, Morel F (2000) Proc Natl Acad Sci USA 97:4627-4631

761 [100] Jameson G, Ibers J (2007) In: Bertini I, Gray H, Stiefel I, Valentine J (eds) Biochemical Inorganic Chemistry:
762 Structure and Reactivity, University Science Books, Sausalito

763 [101] Wolfe-Simon F, Switzer-Blum J, Kulp TR, Gordon GW, Hoeft SE, Pett-Ridge J, Stolz JF, Webb SM, Weber PK,
764 Davies PCW, Anbar AD, Oremland RS (2011) Science 332:1163-1166

765 [102] Schoepp-Cothenet B, Nitschke W, Barge LM, Ponce A, Russell MJ, Tsapin AI (2011) Science 332:1149-d

766 [103] Rosen BP, Ajees AA, McDermott TR (2011) Bioessays 33:350-357

767 [104] Rosen BP, Ajees AA, McDermott TR (2011) Bioessays 33:350-357 and references therein

768 [105] Finney1 LA, O'Halloran TV (2003) Science 300:931-936

769 [106] Banci1 L, Bertini1 I, Ciofi-Baffoni1 S, Finney LA, Outten CE, O'Halloran TV (2002) J Mol Biol 323:883–897

770 [107] Huffman DL, O'Halloran TV (2000) The Journal of Biological Chemistry 275(25):18611–18614

771 [108] O'Halloran TV, Cizewski-Culotta V (2000) The Journal of Biological Chemistry 275(33):25057–25060

772 [109] Miyazaki K, Watanabe C, Mori K, Yoshinda K, Ohtsuka R (2005) Toxicol 208: 357-365

773 [110] Kenyon EM, Hughes MF, Levander OA (1997) Environ Toxicol Pharmacol 51:279-299

774 [111] Christian WJ, Hopenhayn C, Centeno JA, Todorov T (2006) Environ Res 100:115-122

775 [112] Gailer J, George GN, Pickering IJ, Prince RC, Ringwald SC, Pemberton JE, Glass RS, Younis HS, DeYoung DW,
776 Aposhian HV (2000) J Am Chem Soc 122:4637-4639

777 [113] Gailer J (2007) Coord Chem Rev 251:234-254

778 [114] Berry JP, Galle P (1994) J. Submicrosc Cytol Pathol 26:203-210

779 [115] Koeman H, van de Ven WSM, de Goeij JJM, Tjioe PS, van Haaften JL (1975) Sci Total Environ 3:279-287

780 [116] Kosta L, Byrne AR, Zelenko V (1975) Nature 1975 254:238-239

781 [117] Peterson SA, Ralston NVC, Whanger PD, Oldfield JE, Mosher WD (2009) Environ Bioindic 4: 318-334

782 [118] Beijer K, Jernelov A (1978) Environ Health Perspectives 25:43-45

783 [119] Gather HE, Goudie C, Sunde ML, Kopicky MJ, Wagner P, Oh SH, Hoekstra Wg (1972) Science 175:1122-1124

784 [120] Jernelov A, Johansson A, Sorenson L, Svenson A (1976) Toxicol 6:315-321

785 [121] Cabañero AI, Madrid Y, Cámara C (2007) Biol Trace Elem Res 119:195-211

786 [122] Yamashita Y, Amlund H, Suzuki T, Hara T, Hossain MA, Yabu T, Touhata K, Yamashita M (2011) Fish Sci
787 77:679-686

788 [123] Naganuma A, Imura N (1981) Pharmacol Biochem Behav 15:449-454

789 [124] Gasiewicz TA, Smith JC (1978) Chem Biol Interact 23:171-183

790 [125] Fang C (1974) Res Commun Chem Pathol Pharmacol 9:579-582

791 [126] Ayotte P, Carrier A, Ouellet N, Boiteau V, Abdous B, Sidi EA, Chateau-Degat ML, Dewailly E (2011) Environ
792 Health Perspect 119:1077-1083

793 [127] Das K, Jacob V, Bouquegneau JM (2002) Comp Biochem Physiol Part C 131:245-251

794 [128] Gailer J, George GN, Pickering IJ, Madden S, Prince RC, Yu EY, Denton HS, Younis HS, Aposhian HV (2000)
795 Chem Res Toxicol 13:1135-1142

796 [129] Hoffman DJ, Heinz GH (1998) Environ Toxicol Chem 17:161-166

797 [130] Yang DY, Chen YW, Gunn JM, Belzile N (2008) Environ Rev 16:71-92

798 [131] Raimundo J, Vale C, Canario J, Branco V, Moura I (2010) Environ Pollut 158:2094-2100

799 [132] Magos L, Clarkson TW, Sparrow S, Hudson AR (1987) Arch Toxicol 60:422-426

800 [133] Falnoga I, Tusek-Znidaric M (2007) Biol Trace Elem Res 119:212-220

801 [134] Yoneda S, Suzuki KT (1997) Toxicol Appl Pharmacol 143:274-280

802 [135] Dansher G, Stoltenberg M (2006) Prog Histochem Cytochem 41, 57-140

803 [136] Pohaska JR, Ganther HE (1977) Chem Biol Interact 16:155-167

804 [137] Usuki F, Yamashita A, Fujimura M (2011) J Biol Chem 286:6641-6649

805 [138] Clarkson TW (1997) Crit Rev Clin Lab Sci 34:369-464

806 [139] Lund BO, Miller MD, Woods JS (1993) Biochem Pharmacol 45:2017-2024

807 [140] Perottoni J, Rodrigues OED, Paixao MW, Zeni G, Lobato LP, Braga AL, Rocha JBT, Emanuelli T (2004) Food
808 Chem Toxicol 42:17-28

809 [141] Eybl V, Sykora J, Mertl F (1969) Arch Toxicol 25:296-305

810 [142] Su L, Wang M, Yin ST, Wang HL, Chen L, Sun LG, Ruan DY (2008) Ecotoxicol Environ Diet 70:483-489

811 [143] Burk RF, Foster KA, Greenfield PM, Kiker KW (1974) Proc Soc Exp Biol Med 145:782-785

812 [144] Friberg L, Mottet NK (1989) Biol Trace Elem Res 21:201-206

813 [145] Berntssen MGH, Hylland K, Lundebye AK (2004) Food Chem Toxicol 42:1359-1366

814 [146] Harry GJ, Harris WM, Burka LT (2004) Toxicol Lett 154:183-189

815 [147] Bjerregaard P, Andersen BW, Rankin JC (1999) Aquat Toxicol 45:171-180

816 [148] Cuvin-Aralar MLA, Furness RW (1991) Ecotoxicol Environ Safety 21:348-364

817 [149] Heinz GH, Hoffman D (1998) Environ Toxicol Chem 17:139-145

818 [150] Cabañero AI, Madrid Y, Cámara C (2005) J Agric Food Chem 53:2125-2132

819 [151] Yang DY, Ye X, Chen YW, Belzile N (2010) Sci Total Environ 408:1676-1683

820 [152] Liao CY, Zhou QF, Fu JJ, Shi JB, Yuan CG, Jiang GB (2007) Environ. Toxicol 22:69-77

821 [153] Dang F, Wang WX (2011) Environ Sci Technol 45:3116-3122

822 [154] Shrift A (1969) Plant Physiol 20:475-495

823 [155] Setya A, Murillo M, Leustek T (1996) Proc Natl Acad Sci USA 93:13383-13388

824 [156] Sabaty M, Avazeri C, Pignol D, Vermeglio A (2001) Appl Environ Microbiol 143:1181-1189

825 [157] Shaw WH, Anderson JW (1974) Biochem J 139:37-42

826 [158] Brunell JN (1981) Plant Physiol 67:316-324

827 [159] Pilon-Smits EAH, Hwang S, Lytle CM, Ahu Y, Tai JC, Bravo RC, Chen Y, Leustek T, Terry N (1999) Plant
828 Physiol 119:123-132

829 [160] Shaw WH, Anderson JW (1972) Biochem. J 127:237-247

830 [161] Muller S, Heider J, Bock A (1997) Arch. Microbiol 168:421-427

831 [162] Ng BH, Anderson JW (1978) Phytochemistry 17:2069-2074

832 [163] Shrift A, Virupaksha TK (1965) Biochim Biophys Acta 100:65-75

833 [164] de Souza MP, Pilon-Smits EA, Lytle CM, Hwang S, Tai J, Honma TS, Yeh L, Terry N (1998) Plant Physiol
834 117:1487-1494

835 [165] Paciolla C, De Leonardis S, Dipierro S. (2011) Plant Biosystems 145:253-259

836 [166] White CL (1980) Aust J Biol Sci 33:699-707

837 [167] Sanmartín C, Plano D, Font M, Palop JA (2011) Current Cancer Drug Targets 11:496-523

838 [168] Manley SA, Gailer J (2009) Expert Rev Proteomics 6:251-265

839 [169] Manley SA, Byrns S, Lyon AW, Brown P, Gailer J (2009) J Biol Inorg Chem 14:61-74

840 [170] Michalke B, Berthele A, Mistriotis P, Ochsenkuehn-Petropoulou M, Halbach S (2007) J Trace Elem Med Biol
841 21(S1):4-9

842 [171] da Silva MAO, Sussulini A, Arruda MAZ (2010) Expert Rev Proteomics 7:387-400

843 [172] Zeini Jahromi E, Gailer J (2010) Metallomics 2:460-468

844 [173] Pei KL, Gailer J (2009) Metallomics 1:403-408

845 [174] Gómez-Ariza JL, Zeini-Jahromi E., González-Fernández M, García-Barrera T, Gailer J (2011) Metallomics 3:566-
846 577

847 [175] Lobinski R, Schaumloffel D, Szpunar J (2006) Mass Spectrom Rev 25:255-289 and references therein

848 [176] Mounicou S, Szpunar J, Lobinski R (2010) European Journal of Mass Spectrometry 16(3):243-253 and references
849 therein

850 [177] Bettmer J., Montes Bayón, M., Ruiz Encinar, J., Fernández Sánchez, M.L., Fernández de la Campa, M.d.R., Sanz
851 Medel, A. 2009 Journal of Proteomics 72 (6), pp. 989-1005 and references therein

852 [178] Schaumloffel D, Lobinski R (2005) Int J Mass Spectrom 242:217-223 and references therein

853 [179] Rodríguez-González P, García Alonso JI (2010) Journal of Analytical Atomic Spectrometry 25(3):239-259

854 [180] Rodríguez-González P, Marchante-Gayón JM, García Alonso JI, Sanz-Medel A (2005) Spectrochimica Acta - Part
855 B Atomic Spectroscopy 60(2):151-207

856 [181] Rodríguez-González P, Ruiz Encinar J, García Alonso JI, Sanz-Medel A (2003) Analyst 128 (5):447-452

857 [182] Tsai CY, Jiang SJ, (2011) Anal Sci 27(3):271-276

858 [183] Gómez-Ariza JL, Lorenzo F, García-Barrera T (2005) Anal Bioanal Chem 382:485–492

859 [184] Gómez-Ariza JL, Lorenzo F, García-Barrera T (2004) Journal of Chromatography A 1056:139–144

860 [185] Li YF, Chen C, Li B, Wang Q, Wang J, Gao Y, Zhao Y, Chai Z (2007) J Anal At Spectrom 22:925-930

861 [186] Moreno F, García-Barrera T, Gómez-Ariza JL (2010) Analyst 135:2700-2705

862 [187] Kolachi NF, Kazi TG, Wadhwa SK, Afridi HI, Baig JA, Khan S, Shah S (2011) Sci Total Environ 409:3092-3097

863 [188] Palmer IS, Thiex N, Olson OE (1983) Nutr Rep Int 27:249-258

864 [189] Pisciotto PT, Graziano JH (1980) Biochimica et Biophysica Acta 628:241-243

865 [190] Holmberg RE, Ferm VR (1969) Arch. Environ. Health 18:873-877

866 [191] Chung AS Maines MD (1982) Biochem Pharmacol 31:3093-3100

867 [192] Parizek J, Benes I, Ostadolova I, Babicky A, Benes J, Lener J. (1969) Physiol Bohemoslov 18:95-103

868 [193] Miura K, Imura N (1982) J Appl Toxicol 2:145-150

869 [194] Glickstein N (1978) Mar Biol 49:113-117

870 [195] Cabañero AI, Madrid Y, Cámara C (2005) J Anal At Spectrom 20:847-855

871 [196] Hill CH (1974) J Nutr 104:593-598

872 [197] P Frisk, Yaqob A, Nilsson K, Lindh U (2001) Biol Trace Elem Res 80:251-268

873 [198] Weng-Xiong W, Wong RSK, Wang J, Yen YF (2004) Aquat Toxicol 68:39-50

874 [199] Falgona I, Tusek-Znidaric M (2007) Biol Trace Elem Res 119:212-220

875 [200] Nordberg GF, Jin T, Hong F, Zhang A, Buchet JP, Bernard A (2005) Toxicol Appl Pharmacol 206:191-197

876 [201] Yáñez L, Carrizales L, Zanatta MT, Mejía JJ, Batres L, Diaz-Barriga F (1991) Toxicology, 67:227-234

877 [202] Modi M, Kaul RK, Kannan GM, Flora SJS (2006) Journal of Trace Elements in Medicine and Biology 20:197–
878 204

879 [203] Suwalsky M, Rivera C, Villena F, Sotomayor CP, Jemiola-Rzeminskad M, Strzalkad K (2007) Biophysical
880 Chemistry 127:28–35

881 [204] Kasprzak KS, Poirier LA (1985) Toxicology 34:221-230

882 [205] Meinelt T, Playle RC, Pietrock M, Burnison BK, Wienke A, Steinberg CEW (2001) Aquatic Toxicology 54:205–
883 215

884 [206] Adiele RC, Stevens D, Kamunde C (2010) Aquatic Toxicology 96:319–327

885 [207] Chakravarty B, Srivastava S (1997) Agric Ecosys Environ 61:45-50

886 [208] Chaoui A, Ghorbal MH, Ferjani EE (1997) Plant Science 126:21–28

887 [209] Qiu RL, Thangavel P, Hu PJ, Senthilkumar P, Yinga RR, Tang YT (2011) Journal of Hazardous Materials
888 186:1425–1430

889 [210] Rainbow PS, Amiard-Triquet C, Amiard JC, Smith BD, Langston WJ (2000) Aquatic Toxicology 50:189–204

890 [211] Rogalska J, Pilat-Marcinkiewicz B, Brzóska MM (2011) Chemico-Biological Interactions 193:191–203

891 [212] Scheuhammer AM, Onosaka S, Rodgers K, Cherian MG (1985) Toxicol 36:101-108

892 [213] Rogalska J, Brzóska MM, Roszczenko A, Moniuszko-Jakoniuk J (2009) Chemico-Biological Interactions
893 177:142–152

894 [214] Cherif J, Mediouni C, Ammar WB, Jemal F (2011) Journal of Environmental Sciences 23:837–844

895 [215] Herkovits J, Perez-Coll CS (1995) Biol Trace Elem Res 49:171-175

896 [216] Belmonte N, Rivera O, Herkovits J (1989) Bull Environ Contam Toxicol 43:107-110

897 [217] Pelgrom SMGJ, Lamers LPM, Lock RAC, Balm PHM, Bonga SEW (1995) Environmental Pollution 90:415-423

898 [218] Komsta-Szumska E, Chmielnicka J (1983) Toxicology Letters 17:349-354

899 [219] Flora SJS, Behari JR, Ashquin M, Tandon SK (1982) Chem.-Biol. Interactions 42:345-351

900 [220] Mukherjee A, Sharma A, Talukder G (1988) Toxicology Letters 41:23-29

901 [221] Sidhu M, Sharma M, Bhatia M, Awasthi YC, Nath R (1993) Toxicology 83:203-213

902 [222] Bell RR, Soliman MRI, Early JL (1990) Toxicology 65:161-168

903 [223] Caballero Aráuz IL, Afton S, Wrobel K, Caruso JA, Gutiérrez Corona JF, Wrobe K (2008) J Hazard Mat
904 153:1157–1164

905 [224] Sugawara N, Sugawara C (1984) J Appl Biochem 6:199-204

906 [225] Messaoudi I, Banni M, Saïd L, Saïd K, Kerkeni A (2010) Chemico-Biological Interactions 188:94–101

907 [226] Early JL Jr, Schnell RC (1981) Toxicol Appl Pharmacol 58:57-67

908 [227] Prohaska JR, Mowafy M, Ganther HE (1977) Chem-Bio. Interactions 18:253-265

909 [228] Liu Y, Cai YQ (2007) Toxicology in Vitro 21:677–684

910 [229] Newairy AA, El-Sharaky AS, Badreldeen MM, Eweda SM, Sheweita SA (2007) Toxicology 242:23–30

911 [230] Hietanen E, Aitio A, Koivusaaei U, Kilpiö J, Nevalainen T, Närhi M, Savolainen H, Vainio H (1982) Toxicology
912 25:113-127

913 [231] Orisakwe OE, Afonne OJ, Nwobodo E, Asomugha L, Dioka CE (2001) European Journal of Obstetrics &
914 Gynecology and Reproductive Biology 95:92-96

915 [232] Gale TF (1973) Environmental Research 6:95-105

916 [233] Day FA, Funk AE, Brady FO (1984) Chem Biol Interactions 50:159—174

917 [234] Irato P, Sturniolo GC, Giacon G, Magro A, D'Inca R, Mestriner C, Albergoni V (1996) Biol Trace Elem Res
918 51:87-96

919 [235] Irato P, Albergoni V (2005) Chemico-Biological Interactions 155:155–164

920 [236] Filipe PM, Fernandes AC, Manso CF (1995) Biol Trace Elem Res 47:51-56

921 [237] Ramírez-Cárdenas L, Brunoro Costa NM, Pinheiro Reis F (2005) Nutrition Research 25:79–92

[238] Gambling L., Dunford S, McArdlea HJ (2004) Journal of Nutritional Biochemistry 15:366–372

[239] Pimentel JL, Greger L, Cook ME, Stahl JL (1992) J Nutr Biochem 3:140-145

[240] Blanusa M, Prester L, Radić S, Kargacin B (1994) Environ Health Perspect 102:305–307

[241] Khadelwal S, Flora SJS, Tandon SK,(1990) Chem BioL Interactions, 75:341 – 347

[242] Rungy J (1987) Toxicology 45:135—142

[243] Serafín MAH, Wrobel K, Gutiérrez CJF, Wrobel K (2007) Mycological Research 111:626–632

[244] Khayat A, Dencker L (1984) Chem Biol Interactions 50:123--133

[245] Levander OA, Argrett LC (1969) Toxicol Appl Pharmacol 14:308-314

[246] Pelgrom SMGJ, Lamers LPM, Lock RAC, Balm PHM, Bonga SEW (1995) Environmental Pollution 9 415-423

[247] Hall AC, Young BW, Bremner I (1979) J Inorg Biochem 11:57-66

[248] Blalock TL, Dunn MA, Cousins RJ (1988) J Nutr 118 :222-228

[249] Bremner I, Young BW, Mills CF (1976) Brit J Nutr 36:551-561

[250] Agarwal R, Behari JR (2007) Industrial Health 45:388-395

[251] Chen RW, Whanger PD, Weswig PH (1974) Pharmacol Res Commun 6:571-579

[252] Cuvin-Aralar MLA, Furness RW (1990) Bull Environ Contam Toxicol 45:775-782

[253] Sheline J, Schimdt-Nielsen B (1975) Vernberg F (ed) Symposium. Milford, CN.

[254] Hansen JC, Kristensen P, Al-Masri SN (1981) Nord Vet Med 33:57-64

[255] Potter S, Matrone G (1974) J Nutr 104:638-647

[256] Johnson S, Pond WG (1974) Nutr Rep Int 9:135-147

[257] Miura K, Mori R, Imura N (1981) Ecotoxicology and Environmental Safety 5:351-367

[258] Björkman L, Mottet K, Nylander M, Vahter M, Lind B, Friberg L (1995) Arch. Toxicol 69:228-234

[259] Magos L, Webb M, Hudson AR (1977) Arch Toxicol 38:201-207

[260] Brzeznicka EA, Chmielnicka J (1985) Environ Health Perspect 60:423-431

[261] Yamane Y, Fukino H, Aida Y, Imagawa M (1977) Chem Pharmacol Bull 25:2831-2837

[262] El-Begearmi MM, Sunde ML, Ganther HE (1977) Poultry Sci 56:313-322

[263] Glynn AW, Lind Y(1995) Pharmacol Toxicol 77:41-47

[264] Sell JL, Horani FG (1976) Nutrition Reports International 14:439-447

[265] Emerick RJ, Palmer IS, Carlson CW, Nelson RA (1976) Fed Proc 35:577-582

[266] Welsh SO, Soares JH (1974) Fed Proc 33:660

[267] Stoewsand GS (1974) Bull Environ Cantam Toxicol 11:152-156

[268] Ansari MS, Britton WM (1974) Poultry Sci 53:1134-1137

[269] Seppanen K, Laalikainen R, Salonen JT, Kantola M, Lötjönen S, Harri M, Nüurminen L, Kaikkomem J, Nyyssönen K (1998) Biol Trace Elem Res 65:197-210

[270] Ralston NVC, Ralston CR, Blackwell JL, Raymond JL (2008) Neurotoxicol 29:802-811

[271] Kosutzka E, Pribilincova J, Ledec M, Maretta M (2002) Acta Veterinaria (Beograd) 52:355-360

TABLES

Table 1. Main antagonistic and synergistic interactions of elements species

INTERACTION		LIVING ORGANISM	EFFECT	REFERENCES
Interaction of selenium and arsenic containing species				
Se_{total}/As_{total}	A	Humans	DNA hypomethylation/cancer	58
	A	Humans	Se reduces the risk of As-related skin lesions and cancer	52-54
SeO_3^{2-}/iAs(III)	A	Rats	As prevents lethal liver damage caused by Se	19
	A	Rats	As prevents Se induced cataracts	23
	A	Humans	Skin lesion/ Skin cancer	187
	A	Humans cells	As-induced apoptosis is prevented by Se	32
	A	Mice	As prevents carcinogenic effect of Se	30
	A	Rats	As prevents carcinogenic effect of Se	31
	A	Rats	As protection against the toxicity of Se (growth, mortality rate, pathological condition of the livers)	20, 33, 188
	A	Rats	As induces mucosal glutathione synthesis that can explain its protective effect against Se	189
	A	Dogs	Se induces sub-normal growth and restricted food intake antagonized by As	35
	A	Cattle	Protective effect of As in Se toxicity	36
	A	Hogs	Protective effect of As in Se toxicity	38
	A	Steers	Protective effect of As in Se toxicity	39
	A	Mallards	Protective effect of As in Se toxicity	40
	A	Poultry	Protective effect of As in Se toxicity	41-43
	A	Mice	Se prevents the As-induced cytotoxicity	37
	S	Cells	Se inhibits As methylation increasing the toxicity	87
	A	Fish cells	Se reduces the acute cytotoxicities of As	56
SeO_3^{2-}/AsO_4^{3-}	A	Mice	Se decreases the ratio of organic/inorganic As	110
	A	Hamsters	Se decreases arsenic methylation	190
	A	Plants	Se prevents against As toxicity	59

SeO_4^{2-}/AsO_4^{3-}	A	Fish cells	Se reduces the acute cytotoxicities of As	56
	S	Plants Cells	Se increases As toxicity	59
SeMet/iAs(III)	A	Humans cells	Se reduces the As induced cytotoxicity	57
SeBet/iAs(III)	S	Rats	Coadministration enhances the tumour-suppressive effect of Se	86
Interaction of selenium and mercury containing species				
Se_{total}/Hg_{total}	A	Humans	Se prevents Hg induced cardiovascular diseases	66
	A	Brown trout	Se inhibits the induction of metallothionein level caused by Hg	69
$Se_{total}/MeHg^+$	A	Humans	Se inhibits Hg induced neurotoxicity	62
	A	Octopus	Demethylation of $MeHg^+$ by Se	131
	A	Humans	Se inhibits Hg induced cardiovascular diseases	67
	A	Rats	Se may alter $MeHg^+$ reproductive and developmental toxicity	72
SeO_3^{2-}/Hg^{2+}	A	Rats	Se antagonizes Hg induced intestinal necrosis	11
	A	Rats	Se prevents against Hg renotoxicity	132
	A	Rats	Se antagonizes the Hg induced inhibition of the enzymes of glutathione metabolism	191
	A	Tuna	Se prevents the Hg induced intestinal necrosis	60
	A	Mice	Se prolong the half-life of Hg exposed animals	192
	A	Rats	Se changes the subcellular Hg distribution	193
	S	Oysters	High levels of Se increased Hg toxicity	194
$SeO_3^{2-}/MeHg^+$	A	Chickens	Se changes the subcellular and pattern distribution of Hg	195
	A	Medaka fish	Se protects against Hg induced histopathological changes	152
SeO_2/Hg^{2+}	A	Chicks	Se toxicity is decreased by Hg	196
$SeO_4^{2-}/MeHg^+$	A	Mice	Se protects against Hg induced neurotoxicity	63
	S	Humans cells	Se and Hg inhibit DNA synthesis	88
	A	Humans cells	Protection against $MeHg^+$ toxicity	197
	A	Fish	Se affects the Hg bioaccumulation and toxicity	153
$SeMet/Hg^{2+}$	A	Rats	Se inhibits the effects of Hg in organic activities	143
	A	Humans cells	Se prevents Hg induced apoptosis	68
$SeMet/MeHg^+$	A	Rats	Se prevents Hg induced porphyrinuria	75

	A	Zebrafish	Se reduces visual deficits due to developmental Hg exposures	74
	A	Diatoms and mussels	Se significantly inhibits the uptake of Hg	198
SeProt/ Hg^0	A	Humans	Hg detoxification by Se	199
SeProt/$MeHg^+$	A	Humans cells	Hg induces a “selenium-deficient-like” condition	137
	A	Mice	Hg affects the activities of selenoenzymes	71
Interaction of selenium and sulphur containing species				
Se species/S species	A	Bacterial systems	Se appears to use the sulphur enzymatic system	79
	A	Se-hyperaccumulator plant	Important differences between S and Se biochemistries	84
SeO_3^{2-}/S compounds	A	Plants	The reaction between Se and thiol groups induces losses of efficiency in plants defence systems and increases the reactive oxygen species	165
SeO_4^{2-}/S compounds	A	Microalgae	Antimetabolite action of Se on the growth	77
	A	Green Plants	Sulphur metabolites antagonized Se toxicity	80
	A	Yeast	Sulphur antagonized Se toxicity	83
SeMet/sulphur compounds	A	Sheep	More Se is incorporated into wool and plasma protein when dietary S is limiting	166

A: antagonism; S: synergism; SeMet: selenomethionine; SeProt: selenoproteins; $MeHg^+$: methylmercury; SeBet: selenobetaine; iAs(III) : AsO_3^{3-} or AsO_2^-

Table 2. Other interactions between elements species

INTERACTION		LIVING ORGANISM	EFFECTS	REFERENCES
As/Cd	S	Humans	More pronounced renal toxicity than exposure to each of the agents alone	200
	S	Rats	They induce lipid peroxidation, glutathione and metallothionein, and redistribution of essential elements	201
As/Zn	A	Rats	Zn counteracts the As-induced abnormal blood lipids	96
	A	Rats	Zn prevents arsenic-induced tissue oxidative stress	202
As/P	A	Human cells	As perturbs the phospholipid bilayer structures modifying its thermotropic behaviour	203
	A	Bacterial systems	A bacterium that can grow with As instead of P	101
	A	Bacterial systems	Evidences for As in macromolecules that normally contain P	103
Sb/Se	A	Rats	Partial protective effect of Sb against Se toxicity	21, 33, 92
Bi/Se	A	Rats	Partial protective effect of Bi against Se toxicity	21, 33
Cd/Ca	A	Rats	Ca prevents Cd-induced carcinogenesis	204
	A	Zebrafish	Potential detoxification action of Ca against Cd	205
	S	Rainbow trout	Cd and Ca cooperate to impair oxidative phosphorylation in liver mithochondria	206
Cd/Zn	A	Rats	Zn counteracts the toxic effect of Cd	90
	A	Marine diatoms	Cd substitutes Zn in some enzyme families	99
	S	Plants	Zn and Cd at equimolecular concentration may overcome Cd toxicity	207
	S	Bean plants	The roots retains less Cd that is accumulated in shoots	208
	S	Hyperaccumulator plants	Accumulation of Zn and Cd in roots, petioles and leaves are increased significantly with the individual addition	209
	S	Amphipods and crabs	Zn addition induces a depletion of Cd toxicity and accumulation	210
	A	Rats	Zn consumption may be beneficial against Cd hepatotoxicity	211
	A	Rats	Zn reduces the Cd-induced metallothionein synthesis	212
	A	Rats	Zn prevents Cd-induced alterations in lipid metabolism	213
	S	Tomato plants	Zn and Cd produce oxidative stress	214
	A	Toads	Zn increases resistance against Cd toxicity	215
	A	Mice	Zn protects against Cd effects on preimplantation mice embryos	216
Cd/Cu	S	Tilapia	Modify the distribution of metals in the organs	217
Cd/Hg	A	Rats	Cd causes higher Hg levels in the blood and lower levels in heart, muscle and skeleton	218
Cd/Se	A	Humans cells	Se protects against Cd toxicity	89
	A	Rats	Se prevents the Cd-induced oxidative stress	90
	A	Rats	Se protects against Cd-induced nephrotoxicity and hepatotoxicity	219

	A	Mice	Se protects against Cd-induced chromosomal aberrations	220
	A	Monkeys	Se protects enzyme systems	221
	S	Rats	Se and Cd affect the hepatic gluconeogenic pathway	222
	A	Bacterial systems	Se protection against lipid peroxidation from Cd	223,224
	A	Rats	Se partially restores Cd-induced oxidative stress and decrease in sperm count and motility	225
	A	Rats	Se antagonizes the Cd-induced inhibition of hepatic drug metabolism	226
	A	Rats	Se antagonizes Cd-induced testicular damage	227
	A	Porcine cells	Se prevents Cd-induced apoptosis	228
	A	Rats	Hepatoprotective effects of Se against Cd	229
Zn/Pb	A	Rabbits	Zn might delay the Pb accumulation in the cerebrum	230
Zn/Hg	A	Mice	Low-dose Hg induces testicular damage protected by Zn	231
	A	Hamsters	Teratogenic and embryopathic effects	232,233
	A	Rats	Displacement of Zn from metallothionein by Hg	
Cu/Zn	A	Humans	Zn induces a decrease in Cu absorption	95
	A	Rats	Zn decreases Cu concentrations in kidney and liver	234
	A	Rats	Zn competes with Cu	235
	A	Humans and rats	Zn influences the Cu-induced lipid peroxidation	236
Cu/Fe	A	Arthropods and molluscs	Fe substitutes Cu in some enzyme families	100
	A	Rats	Cu influences Fe metabolism and formation of haemoglobin	237
	A	Rats	The changes in Cu levels that accompany Fe deficiency are not mediated by changes in transcription of the genes involved in Cu transport.	238
Cu/Fe/Zn	A	Chicks	Ingestion of large amounts of Zn induces anemia primarily by depressing Fe absorption in chicks Cu partially counteracts the effect of high levels of Zn on endogenous excretion of Fe but did not alter Zn effect on iron absorption	239
Cu/Hg	A	Rats	Hg may alter metabolism of Cu	240
Cu/Mo	A	Humans	Mo removes Cu from tissues affecting diabetes mellitus	97
Ge/Se	A	Rats	Partial protective effect of Ge against Se toxicity	21, 33
Ni/Se	A	Rats	Deleterious effects of Ni in the reproduction may be antagonized by Se	93,241
	A	Rats	Se produces depletion of hepatic, renal, cardiac and blood Ni burden	
Se/Ag	S	Mice	Se protects against Ag-induced lipid peroxidation in the liver	242,243
	A	Mushrooms	Protective effect of Se in lipid peroxidation under exposure to Ag	
Te/Se/Hg	S	Mice	Retention of Hg is increased by pre-administration of Te or Se	244

W/Mo	S	Humans	They are incorporated in the active sites of enzymes	98
W/Se	A	Rats	Partial protective effect of W against Se toxicity	21,33

A: antagonism; S: synergism

Table 3. Traffic of elements species in living organisms

INTERACTION	LIVING ORGANISM	EFFECT	REFERENCES
As/Se	Pregnant women	Se sufficiency↑[As] excretion	111
iAs(III)/ SeO_3^{2-}	Rats	↑[Se, As] gastrointestinal excretion ↓ [Se] in carcass, blood, expired air High As doses↑[Se] in kidneys Low As doses↑[Se] in urine	34
	Mice	Se deficiency↑[As] in liver	110
	Mice	Excess of Se in diet↑[As] excreted (more marked in inorganic than in methylated forms)	110
	Mice	Se sufficiency↑[As] excretion Se deficiency ↓[As] excretion	109
	Rat	↓ pulmonary excretion of volatile selenium	245
Sodium arsanilate/Se	Rats	↓[Se] in gastrointestinal contents and carcass ↑[Se] expired air	34
MA,DMA/Se	Humans	Plasma Se concentrations are inversely related to total As in blood and urine, inversely related to %MA in blood, and positively associated with %DMA in blood	58
Cd/Cu	Tilapia	↑[Cu, Cd] in intestinal wall	246
Cd/Hg	Rats	↑[Hg] in blood ↓[Hg] in heart, muscle and skeleton	218
Zn/Cu	Rats	↓[Cu] in kidneys and liver	234
	Rat	Excessive Zn ↓[Cu] intestine, liver and placenta. Excessive Cu affects hepatic Zn metabolisms.	247 248
	Sheep	Excessive Zn ↓[Cu] intestine, liver and placenta	249
Zn/Pb	Rabbits	↓[Pb] in the cerebrum	230
Cu/Fe	Rats	Reduced dietary iron↑[Cu] in liver, serum and placenta	238
Cu/Mo	Humans	↓[Cu] in tissues ↑[Cu] in serum and urine	97
Se_{Total}/Hg_{Total}	Mammals, birds, and fish	↑[Hg] in the food chain	118
Hg^0/ Se_{Total}	Rats	↓[Hg] in kidney cortex, kidney medulla and thyroid	199
Hg^{2+}/SeO_3^{2-}	Mice	↓[Hg] in kidneys	141
	Mice	↑[Hg] in kidneys, liver and brain	250
	Trout	↓[Hg] muscle and kidneys Liver, erythrocytes, bile and	147

		blood plasma was not affected	
	Rats	↓[Hg] in kidneys	251
	Chicken	↑[Hg] in liver and muscle	150
	Minnows	↓[Hg] in kidneys	252
	Killifish	↓[Hg] in kidneys ↑[Hg] in liver	253
	Rabbits	↓[Hg] in kidneys	70
	Pigs	↓[Hg] in kidneys ↑[Hg] in liver, spleen and lungs ↑[Se] in liver, spleen and lungs	254
	Rats	↓[Hg] in kidneys ↑[Hg] in liver and spleen	255
	Rats	↑[Hg] in liver	256
	Rats	↓ [Hg] in lysosomes in proximal tubular cells	257
	Rats	↓ pulmonary excretion of volatile selenium	245
Hg^{2+}/SeO_4^{2-}	Fish	↓ dietary Hg assimilation efficiency	153
Hg^{2+}/ SeMet	Rats	↓[Hg] in kidneys ↑[Hg] in liver and blood	143
	Fish	↓ dietary Hg assimilation efficiency	153
Hg^{2+}/SeCys	Fish	↓ dietary Hg assimilation efficiency	153
$MeHg^{+}$/Se	Walleye fish	↓[Hg] in liver and muscle	151
	Monkey	↑[Se] and↑[Hg] in occipital pole and thalamus	258
$MeHg^{+}$/ SeO_3^{2-}	Trout	↓[Hg] in liver, muscle, kidneys, bile and erythrocytes Blood plasma is not affected	147
	Chicken	↑[Hg] in kidneys and muscle	150
	Medaka fish	↑[Se] bioaccumulation	152
	Rats	↓[Hg] in kidneys ↑[Hg] in liver and spleen	255
	Rats	↑[Hg] in liver	121
	Rats	↑[Hg] in brain	259,260
		Se changes the ratio between Hg^{2+} and $MeHg^{+}$ in liver but not in brain	260
	Rats	↑$MeHg^{+}$ demethylation in brain	261
	Quails	↑[Hg] in liver and brain ↑[Se] in liver, brain, blood and kidneys	262
	Mice	↑[Hg] in liver	263
	Chickens	↓[Hg] in liver and muscle	264
	Quails	↑[Hg] in liver	264

	Hens	↑[Hg] in liver	265
	Quails	↓[Hg] in liver	266,267
	Chickens	↓[Hg] in liver	268
$MeHg^{+}$/ SeO_2	Rats	↓[Hg] in blood and liver	269
$MeHg^{+}$/SeO_4^{2-}	Rats	↑[Hg] in kidneys and liver ↓ [Hg] in brain	270
$MeHg^{+}$/ SeMet	Ducks	↑[Se] in liver and eggs ↑[Hg] in liver and eggs	149
	Rats	↑[Hg] in blood and liver	269
	Ducks	↑[Se] in liver and eggs ↑[Hg] in liver and eggs	149
$PheHg^{+}$/ SeO_3^{2-}	Chickens	↓[Hg] in liver, kidneys and muscle	271
TlAc/SeO_3^{2-}	Rat	↓ pulmonary excretion of volatile selenium	245
Te/Se/Hg	Mice	↑[Hg] in kidneys and spleen	244

iAs(III) : AsO_3^{3-} or AsO_2^{-}; SeMet: selenomethionine; SeCys: selenocystine; $MeHg^{+}$: methylmercury; $PheHg^{+}$: phenylmercury; MA: methylarsonate; DMA: dimethylarsinate; TlAc: thallium acetate;↑[]: increase of the concentration; ↓[]: decrease of the concentration