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Mercury and Selenium Interaction: A Review

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This paper reviews studies on mercury and selenium interaction. It includes the effects of selenium on mercury toxicity on the organism, organ/tissue, and subcellular levels. The paper also touches on possible mechanisms for the "protective action" of selenium against mercury toxicity and deals briefly with the synergism between the two elements. © 1991 Academic Press, Inc.

1. INTRODUCTION

Mercury and selenium have long been considered environmental pollutants, although selenium has also been shown to be an essential element in human and animal nutrition. The mutual antagonism between these two elements has become one of the strongest and most general examples of interaction between heavy metals. The protective effect of selenium against mercury toxicity and vice versa has been observed in a number of different organisms.

2. STUDIES ON THE EFFECTS OF SELENIUM ON MERCURY TOXICITY

2.1. Manifestations of Mercury and Selenium Interaction

One of the earliest studies on the protective effect of selenium on mercury toxicity was conducted by Parizek and Ostadalova (1967) using laboratory rats. They showed that in the presence of sodium selenite, Na_2SeO_3, the kidneys of rats were protected from the toxic action of mercuric chloride, $HgCl_2$. The kidneys of selenite-treated rats showed no macroscopic changes or histological damage such as necrosis in the renal tubules, in contrast to rats treated only with mercuric chloride. This study prompted a number of investigations into selenium and mercury interactions in other organisms and biological systems, as well as investigations into possible mechanisms of protection.

Among the lines of investigation carried out was to consider a number of organisms which had been reported to have high mercury concentrations and yet showed no apparent signs of mercury poisoning. In addition to measuring mercury levels, selenium concentrations were also determined to see if there was any correlation between the levels of these two elements in individual animals. Koeman *et al.* (1973, 1975) found a 1:1 molar ratio between mercury and selenium in livers of marine mammals. A strong linear correlation between mercury and selenium concentrations was also demonstrated in miners, who showed mercury–selenium increments of approximately 1:1 (Kosta *et al.*, 1975). Such a correlation between mercury and selenium concentrations in fish is not well established. Studies of levels in fish have given conflicting results.

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Ganther and Sunde (1974) demonstrated that the selenium content in high-mercury tuna was greater than that in low-mercury tuna and on a molar basis, the increment in selenium is in an approximate 1:1 ratio with the increment in mercury. In the muscle of the albacore *Thunnus alalunga* the ratio of selenium to mercury also tended to approach unity in the kidney (Kai *et al.*, 1983). In the gonads of marlins, the selenium/mercury ratio also tended to approach 1 with the increase in total mercury (Kai *et al.*, 1986). On the other hand, in the swordfish *Xiphias gladius*, a molar excess of selenium in relation to mercury was shown to be the case for almost all samples analyzed (Freeman *et al.*, 1978). Likewise, in nearly all marine fish sampled by Luten *et al.* (1980) the stoichiometric mercury-to-selenium ratio was less than 1. In contrast, freshwater fish accumulated mercury in such a way that the stoichiometric ratio was greater than 1. In the blue marlin *Makaira nigricans*, a positive correlation between total mercury and selenium concentrations among the different organs and tissues was observed, although the mercury and selenium molar ratio was lower than 1 in all the tissues studied (Shultz and Ito, 1979).

It is interesting to note at this point that Koeman and his co-workers' (1973, 1975) observation of a 1:1 molar relationship between mercury and selenium in marine mammals does not hold true for a large number of marine fish. These fish make up a very significant part of the diet of these marine mammals and presumably play an important role in the transfer of mercury and selenium. The results of these studies indicate that the establishment of a 1:1 molar ratio between mercury and selenium in marine mammals occurs within the animals themselves, regardless of the molar relationship between these two elements in their food. Unfortunately, reports on mercury and selenium relationships in fish seldom include the concentrations of these elements in the water and in the fish food source. Hence, it is difficult to establish whether mercury to-selenium ratios in fish correlate with those of their food or not.

The highest levels of mercury and selenium that have been reported in marine mammals have values reaching up to 510 ppm wet wt mercury (mean = 230 ppm) and 270 ppm wet wt selenium (mean = 81 ppm) in livers of ringed seals *Phoca hispida* (Wagemann and Muir, 1984). Despite such extremely high values for mercury and selenium, the animal in question did not show any overt signs of mercury or selenium intoxication. This suggests that the presence of the two elements together may provide protection to the animal by virtue of their mutually protective effect against the toxicity caused by the other. Table 1 gives the molar ratio of mercury to selenium in a number of aquatic organisms.

It appears that selenium levels in fish are high enough to give protection against mercury toxicity. Studies on the protective effect of freeze-dried swordfish on methyl mercury toxicity in rats were done by Friedman *et al.* (1978). Results showed that rats that were experimentally administered methyl mercury and fed a swordfish diet showed no signs of neurotoxic effects characteristic of mercury poisoning, while rats fed other diets did. Analysis of selenium concentrations in the swordfish showed levels which were at least twice as high as the mercury content. It was suggested that the excess selenium in the swordfish was able to protect the rats from the effects of experimentally administered methyl mercury.

In other laboratory experiments with rats, among the manifestations of the protective effects of selenium against mercury toxicity were lower mortality, better growth rates, and weight gains in selenium- and mercury-treated animals compared with those treated with mercury alone (Potter and Matrone, 1974; Stillings *et al.*, 1974; Burk *et*

TABLE 1

MEAN MERCURY AND SELENIUM MOLAR RATIOS IN SELECTED AQUATIC ORGANISMS

Habitat	Organism	Hg:Se ratio	Reference
Freshwater	Cisco	0.14[a]	Froslie *et al.*, 1985
Freshwater	Brown trout	2.03[a]	Froslie *et al.*, 1985
Freshwater	Smelt	0.51[a]	Froslie *et al.*, 1985
Freshwater	Burbot	1.56[a]	Froslie *et al.*, 1985
Freshwater	Pike	2.10[a]	Froslie *et al.*, 1985
Freshwater	Perch	1.06[a]	Froslie *et al.*, 1985
Freshwater	Largemouth bass	0.62	Cappon and Smith, 1982
Freshwater	Muskellunge	0.76	Cappon and Smith, 1982
Marine	Mackerel	0.15	Cappon and Smith, 1982
Marine	Pink salmon	0.13	Cappon and Smith, 1982
Marine	Mako shark	2.81	Cappon and Smith, 1982
Marine	Squid	0.08	Cappon and Smith, 1982
Marine	Oyster[b]	0.09	Cappon and Smith, 1982
Marine	Mussel[b]	0.09	Cappon and Smith, 1982
Marine	Crab[b]	0.30	Cappon and Smith, 1982
Marine	Shrimp[b]	0.15	Cappon and Smith, 1982
Marine	Ringed seal[c]	1.12[a]	Wagemann and Muir, 1984
Marine	Gray seal[c]	0.82[a]	Wagemann and Muir, 1984
Marine	Harbor seal[c]	0.94[a]	Wagemann and Muir, 1984
Marine	Swordfish	0.19[a]	Friedman *et al.*, 1978
Marine	Yellowtail[d]	0.05	Takeda and Ueda, 1979

[a] Values were computed from ppm concentrations given in references.
[b] Samples which underwent food processing prior to analyses.
[c] Liver samples only.
[d] Muscle samples only.

al., 1977). In creek chubs, pretreatment of selenium as selenium dioxide, SeO_2, before mercury (as mercury chloride) administration also gave lower mortality rates than for those subjected to mercury treatment only. At relatively low mercury concentrations (0.1–0.16 ppm), a new trend was observed: selenium-pretreated animals showed lower mercury body burden than those not pretreated (Kim *et al.*, 1977). In minnows, those exposed to mercury in combination with selenium showed significantly higher survival rates than those exposed to mercury alone (Cuvin and Furness, 1988). In the mussel *Mytilus edulis,* acute lethal toxicity tests using mercury and mercury–selenium treatments showed that the best protection was obtained by simultaneous addition of selenium on an equimolar basis with mercury (Micallef and Tyler, 1987). Conversely, the toxic effects of selenium can also be reduced by mercury. The addition of low levels of mercuric chloride into diets containing toxic concentrations of selenium dioxide protected chicks from growth retardation and mortality. As mercury was increased in the diet, the effect of selenium was progressively decreased, although the highest level of mercury used was one which achieved a molar ratio of 1 to selenium (Hill, 1974).

Cultures of nervous tissue from the cerebella of rats also demonstrated that both sodium selenate and selenite showed remarkable protective effect against the neurotoxicity of methyl mercury. Sodium selenate concentrations from 0.2×10^{-5} to 1.0×10^{-5} *M* protected the nervous tissue from the toxicity of 1.0×10^{-5} and 1.5×10^{-5}

M methyl mercury concentrations (Kasuya, 1976). This suggests that selenium molar concentrations lower than those of mercury are able to protect against mercury toxicity.

Aside from laboratory studies, there were also studies conducted in experimental ecosystems to demonstrate possible mercury and selenium interactions. It was shown that the ability of selenium to reduce bioaccumulation of mercury in biota was dose dependent. These reductions appeared to depend on the position of the organism in the food web. In fish, the reduction was proportional to the amount of selenium accumulated; i.e., at the lowest levels in the food web, there was little or no selenium effect but at higher levels, a reduction in the accumulation of mercury was apparent (Turner and Rudd, 1983). Moreover, there are indications that selenium added to aquatic ecosystems and incorporated subsequently in the food web would interfere with biomagnification of mercury. Increased selenium reduced the assimilation of mercury from food by 5–10% (Turner and Swick, 1983).

Selenium can also be used as a mercury ameliorating agent in the field. The addition of selenium (selenite) to river systems with severe mercury pollution problems has been done in experimental studies. When 100 μg Se/liter was added to river enclosures, the rate of accumulation of mercury by fish and other aquatic biota was reduced by a factor of 2, although the effect was both dose and species dependent (Rudd *et al.*, 1980).

Elimination studies revealed that the presence of selenium does not improve the rate of elimination of mercury in fish (Cuvin and Furness, 1988). In fact, the release of mercury in the presence of selenium was significantly decreased compared with groups treated only with mercury. The release of selenium was also significantly diminished by the presence of mercury (Lucu and Skreblin, 1981).

2.2. Interactions of Different Chemical Forms of Mercury and Selenium

It has been demonstrated that the chemical forms of mercury and selenium are important in the toxicology of both elements. Likewise, the interactions between mercury and selenium also rely, to a large extent, on the chemical state in which the elements exist. In fact, the presence of other compounds was also shown to affect the interaction between mercury and selenium.

In pike *Esox lucius,* the amount of mercury taken up from food (perch *Perca flavescens*) was shown to be affected by the amount of selenium taken up from food. Increased selenium in food reduced the assimilation of mercury from food by 5–11%. In contrast, when mercury and selenium were taken up from water, the mercury concentrations in various tissues of the fish were not affected by the selenium status of the animal (Turner and Swick, 1983). The mercury and selenium used to treat the water were in the form of $^{203}Hg(NO_3)_2$ and H_2SeO_3. The same chemical forms were used to label the perch which eventually served as food to the pike. This suggests that the difference in the assimilation of mercury may have been caused, in part, by possible transformations of both mercury and selenium into other forms in the perch prior to consumption by the pike.

The effectiveness of selenium in detoxifying mercury from other fish known to have high concentrations of the element, such as tuna, has also been compared with the effectiveness of inorganic selenite to determine if there are differences in the degree of protection given by both forms of selenium. Selenium from tuna and selenite both have the same protective effect in weanling rats exposed to methyl mercury. Both

improved the growth rates and decreased the weight loss and mortality of the rats. However, selenite proved to be more effective than selenium in tuna in preventing neurological manifestations of mercury toxicity (Ohi *et al.,* 1976). Little is known about the forms of selenium in tuna but available studies indicate that selenium in fish is associated with proteins (Lunde, 1972).

Since the kidney is one of the most sensitive tissues to mercury poisoning, studies on the effectiveness of four different selenium compounds in reducing renal mercury levels (administered as mercuric chloride) in rats were conducted. The results showed that on an equimolar basis, the efficiency of the four selenium compounds in reducing renal mercury in order of effectiveness was selenomethionine > selenocystine > selenate > selenite (Fang, 1977). Organic selenium compounds appeared to be more effective than the inorganic forms in preventing mercury from reaching the target tissues. However, other studies have given different results. Sharma and Davis (1980b) found that a slight protection was given by selenium in the form of sodium selenite against both mercuric chloride and methyl mercury in the goldfish *Carasius auratus,* whereas selenomethionine gave no protective effect at all. A comparison of the two forms of selenium in rats also showed that sodium selenite was slightly more effective than selenomethionine in reducing signs of mercury toxicity (Stillings *et al.,* 1974). These varying results of the effectiveness of different chemical forms of selenium against mercury poisoning are possibly indications of different modes of action of the different forms of selenium.

Neurotoxicity of methyl mercury was also prevented by both sodium selenate (Se(VI)) and selenite (Se(IV)), although selenite was four times more effective than selenate. Doses of as low as 0.8×10^{-5} *M* selenate and 0.2×10^{-5} *M* selenite were effective concentrations against 1×10^{-5} *M* methyl mercury (Kasuya, 1976). Physiological studies showed that the transport of methyl mercury in rat small intestine was greatly increased by the addition of increasing amounts of selenite and selenate, although selenate had a weaker increasing effect on methyl mercury transport than selenite (Matsumoto and Miki, 1981).

Different forms of mercury also interacted differently with different forms of selenium. Studies on the bioaccumulation of selenium and mercury in the blue mussel *Mytilus edulis* by Pelletier (1986) showed that when mercury was not present, the mussels accumulated inorganic selenium at a slow rate, but they did not accumulate the organic selenium. When inorganic mercury was added to the water (30 μg Hg liter^{-1}) the accumulation rate of inorganic selenium doubled while it tripled with the addition of the same amount of methyl mercury. Even organic selenium seemed to become bioavailable in the presence of methyl mercury. However, the phenomenon is not reciprocal; that is, the presence of selenium regardless of concentration and chemical form had no effect on the accumulation rate of mercury.

In another study, Matsumoto and Miki (1981) showed that although methyl mercury transport was enhanced by selenite, mercuric chloride transport was, in fact, decreased with increasing amounts of selenite. Selenate, on the other hand, slightly increased mercuric chloride transport, despite having less effect on methyl mercury transport.

Studies on the effect of different mercury compounds (mercuric chloride, methyl mercuric chloride, and phenylmercuric acetate) on the tissue distribution of selenium gave no definite trend in terms of one compound being more effective than the others in altering tissue selenium levels. Methyl mercury increased selenium in the brain while mercuric chloride and phenylmercuric acetate caused a reduction. A greater

reduction of liver selenium was observed with methyl mercury but mercuric chloride and phenylmercuric acetate exerted greater influence on the kidney. Blood selenium levels were also increased by methyl mercury and phenylmercuric acetate but not by mercuric chloride (Fang, 1977). The toxicity of phenylmercuric acetate in chicks was shown to be decreased by selenium in the form of diphenyl selenium. However, mercury as mercuric chloride showed no significant biological interaction with diphenyl selenium. Furthermore, there are indications that the interaction of phenylmercuric acetate and diphenyl selenium is different from that of mercuric chloride and selenium dioxide. The effect of diphenyl selenium on the toxicity of phenylmercuric acetate was evident at molar ratios of 1:4 in contrast to the 1:1 ratio found to be most effective in the interaction of mercuric chloride with selenium dioxide (Hill, 1974). The foregoing suggests that the interactions between different selenium and mercury compounds are extremely complex and not well understood at present.

The presence of other elements and compounds can also modify the interaction between mercury and selenium. For instance, the presence of arsenic as sodium arsenite, Na_2AsO_3, altered the ability of selenite to modify methyl mercury toxicity in quails. Although arsenite alone has no protective effect on methyl mercury toxicity, it improved the effectiveness of selenite in prolonging the survival of mercury-intoxicated quails (El Begearmi *et al.*, 1982). The combination of cystine and selenite also has a considerable additive effect in reducing mercury toxicity as measured by increased growth and survival time in rats (Stillings *et al.*, 1974).

3. EFFECTS OF SELENIUM ON THE DISTRIBUTION OF MERCURY

3.1. Organ and Tissue Distribution

One of the observed effects of the selenium treatment of mercury-intoxicated animals is an apparent modification of the distribution pattern of mercury in the different organs and tissues. Of particular interest is the effect of selenium on mercury levels in the kidney because this is one of the target organs of mercury. It is therefore not surprising that a number of studies has been done on the kidney. In rats, pretreatment with selenite followed by injections of mercuric chloride markedly decreased the mercury in the kidneys to one-tenth of control (Chen *et al.*, 1974). Potter and Matrone (1974) also demonstrated a decreased percentage of mercury in the kidneys of rats fed with selenite. It appears that selenium causes a reduction in the rate at which mercury is taken up by the kidney. In minnows, *Phoxinus phoxinus*, a slight reduction in renal mercury was also observed with selenium treatment (Cuvin-Aralar and Furness, 1990). It has also been shown that selenite not only affects mercury uptake by the kidney but also its retention. Selenium pretreatment in the killifish *Poecilia reticulata* also decreased mercury retention in the kidney. Four-and-one-half hours after mercury injection, the mercury concentration in the kidney of selenium-pretreated fish was one-half the concentration in controls (Sheline and Schmidt-Nielsen, 1977). From these works, it is reasonable to conclude that selenium, whether administered prior to mercury treatment or simultaneously, resulted in the lowering of mercury levels in the kidney. However, findings to the contrary were reported by Groth *et al.* (1972). It was reported that the presence of selenium increased the concentration of mercury, fed as mercuric chloride, in kidneys. Despite this increase in kidney mercury, selenium levels in the kidney increased with simultaneous administration of mercury (Komsta-Szumska and Chmielnicka, 1977).

In the liver, higher mercury levels were found in rats fed with selenite, regardless of the form of mercury administered (Potter and Matrone, 1974). The same results were observed by Fang (1977) at equimolar doses of mercury and selenium. On the other hand, in killifish liver, mercury concentrations were slightly, but not significantly, lowered after selenium treatment (Sheline and Schmidt-Nielsen, 1977). The levels of selenium in the liver were also increased when mercury was administered simultaneously (Komsta-Szumska and Chmielnicka, 1977).

In vivo and *in vitro* studies of mercury and selenium in rabbit blood after simultaneous administration of methyl mercuric chloride and selenite showed that the rate of mercury uptake by erythrocytes was very rapid in comparison with the case where methyl mercury was added alone. However, the degree of incorporation of selenium in the blood was reduced in the presence of mercury (Naganuma *et al.*, 1981a). In rats, significant increases in mercury levels were also observed after selenium treatment (Chen *et al.*, 1974; Fang, 1977). Contrary to these findings, the blood of killifish showed 3.5 times lower retention values for mercury after selenium treatment, in contrast to those given mercury alone (Sheline and Schmidt-Nielsen, 1977).

Mercury diverted away from the kidney is believed to be redistributed in the muscle. In rats, there was as much as three times more mercury in the muscle of the selenium-treated group compared with the group receiving mercuric chloride only (Fang, 1977). Increased mercury retention in the muscles has also been shown in killifish upon selenium treatment. Selenium was also increased by both methyl mercury and inorganic mercury in this tissue (Sheline and Schmidt-Nielsen, 1977).

In the gut, selenium promoted mercury transport across the rat small intestine. Accumulation of mercury was hardly changed with increasing addition of selenite or selenate in the case of methyl mercury but mercuric chloride accumulation was increased significantly (Matsumoto and Miki, 1981).

In other organs and tissues the presence of selenium showed a general trend toward higher mercury levels in the heart, pancreas, brain (Fang, 1977), testis (Chen *et al.*, 1974), and spleen (Potter and Matrone, 1974; Fang, 1977).

3.2. Subcellular Distribution

In the foregoing section it was clear that the mutual interaction between mercury and selenium is manifested by changes in the organ and tissue distribution pattern of each element in the presence of the other. With the exception of the kidney, selenium promoted levels of mercury in almost all the tissues studied. The logical step now is to determine whether the presence of selenium influences subcellular distribution of mercury and vice versa to understand better the mutual antagonism between the two elements.

Chen *et al.* (1974) did an extensive study of selenium effects on subcellular distribution of mercury in different tissues of rats, primarily in the kidney, liver, testis, and plasma, using differential centrifugation and chromatography. This work will be the basis of the following discussion but other studies will be referred to as well.

Mercury concentrations in all subcellular fractions (crude nuclear, mitochondrial, microsomal, and soluble fractions) of the kidney also decreased with selenium pretreatment, probably as a consequence of decreased mercury content in the whole organ (Chen *et al.*, 1974). Basically similar results were reported by Komsta-Szumska and Chmielnicka (1977), except that the mercury level in the nuclear fraction was not

diminished by selenium treatment. Although there was no observed change in total mercury level in the nuclear fraction, it appeared that selenium treatment induced a change in mercury distribution within the renal nuclei itself. In the absence of selenium, mercury was retained mainly by nonhistone proteins (71%). Selenium administered with mercury slightly heightened the content of mercury in proteins soluble in NaCl and lowered the levels in histones but no significant change was observed in the nonhistone fraction. Since the redistribution occurred only within the renal nuclei, the total mercury level in the nuclear fraction was not affected by selenium.

It was also observed that in the absence of selenium more than 50% of the total amount of mercury retained in the kidneys was located in the soluble fraction. Under the influence of selenium, the level of mercury in this fraction was diminished more than 15 times. Studies by both Chen *et al.* (1974) and Komsta-Szumska and Chmielnicka (1977) showed that in rats not treated with selenium, nearly all the mercury in the soluble fraction was bound to low molecular weight proteins presumed to be metallothionein. Metallothionein has been identified as the compound responsible for the selective binding and retention of mercury. It appears likely that this protein plays the part of a shielding factor against mercury, thus playing a positive role in mercury detoxification (Wisniewska *et al.*, 1970). On the other hand, the mercury–metallothionein complex shows considerable stability and therefore causes long-term retention of mercury in the body (Jakubowski *et al.*, 1970; Piotrowski *et al.*, 1974). In contrast, selenium treatment diverted the binding of mercury to higher molecular weight proteins. Thus, selenium prevented the binding of mercury to metallothionein.

Burk *et al.* (1977) also reported that most of the kidney mercury in rats was found in the soluble fraction, but they found that the selenium status of the animal had no effect on the distribution of mercury in the kidney cell. They showed that most of the mercury in the soluble fraction in both selenium-deficient rats and those with dietary selenium was bound to metallothionein.

There are inferences that prolonged exposure to both mercury and selenium might eventually achieve the binding of these elements into the high molecular weight group. Since Chen and his co-workers' studies with rats demonstrated mercury redistribution in the high molecular weight fraction within an hour after mercury and selenium treatment, it appears that the time factor is not the only cause for these different results. The differences in chemical form of both mercury and selenium administered can also be ruled out since both studies used mercuric chloride and sodium selenite. One other possible explanation for these different observations is the ratio of mercury and selenium dosages. When rats were given 3 μmol of mercuric chloride and various dosages of selenite (0.75 to 6 μmol) a continuous increase in mercury incorporation in the crude nuclear fraction and decrease in the insoluble fraction were observed, with maximum effects observed at 6 μmol selenite. However, when rats were given 9 μmol mercuric chloride with the same selenite concentrations employed, selenite induced an increase in mercury in the soluble fraction with no significant change in the others (Fang, 1977). It seems that dietary levels of selenium, as used by Burk and coworkers, promote mercury binding to metallothionein but higher levels of selenium seem to inhibit metallothionein binding in favor of binding to higher molecular weight proteins.

In the insoluble fraction of the rabbit kidney, it was shown that simultaneous injection of mercuric chloride and selenite did not result in any increase in the levels of either mercury or selenium in the higher molecular weight fractions. Mercury and

selenium seemed to coexist separately even after simultaneous administration (Naganuma *et al.*, 1981b).

Selenium levels in the kidney are enhanced by mercury administration. This increase is also manifested in renal subcellular fractions. In the presence of mercury, the level of selenium rose by about 10-fold in the microsomal fraction and four to six times in other fractions. Nevertheless, the highest level of selenium remained characteristic of the nuclear fraction, accounting for 61% of selenium in the subcellular fraction (Komsta-Szumska and Chmielnicka, 1977).

Studies in the subcellular binding of mercury in the liver after selenium pretreatment are more in agreement with each other. In the crude nuclear, mitochondrial, and microsomal fractions of the liver, the mercury content was increased by selenium, whereas the mercury content in the soluble fraction was decreased. The mercury in the soluble fraction, a major subcellular mercury binding component, was diverted from low molecular weight proteins to larger ones. In rats not receiving selenium, mercury was bound almost exclusively to a protein about 10,000 MW which was presumed to be metallothionein (Chen *et al.*, 1974). Identical results were obtained by Fang (1977) and it was further demonstrated that the magnitude of increase in the mercury levels of the crude nuclear and mitochondrial fractions and decrease in those of the soluble fractions were correlated with increasing selenite concentrations. Selenate, selenomethionine, and selenocystine induced similar effects in subcellular mercury distribution in the liver, but to a greater degree.

In the absence of mercury, selenium was located mainly in the liver nuclear and insoluble fractions, but in the presence of mercury, selenium levels rose in all examined liver fractions, especially in the nuclear and mitochondrial fractions (Komsta-Szumska and Chmielnicka, 1977). Studies of the insoluble fraction of the rabbit liver showed that simultaneous treatment with mercury and selenium resulted in both elements being distributed in the high molecular weight fraction at a molar ratio of 1:1 (Naganuma *et al.*, 1981b). The same molar ratio was reported in the nuclei and cell membrane material of the liver of seals (Koeman *et al.*, 1973).

Mercury in the plasma of rats not treated with selenium is bound to at least three different molecular weight proteins. In selenium-treated rats, nearly all of it was bound to one protein (Chen *et al.*, 1974). Burk *et al.* (1974) also showed that the molar ratio of selenium to mercury in the protein remains close to 1 even when varying doses of both mercury and selenium were used.

Fractionation of the skeletal muscle of marine fish into subactomyosin and actomyosin fractions elucidate the distribution of total mercury, and selenium in the myofibrillar protein fraction of skeletal muscle showed different results for different fish. In skipjack *Katsuwonus pelamis* muscle, 50–70% of the total mercury in the myofibrillar protein was found in the subactomyosin fraction, whereas 70–75 and 85–90% of the total mercury in the myofibrillar protein was found in the actomyosin fraction of Japanese sea bass *Lateolabrax japonicus* and red sea bream *Chrysophys major,* respectively. For all three fish, 90% of selenium in the myofibrillar protein was found in the actomyosin fraction. This indicates that the concentration ratio of mercury to selenium in the subactomyosin of skipjack was 10–30 times that in the actomyosin fraction. There was no significant difference in the mercury-to-selenium ratios between the two fractions in the case of the red sea bream. Contrary to what has been observed in the subcellular fractions of other tissues, the ratios of mercury to selenium concen-

trations in the subactomyosin fraction of skipjack were far higher than 1:1 on a molecular basis (Itano *et al.*, 1982).

In the testis of rats treated with selenium, the testicular subcellular fractions showed higher mercury levels than those of control groups. Mercury in the soluble fraction of groups without selenium pretreatment was bound to a number of different proteins, whereas in the selenium-treated group, mercury was diverted to high molecular weight proteins (Chen *et al.*, 1974).

A 1:1 mercury-to-selenium molar ratio has been demonstrated in the subcellular fraction of seal brains (Koeman *et al.*, 1975), as well as the whole liver of many marine mammals.

4. POSSIBLE MECHANISMS OF PROTECTION

The exact mechanisms of interaction between mercury and selenium are not well understood. Most of the available information on these are inferences from observed results of a number of different studies. The following are some of the possible mechanisms for the protective effect of selenium against mercury toxicity: (1) redistribution of mercury in the presence of selenium, (2) competition for binding sites between mercury and selenium, (3) formation of a mercury–selenium complex, (4) conversion of toxic forms of mercury to other forms, and (5) prevention of oxidative damage. Each of these possible mechanisms will be discussed further in the following sections.

4.1. Redistribution

Mercury uptake is not diminished by the presence of selenium. In fact, some studies indicate that in certain instances, mercury uptake is enhanced in the presence of selenium. It was also shown that selenium does not enhance mercury elimination. A number of observations to the contrary have been presented. Enhancement of mercury retention by selenium was, for example, shown by Stillings *et al.* (1974). These findings indicate that the mechanisms for the observed protective action of selenium against mercury toxicity lie along different lines.

Mercury redistribution within the organism has been discussed in the preceding section. It is believed that the rechanneling of mercury from one organ to another and from one subcellular fraction to another is one of the general mechanisms involved in the protective action of selenium against mercury toxicity. This was strengthened by observations that toxic levels of mercury and selenium were found in animals not showing signs of mercury or selenium poisoning (Wagemann and Muir, 1984). Earlier studies show that selenium promotes the redistribution of mercury from highly sensitive organs and tissues (like the kidney) to less sensitive ones (like the muscle) (Chen *et al.*, 1974; Sheline and Schmidt-Nielsen, 1977). Reduction in mercury levels in the kidney may explain Parizek and Ostadalova's (1967) results, wherein they found neither macroscopic nor histological damage to the kidney of rats treated with sublethal levels of mercury and selenium.

In the subcellular soluble fraction, mercury is bound chiefly to metallothionein, a low molecular weight protein. The formation of metallothionein is induced by the presence of certain metals, including mercury (Winge *et al.*, 1975). Aside from decreases in mercury levels in the soluble fraction, the presence of selenium also resulted in the diversion of the remaining mercury from metallothionein to high molecular weight proteins (Chen *et al.*, 1974; Komsta-Szumska and Chmielnicka, 1977). This suggests

that selenium, in one way or another, blocks the binding of mercury to metallothionein or it may even inhibit the induction of metallothionein by mercury. Other data support the view that selenium induces the release of mercury bound to proteins. It was also demonstrated that selenium is effective in releasing mercury bound to cysteine (Sumino *et al.,* 1977). Since cysteine is a major component of the protein metallothionein and mercury is known to interact with the sulfhydryl group of this amino acid (Winge *et al.,* 1975), the blocking of the induction of metallothionein by selenium would thus leave mercury free to bind with other proteins, possibly to those with sulfhydryl groups. The higher molecular weight proteins to which mercury is diverted are not yet characterized but they are presumed to be less sensitive to mercury.

In contrast to the preceding studies, Burk *et al.* (1977) found that the presence of dietary levels of selenium facilitated the accumulation of mercury in the kidney. Moreover, no change in the mercury-binding pattern was observed regardless of the presence of selenium; i.e., mercury in the kidney remained bound to metallothionein. No diversion of mercury to higher molecular weight proteins was reported. This study led to the assumption that selenium may mediate the binding of mercury to metallothionein or may even be a permissive factor in the induction of metallothionein by mercury. It is interesting to note that this is not in agreement with other workers' ideas on the effects of selenium on mercury redistribution.

The redistribution of mercury from more sensitive targets to less sensitive sites cannot fully explain the results of a number of other studies. For instance, the brain is also highly sensitive to mercury and the presence of selenium enhances mercury accumulation in this organ. It is apparent that redistribution of mercury cannot satisfactorily explain the reduction of neurological damage induced by selenium treatment and that more complex mechanisms are involved in the interaction between these two elements.

4.2. Competition for Binding Sites

The variability of mercury-to-selenium ratios in fish compared with the concentrations of these two elements in the environment led to the assumption that mercury and selenium compete for the same receptors located in the animal tissue. This could also explain their toxicological antagonism. It is believed that these binding sites are selenium receptors which increase in numbers with age. It is likely that these receptors can be occupied by mercury in proportion to its bioavailability in the environment (Leonzio *et al.,* 1982). The idea of competition for binding sites has also been used not only to explain the varying accumulation rates of mercury and selenium but also to explain the rates of elimination of these two elements.

In shrimps *Palaemon elegans,* it is believed that the permeable membrane barrier of the gills is the main route of mercury and selenium release and that urine and feces contribute to a lesser degree. The slower rate of excretion of both mercury and selenium when present together may be due to the competition between the two elements for the same carrier protein at transport sites (Lucu and Skreblin, 1981). Further studies still need to be done to support this hypothesis. The fact that both mercury and selenium have high affinities for sulfhydryl groups of amino acids lends credibility to the idea of competition for carrier proteins, as well as other binding sites.

4.3. Formation of a Mercury–Selenium Complex

Simultaneous administration of mercuric chloride and selenite to rats radically altered plasma protein binding of selenium and mercury compared with those which

were given each element alone. After simultaneous administration, both mercury and selenium were present in the plasma in much greater quantities due to their binding to a single plasma protein. Despite variations in mercury and selenium dose, the molar ratio of selenium to mercury in the protein remained close to unity. Further analyses showed that selenium was attached to sulfhydryl groups and that mercury was attached to the selenium. This mercury–selenium–protein complex is presumed to play a role in preventing acute inorganic mercury toxicity by binding the mercury and, thus, preventing it from reaching target tissues (Burk *et al.*, 1974). This principle might also explain the consistent 1:1 molar ratio between mercury and selenium found in tissues of organisms such as seals and other marine mammals (Koeman *et al.*, 1973; 1975). Clearly fish differ from marine mammals in this respect.

Later studies with rabbit blood by Sumino *et al.* (1977) showed that methyl mercury bound to the proteins of rabbit blood was converted *in vitro* to free methyl mercury soluble in benzene by the addition of selenite under physiological conditions. Subsequent studies now show that when methyl mercuric chloride and sodium selenite are added to rabbit blood, benzene extraction shows a 2:1 molar ratio of mercury to selenium. Further studies show that both mercury and selenium form a single compound identified as bis(methyl mercuric)selenide, $(CH_3Hg)_2Se$ (Naganuma and Imura, 1980). The formation of this compound depends on the conversion of selenite to selenide (Magos *et al.*, 1979).

The participation of glutathione (GSH) in the formation of bis(methyl mercuric)selenide was also investigated (Naganuma and Imura, 1980). Glutathione is assumed to reduce sodium selenite chemically. Results of addition of glutathione to methyl mercuric chloride and sodium selenite in blood suggest that glutathione mediates the production of bis(methyl mercuric)selenide in the blood. The exact mechanism by which glutathione mediates the formation of this reaction product is still to be investigated. It is thought, however, that this plays a role in the protective effect of selenium against methyl mercury toxicity.

It appears that the processes involved in the formation of a mercury–selenium–protein complex and bis(methyl mercuric)selenide in the blood are quite different. For one thing, the formation of the two complexes results in different molar ratios between mercury and selenium. Furthermore, there are two different forms of mercury involved in the formation of these complexes, although there is a possibility that methyl mercuric chloride can also form the mercury–selenium–protein complex reported by Burk and his co-workers. It is certain, however, that inorganic mercury has to undergo methylation first before it can form bis(methyl mercuric)selenide. Whether the processes for the formation of these two complexes occur simultaneously or are mutually exclusive is not clear at the present time.

4.4. Conversion of a Toxic Form of Mercury

Different forms of mercury have different toxicities. Methyl mercury is known to be more toxic than most other forms. The conversion of methyl mercury to less toxic forms may be one of the possible mechanisms of detoxification. Norseth and Clarkson (1970) showed that a small amount of methyl mercury can be converted to inorganic mercury. Inorganic mercury is less toxic than methyl mercury and has a shorter biological half-life due to its preferential excretion in the feces (Norseth and Clarkson, 1971). It would therefore be an advantage to the organism if methyl mercury could

be converted to inorganic mercury. Stillings *et al.* (1974) suggested that the protective effect of selenium and cysteine against methyl mercury may be due to an increased rate of conversion of methyl mercury to inorganic mercury. Results indicating that this does not occur have been reported by Sheline and Schmidt-Nielsen (1977) for the killifish. They tested for indications of whether demethylation and conversion to inorganic mercury occur by determining whether a breakage of the carbon–mercury bond of methyl mercury occurs. They used ^{14}C and ^{203}Hg to label methyl mercury and determined the tissue distribution of the two isotopes. Results showed that there was no difference in the distribution of the two isotopes in the tissues. This led to the conclusion that no breakage of the carbon–mercury bond of methyl mercury had occurred.

Earlier studies by Fang (1974) on the effect of dietary selenite on the activity of C–Hg cleavage enzymes in rat liver and kidney showed that the activity of the methyl mercuric chloride cleavage enzyme was unchanged. No measurable cleavage of the methyl mercuric chloride either with or without selenium was observed, supporting Sheline and Schmidt-Nielsen's data. There was also no evidence that methyl mercury is converted to dimethyl mercury or to inorganic mercury (Sumino *et al.*, 1977).

4.5. Prevention of Oxidative Damage

Selenium is an intrinsic component of glutathione peroxidase which is an antioxidative enzyme. Mercury is known to have an inhibitory effect on the activity of this enzyme (Hirota *et al.*, 1980). This explains part of the damaging effect of mercury, particularly in liver and nervous tissue. Glutathione peroxidase failed to protect these tissues from oxidative changes. Ganther (1978) has proposed the possible role of the free radicals formed from the homolytic breakdown of methyl mercury in inducing neurotoxic effects. Methyl mercury would be taken up by membranes in target tissues, such as the brain, in close proximity to lipids and then initiate a chain reaction peroxidation of various lipid constituents as a result of methyl mercury's tendency to undergo homolytic fission. Without selenium treatment, methyl mercury will thus inhibit glutathione peroxidase activity, making it unable to decompose peroxides that may initiate methyl mercury breakdown into methyl and mercury free radicals, and consequently this will result in tissue damage. Treatment with selenium will totally alleviate the inhibitory effect of methyl mercury on glutathione peroxidase, as shown by Chang and Suber (1982), by securing the integrity of the biological components of cells and tissues via antioxidation. This also explains why vitamin E, also an antioxidative agent, showed protective effects against methyl mercury toxicity (Ganther, 1978).

Other workers have reported that they observed no evidence of breakage of the C–Hg bond in a number of tissues (Sheline and Schmidt-Nielsen, 1977), but this does not necessarily negate Ganther's free radical hypothesis. Even if there was homolytic fission of methyl mercury into CH_3 and Hg free radicals, such radicals do not have time to redistribute independently to other tissues. Because of their highly unstable nature, they would immediately interact with other molecules, for instance, with lipids and other tissue components, and eventually become bound to them.

5. SYNERGISM BETWEEN MERCURY AND SELENIUM

Despite the large body of information indicating the protective effects of selenium against mercury poisoning, there are also observations of an additive, or even synergistic, effect of mercury and selenium.

Huckabee and Griffith (1974) demonstrated a strong synergism between mercury and selenium mixtures on embryonic development of carp *Cyprinus carpio* eggs. Eggs placed in water containing trace amounts of mercuric chloride and selenite had a significantly reduced percentage of hatchability compared with eggs exposed to the same concentrations of mercury or selenium alone. These results show that selenium can sometimes enhance mercury toxicity. The exact mechanism of this synergism is yet to be established. Since both mercury and selenium have affinity for sulfhydryl groups, it is possible that these elements in the ambient water are reacting directly with sulfhydryl groups in the outer membrane of the egg to kill it. Years later, Klaverkamp *et al.* (1983) conducted a similar study with fertilized eggs of rainbow lake trout *Salvelinus namaycush* and compared the results with those obtained by Huckabee and Griffith with carp eggs. Their results showed that mercury produced concentration-dependent decreases in median survival times and median hatch times. But in contrast to Huckabee and Griffith's results, at concentrations of 100 mg Se $liter^{-1}$ and higher, an apparent protective effect of selenium on mercury toxicity was observed.

For chick embryos, a moderate degree of synergism between mercury and selenium has been reported (Birge *et al.*, 1976). When mercuric chloride and sodium selenate were injected into the yolk of chicken eggs, actual hatchability frequencies for different concentrations of mercury and selenium mixtures were 10–13% lower than predicted additive values.

Glickstein (1978) studied the interaction of selenium and mercury toxicity in embryos of the oyster *Crassostrea gigas* and the larvae of the crab *Cancer magister.* It was reported that high levels of selenium increased mercuric chloride toxicity, while moderate selenium concentrations protected the animals against mercuric chloride toxicity.

In early developmental stages of the Japanese ricefish *Oryzias latipes,* no additive or synergistic effect was observed between mercury and selenium, nor did selenium show any protective effect against mercury in the preliver embryos; i.e., in embryos that had started the formation of the liver rudiment, selenium treatment prior to mercury administration markedly lowered the mortality rate compared with those receiving mercury alone (Bowers *et al.*, 1980). It was already shown that when high concentrations of selenium are present, the location of protein-bound mercury changes from soluble renal fraction to the liver (Fang, 1977). It is under high selenium concentrations that the liver plays a critical role in mercury–selenium interactions. The failure of selenium to protect against mercuric chloride toxicity in carp eggs and in chicks might also be due to the absence of a liver in the early stages of development to act as a biological sink. The findings of Bowers and his co-workers strongly indicate the importance of the liver in mercury–selenium interactions.

The chemical form of both mercury and selenium may also determine the kind of interaction between these two elements. For instance, selenium in the animal body may undergo methylation and form dimethyl selenide. From the point of view of selenium detoxification, methylation is an effective mechanism since dimethyl selenide is 500 times less toxic than the selenite form of selenium. Unfortunately, dimethyl selenide acts strongly synergistically with mercury (Wilber, 1980). The interaction of methylated selenium and mercury cannot be overlooked as a possible cause of the observed synergism between mercury and selenium.

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