Mercury: selenium interactions and health implications

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Abstract

Measuring the amount of mercury present in the environment or food sources may provide an inadequate reflection of the potential for health risks if the protective effects of selenium are not also considered. Selenium's involvement is apparent throughout the mercury cycle, influencing its transport, biogeochemical exposure, bioavailability, toxicological consequences, and remediation. Likewise, numerous studies indicate that selenium, present in many foods (including fish), protects against mercury exposure. Studies have also shown mercury exposure reduces the activity of selenium dependent enzymes. While seemingly distinct, these concepts may actually be complementary perspectives of the mercury-selenium binding interaction. Owing to the extremely high affinity between mercury and selenium, selenium sequesters mercury and reduces its biological availability. It is obvious that the converse is also true; as a result of the high affinity complexes formed, mercury sequesters selenium. This is important because selenium is required for normal activity of numerous selenium dependent enzymes. Through diversion of selenium into formation of insoluble mercury-selenides, mercury may inhibit the formation of selenium dependent enzymes while supplemental selenium supports their continued synthesis. Further research into mercury-selenium interactions will help us understand the consequences of mercury exposure and identify populations which may be protected or at greater risk to mercury's toxic effects.

Key words mercury, selenium, mercury-selenide, selenocysteine, selenoenzymes, bioavailability, pathophysiology, mercury toxicity, selenium deficiency

Exposure to mercury

Mercury is a heavy metal of increasing concern as a global pollutant. The primary human exposure to methyl mercury is dietary from fish consumption. The toxic effects of MeHg can make it a potential health problem, and it is listed by the International Program of Chemical Safety as one of the most dangerous chemicals in the environment (1). In June of 2003, 48 scientists from 17 countries participated in the 61st meeting of the Joint Expert Committee for Food Additives and Contaminants (JECFA). Established by the Food and Agriculture Organization and the World Health Organization, JECFA recommended to the Codex Alimentarius Commission that the provisional tolerable weekly intake of methyl mercury be reduced from 3.3 to 1.6 μg per kg of body weight per week (2: ftp://ftp.fao.org/es/esn/jecfa/jecfa61sc.pdf).

Although adults can experience neurological effects when exposed to high concentrations of methyl mercury, advisories have mainly arisen because of the increasing concerns regarding methyl mercury's effects in the developing nervous systems of unborn and growing children. Alarmingly, while the placental barrier can stop many toxic elements, methyl mercury is an exception in that it not only crosses the placenta, it accumulates at higher concentrations on the fetal side than on the maternal (3). Worsening the situation for the developing fetus, mercury also crosses the blood-brain barrier and exhibits long-term retention once it gets across (4). These factors exacerbate mercury's neurotoxicity and conspire to intensify the pathological effects in this most important and most vulnerable of the body's tissues. Destruction of an early generation of brain cells will naturally preclude development of further generations of cells, constraining development of brain and nerve tissues. While these are the expected consequences from high doses of mercury exposure, the effects of chronic low exposure are undetermined.

Several episodes of fetal MeHg poisoning have been reported and confirm that the developing fetal brain is especially susceptible (5-8). However, only in Minamata (9) and Niigata (10), Japan was the poisoning because of fish consumption. Minamata disease, or methyl mercury poisoning, was first recognized in 1956, around Minamata Bay and occurred again in 1965 in the Agano River basin in Niigata, Japan. It has been estimated that 27 tons of mercury compounds were dumped into the Minamata Bay from 1932 to 1968. Minamata disease was caused by the consumption of mercury contaminated fish and shellfish obtained from these waters. Typically, marine fish contain less than 0.5 ppm MeHg, with some high predator fish frequently having levels over 1 ppm. Certain Canadian waters polluted with MeHg have fish levels exceeding 10 ppm. However, fish from Minamata Bay were reported to contain up to 40 ppm MeHg. Over 3000 victims were recognized as having Minamata disease. Children showed severe neurodevelopmental impairment even though the mothers experienced minimal or no clinical symptoms (3). No other children with symptoms of fetal poisoning from fish consumption have been described since the Minamata and Niigata episodes. This has caused much controversy over fish consumption and the risks of methyl mercury ingestion. However, recent research is beginning to provide insight regarding possible mechanisms involved in methyl mercury poisoning and why the discrepancies may occur among observations from various studies.

It is well recognized that mercury and sulphur bind together to form complexes. This binding property is the basis of chelating therapy used as a treatment in cases of acute mercury poisoning. The complexes between mercury and selenium are less generally known but of much higher affinity. Physiologically, sulphur is far more abundant than selenium, yet because of selenium's higher affinity, mercury selectively binds with selenium to form insoluble mercury selenides (11-12). This interaction has been assumed to be a 'protective' effect whereby supplemental selenium complexes the mercury and prevents negative effects in animals fed otherwise toxic amounts of mercury (13-14). The first report on the protective effect of selenite against mercury toxicity appeared in 1967 (15). Since then, numerous studies have shown selenium supplementation counteracts the negative impacts of exposure to mercury, particularly in regard to neurotoxicity, fetotoxicity, and developmental toxicity. The ability of selenium compounds to decrease the toxic action of mercury has been established in all investigated species of mammals, birds, and fish (16-17).

Selenium as a nutrient

Ironically, until approximately 40 years ago, selenium was known only as a poison. It is now known that selenium is essential for the normal function of many of the systems of the body and selenium deficiency can have adverse consequences on these systems. Selenium can act as a growth factor; has powerful antioxidant and anticancer properties; and supports normal thyroid hormone homeostasis, immunity, and fertility (see table). Although still omitted from many biochemistry textbooks, two of the 22 primary amino acids are distinguished by their possession of selenium: selenomethionine and selenocysteine. Selenomethionine is biochemically equivalent to methionine and is chiefly regarded as an unregulated storage compartment for selenium. In contrast, selenocysteine is tightly regulated and specifically incorporated into numerous proteins that perform essential biological functions.

Table Mammalian selenoprotein / selenoenzymes

Mass	Selenoprotein name: information
65kDa	Selenoprotein P: primary Se transporter in plasma (10 selenocysteines/molecule)
58kDa	Selenoprotein N: enriched in pancreas, ovary, prostate and spleen; function unknown
57kDa	Thioredoxin reductase: active in DNA synthesis; has immunoregulatory influences (3 forms)
50kDa	Selenophosphate synthetase: present in all tissues; required for selenoprotein synthesis
48kDa	Selenoprotein Z: enriched in kidney, liver, testis, prostate, and thymus; function unknown (2 forms)
27kDa	Phospholipid glutathione peroxidase: detoxifies lipid peroxides
23kDa	Cytosolic glutathione peroxidase: detoxifies peroxides in aqueous compartment of cytosol
23kDa	Plasma glutathione peroxidase: primarily synthesized in kidney; active in Se transport
23kDa	Sperm glutathione peroxidase: required for normal sperm activity; function unknown
23kDa	Gastrointestinal glutathione peroxidase: tissue specific
18.8kDa	Selenoprotein T: function unknown
18-kDa	Unknown: found to be one of the most preferentially selenium-supplied proteins; function unknown
16kDa	Selenoprotein X: present in liver, leukocytes, lung, placenta and brain; function unknown
15kDa	15kDa selenoprotein: discovered in leukocytes, but broadly distributed; function unknown
14kDa	Thyroid hormone 5'deiodinase: present in tissues that convert T4 → T3 (thyroxine)
12.6kDa	Selenoprotein R: function unknown
10kDa	Selenoprotein W: first found in muscle, but widely distributed; function unknown
8kDa	8kDa selenoprotein: tissue-dependent occurrence and distributions; function unknown
7kDa	7kDa selenoprotein: tissue-dependent occurrence and distributions; function unknown
5kDa	5kDa selenoprotein: tissue-dependent occurrence and distributions; function unknown
<5kDa	LMW selenomolecules: present in varying amounts in all tissues; function unknown

The recognition of selenium's role in health has prompted worldwide response. Selenium status in China and northern Europe is sufficiently low that nationwide trials of selenium supplementation are under way (18-19). Finland has instituted selenium supplementation in its fertilizers (20), and Sweden has experimented with adding selenium to its lakes (21). Many nations are making efforts to introduce imported food sources with higher selenium contents into their diets. European hospital trials have reported successful therapeutic application of selenium supplementation to assist recovery of critically ill patients with severe systemic inflammatory conditions (22-25). The study of selenium physiology has become one of the fastest growing areas in biomedical research, and its role in protection against mercury toxicity is also gaining increased attention.

Occurring in tissue-specific distributions, approximately 35 selenoproteins or protein subunits have been detected in animal cells. Selenoprotein activities may be especially important in the brain, pituitary, and thyroid, as it is virtually impossible to deplete the selenium present in these tissues. Even after extreme experimental selenium depletion in animal studies conducted over six generations which led to a drastic decrease of selenium concentrations in liver, skeletal muscle, and blood (below 1% of normal levels), the brain still retained 60% of the selenium concentration found in control animal brains. Further studies showed rats maintained this brain concentration of 60% normal value through 16 generations of selenium-deficient diets (26). Hill and colleagues found that feeding diets containing less than 0.1 ppm selenium to selenoprotein P knockout mice caused their brain selenium levels to be reduced to 43% of normal, the lowest brain selenium concentration achieved thus far (27). These mice lost weight, developed poor motor coordination, and males demonstrated sharply reduced fertility. Feeding diets containing 2 ppm Se to these mice restored their brain selenium concentration and motor coordination to normal. Additionally, the total disruption of selenoprotein synthesis in mice, achieved by knocking out the selenocysteinyl-tRNA gene, resulted in early embryonal lethality (28). These studies further support the concept of tight regulation of selenium in the brain.

Methyl mercury and selenium interaction

Accordingly, if a toxin can enter the brain and disrupt selenoprotein synthesis, detrimental effects would be expected. Methyl mercury not only has the ability to cross the blood-brain barrier, but its exceptionally high affinity for selenium may enable it to specifically sequester the brain's selenium and diminish selenoprotein synthesis. The affinity constant for selenocysteine's selenium and mercury is ~10^{-22}, and the free selenides that form during each cycle of selenocysteine synthesis have an exceptionally high affinity constant for mercury: 10^{-45} (29). Mercury selenide precipitates have extremely low solubility, ranging from 10^{-58} to 10^{-65}; thus they are thought to be metabolically inert (30). It is reasonable then to assume that not only does selenium have an effect on mercury's bioavailability, but mercury may also have an effect on selenium bioavailability. Therefore, the understanding of the 'protective effect' of selenium against mercury exposure may actually be backwards. Mercury's propensity for selenium sequestration in brain and endocrine tissues may inhibit formation of essential Se-dependent proteins (selenoproteins). Hence, selenium's 'protective effect' against mercury toxicity may simply reflect the importance of maintaining sufficient free selenium to support normal selenium-dependent enzyme synthesis and activity (see figure).

Although the selenium-mercury interaction has been the focus of extensive research, there have been few laboratory studies concerning the interactions between the nutritional level of selenium and the negative effects of methyl mercury. Selenium-deficient rodents are more susceptible to the prenatal toxicity of methyl mercury, and it is noteworthy that exposure to mercury reduced the activity of the selenoprotein glutathione peroxidase in the fetal/neonatal brain (31). Additionally, when rodents are depleted of selenium

perinatally, the thyroid hormone economy of the fetus is disturbed (32). Thyroid hormones are essential for normal neurological development. Should disruption of thyroid hormone regulation occur at vulnerable periods of development, irreversible neurological damage can result. Iodothyronine deiodinases are selenoproteins which regulate the tissue levels of thyroid hormones. Therefore, severe selenium deficiency may be detrimental to the developing brain. Considering mercury's extremely high binding affinity for selenium and its ability to cross the blood-brain barrier, it is reasonable to suspect the mercury-selenium interaction may have a role in developmental pathophysiology.

Through intense laboratory research and epidemiological studies, Dr. Clarkson and his colleagues from the University of Rochester, New York, have been addressing the health effects from methyl mercury exposure for nearly half a century. (For a review of their work, see Myers et al 2000 (33).) Their research confirmed the neurological deficits reported from MeHg poisoning incidents in Japan. However, they found no adverse associations from consuming fish containing typical mercury levels. Additionally, their studies of both prenatal and postnatal measures of MeHg exposure from fish consumption in Seychellois children have been associated with beneficial effects. Their results, however, contrast with those found in studies being carried out in the Faroe Islands (34-35), which reported adverse associations from prenatal MeHg exposure. There are several differences between these studies and the populations in general. However, the most intriguing distinction may be the source of MeHg exposure.

The diet consumed by Faroe Islanders includes whale whereas the Seychelles Islanders' diet does not. Whale is known to contain PCBs (36-38) as well as possibly other toxins not typically found in fish. Additionally, the amount of MeHg in some types of whale meat analysed has been reported to be exceedingly high. The concentration of mercury present in whale rises continually with age and can exceed the selenium content (39). This is seen in high-end predator whales such as pilot whales rather than filter feeders such as bowhead whales. Mercury concentrations in samples of pilot whale have been 5000 times greater than the Japanese government's limit for mercury contamination of 0.4 ppm (40). In contrast to whales, methyl mercury concentrations in fish rise with age, but as their mercury contents increase, so do their selenium concentrations (41). To our knowledge, there are no reports of mercury exceeding selenium concentrations in any ocean fish.

Friedman et al. studied the protective effect of freeze-dried swordfish on methyl mercury toxicity in rats. The rats that were experimentally administered methyl mercury and fed a swordfish diet showed no signs of neurotoxic effects characteristic of mercury poisoning, while rats not fed swordfish did. Analysis of the swordfish showed selenium concentrations were at least twice as high as the mercury levels. The authors suggested that the excess selenium protected the rats from the effects of the administered methyl mercury (42).

Although several population studies have suggested an association between high fish intake and reduced coronary heart disease (CHD), men in eastern Finland who consume large amounts of freshwater fish have an exceptionally high CHD mortality. Salonen et al studied the relationship between mercury intake from fish and CHD in Finland (43). The authors hypothesized that the high mercury levels from fish contributed to increased incidence of CHD. Before soil supplementation, Finland had the lowest selenium levels throughout Europe.

The authors suggested that mercury might contribute to CHD risk by complexing to selenium and reducing its bioavailability for glutathione peroxidase, thus promoting lipid peroxidation. They further suggest that the lack of a similar correlation between CHD and fish consumption in other population studies was owing to high intakes of selenium.

Furthermore, because of the binding interaction between these two elements, selenium appears also have an effect on the bioavailability of mercury, both biologically and environmentally. Several studies suggest an important role of selenium in the bioaccumulation of mercury in fish (44-46). Paulsson and Lindbergh reported selenium supplementation to lake waters in Sweden resulted in a 75%-85% reduction in mercury levels of fish when measured over a three-year period (47). Southworth et al (48-49) reported that the elimination of selenium-rich discharges of fly ash to Rogers Quarry in Tennessee in 1989 caused a steady increase in mercury concentrations. The aqueous selenium concentrations decreased from 25 to < 2 μg /L. The mean selenium concentrations in bass declined from 3 to 1 mg/kg over the first 5 years and remained at 1–1.5 mg/kg for the last three years of the study. During this time, the mean mercury concentrations in bass rose from 0.02 to 0.61 mg/kg. Studies such as these confirm the importance of selenium consideration in providing mercury exposure management.

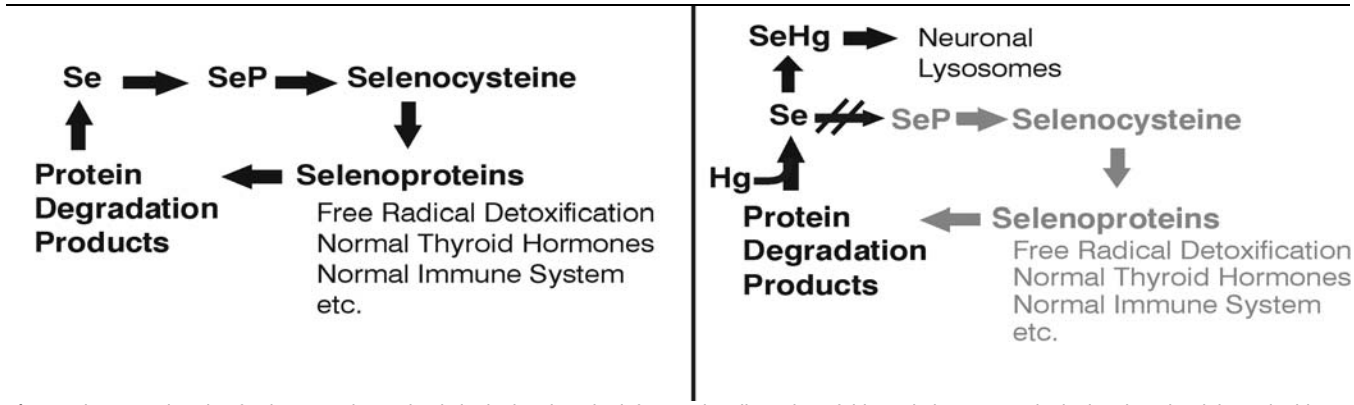

Figure The normal cycle of selenoprotein synthesis is depicted on the left. Putative disruption of this cycle by mercury is depicted on the right. Selenide freed during selenoprotein breakdown becomes available to bind with mercury. Formation of insoluble mercury selenides may reduce the bioavailability of selenium for protein synthesis

Consequently, it is possible that the health risks of methyl mercury exposure may vary in response to individual and regional differences in selenium intake. The geological distribution of selenium can be highly variable: abundant in soils of one area and deficient in regions only miles away. These variances will influence the amounts of selenium in foods, predisposing for or protecting against consequences of mercury exposure. Furthermore, variations in relative quantities and quality of food choices can result in individual differences in selenium status. Conceivably, a 'transient selenium deficiency' may briefly occur after ingesting a high-mercury-containing food, such as certain whale meat. This 'transient' deficiency could then be recovered from consuming adequate amounts of selenium to compensate for the loss. However, if a deficiency such as this were to happen during pregnancy, the fetus might be affected depending upon the severity of the deficiency and the time of development. This would only appear likely in populations with a compromised selenium status along with exposure to foods containing unusually high levels of mercury.

Recommended selenium intake

The standard of recommended intake levels of selenium is under debate. (For a full review, see Rayman (50).) The UK reference nutrient intake (RNI) of 75 μg per day for men and 60 μg per day for women has been determined as the intake believed to be necessary to maximize the activity of the antioxidant selenoenzyme GPx in plasma (51). The American recommended dietary allowance (RDA), set at 55 μg per day for both men and women, is based on the investigations of the selenium intake required to achieve plateau concentrations of plasma GPx (52). The WHO/FAO/IAEA expert group recommended an intake level of only 40 μg per day for men and 30 μg per day for women, assuming only two-thirds of the full expression of GPx activity is required (53). However, as Rayman (50) points out, if levels of GPx activity saturation are determined using platelets rather than plasma, then the intake levels needed should be approximately 80-100 μg per day. Additionally, intake levels which saturate plasma GPx activity are insufficient to optimise the immune response, and reduce cancer risk. This insufficiency is amplified at intake levels suggested by the WHO/FAO/IAEA which only accommodate two thirds of plasma GPx activity. Currently, the UK and other European countries have intake levels of approximately half the RNI, and areas of China have intakes of less than 19 μg per day for men and less than 13 μg per day for women. Likewise, low-selenium soils are prevalent in many areas of the world including New Zealand, Russia, and Africa, thus compromising the selenium status of these populations.

It should be noted that selenium toxicity has also been a concern. Although selenium toxicities have been reported, human toxicity is rare. Consumption of selenium-toxic food was reported in Enshi County, China (54). Chronically intoxicated individuals ingested an average of 4.99 mg selenium/day, with some individuals consuming as much as 38 mg selenium/day. Signs of selenosis included loss of hair and nails, skin lesions, tooth decay, and abnormalities of the nervous system. Selenium poisoning was also reported in 13 persons in the United States who consumed a "health food" supplement that contained ~182 times more selenium than stated on the label (55-56). The total amount of selenium ingested by the victims was calculated to be 27–2387 mg. The most common symptoms were nausea, vomiting, hair loss, nail changes, irritability, fatigue, and peripheral neuropathy. Since the biochemical basis of selenosis is not understood, the upper limit of the estimated safe and adequate dietary intake is currently set at 200 μg per day (57).

Conclusion

In summary, studying the pathology of mercury toxicity may require a more insightful question than simply, 'How much mercury is consumed?' The more appropriate question may be, 'Is a sufficient amount of free selenium available in the cell to create the necessary selenoenzymes or is too much selenium lost by binding to mercury?' In this regard, the sensitivity to mercury-induced neurotoxicity may be due to the balance of mercury and selenium. Selenium's involvement is apparent throughout the mercury cycle, influencing its transport, biogeochemical exposure, bioavailability, toxicological consequences, and remediation. Therefore, measuring the amount of mercury present in the environment or food sources may provide an inadequate reflection of the potential for health risks if the protective effects of selenium are not also considered. Further research in these areas will provide valuable information that is needed to understand the true impact of mercury exposure as well as identify areas which may be protected or at greater risk to mercury's toxic effects.

Competing interests None declared.

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Nutrition and neurodevelopment: the search for candidate nutrients in the Seychelles Child Development Nutrition Study

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Abstract

This review examines the role of nutrients in child development and outlines the key nutrients identified as potentially important to neurodevelopment among high fish consumers in the Seychelles Child Development Nutrition Study (SCDNS). It describes the clinical assessment of these nutrients in the blood and breast milk samples collected from the cohort of 300 pregnant women who were recruited, at their first antenatal visit, on the SCDNS. These key nutrients include the long chain polyunsaturated fatty acids (LCPUFA), docosohexaenoic acid (DHA) and arachidonic acid (AA), both of which may affect neurodevelopment in the later stages of fetal growth. Only DHA, however, is strongly associated with fish consumption, the predominant source of the neurotoxicant methyl mercury (MeHg). Any benefits of increased selenium status on neurodevelopment are likely to accrue via detoxification of MeHg during fetal growth, while benefits of optimal iodine or thyroid status are likely to be directly related to neurodevelopment during late fetal growth. Unlike LCPUFA, Se, and I, the status of the B vitamins, folate, vitamin B12, vitamin B6, and riboflavin are unlikely to be closely related to fish consumption but the status of each of these B vitamins is likely to impinge on overall status of choline, which is expected to have direct effects on neurodevelopment both prenatally and postnatally and may also impact on MeHg toxicity. Choline status, together with the status of two other candidate nutrients, zinc and copper, which are also likely to have effects on neurodevelopment prenatally and postnatally, are expected to have some correlation with fish consumption.

Key words long chain polyunsaturated fatty acids, iodine, selenium, choline, B-vitamins, iron, child development

Introduction

The Seychelles Child Development Study (SCDS) was initiated in 1987 to test for adverse effects of methyl mercury exposure from fish consumption on child development. Contrary to expected findings, no adverse outcomes on child development have been associated with increasing mercury exposure (1). As fish intake has been shown to correlate with hair mercury, researchers from the SCDS have since hypothesised that various micronutrients in fish may be responsible for the lack of adverse effects. It is hypothesised that these nutrients in fish may either be beneficial to child development and/or protective against the neurotoxic effects of methyl mercury. The Seychelles Child Development Nutrition Study (SCDNS) was subsequently established to examine this proposed interrelationship between nutrition and child development. A cohort of 300 pregnant women was recruited at first antenatal visit and blood samples taken at enrolment, 28 weeks gestation, and post-delivery. A total of 24 were excluded subsequently because of miscarriage, neonatal death or deliveries overseas. Cord blood samples and breast/formula milk samples were also collected. An extensive battery of psychological tests have been carried out on the infants with more tests yet to be completed; the intention being to correlate neurodevelopmental outcome with prenatal and postnatal nutrient exposure. The aim of this paper is to examine the role of nutrients in child development and to outline the key nutrients identified as important in the SCDNS and to describe their clinical assessment in the collected blood and milk samples.