The Influence of Nutrition on Methyl Mercury Intoxication

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This article reviews progress in the research of methyl mercury (MeHg) and nutrient interactions during the past two decades. Special emphasis is placed on the following three major areas: *a*) effects on kinetics, *b*) effects on toxicity, and *c*) possible mechanisms. Dietary information is not usually collected in most epidemiologic studies examining of the effects of MeHg exposure. However, inconsistency of the MeHg toxicity observed in different populations is commonly attributed to possible effects of dietary modulation. Even though the mechanisms of interaction have not been totally elucidated, research in nutritional toxicology has provided insights into the understanding of the effects of nutrients on MeHg toxicity. Some of this information can be readily incorporated into the risk assessment of MeHg in the diets of fish-eating populations. It is also clear that there is a need for more studies designed specifically to address the role of nutrition in the metabolism and detoxification of MeHg. It is also important to collect more detailed dietary information in future epidemiologic studies of MeHg exposure. *Key words:* animal, antioxidants, diet, fish, human, *in vitro*, *in vivo*, methyl mercury, minerals, nutrition, review, selenium, vitamins. — *Environ Health Perspect* 108(suppl 1):29–56 (2000).
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Introduction

The Risk of Organic Mercury in the Diet

Methyl mercury (MeHg) intoxication has been a public health problem for many decades (*1*). Consideration of the role of environmental factors in determining susceptibility to MeHg toxicity has recently been renewed by evidence from epidemiologic studies in the Amazon (*2*), the Republic of the Seychelles (*3*), and the Faroe Islands (*4*). Although many of these populations have been exposed to similar doses of MeHg through the consumption of fish and seafood, some populations have experienced subsequent neurotoxic effects, whereas others have not (*5*). Growing awareness of the use of nutrition to maintain optimum health emphasizes the relevance of considering the way that nutritional factors may affect heavy metal toxicity. There are many reviews on human susceptibility to toxic heavy metals (e.g., *6–10*). However, most reviews do not give enough attention to nutritional factors that might influence human response to heavy metal intoxication. This review focuses on nutrition as a potential modifier of MeHg toxicity. Reviews of the pharmacology and chemistry of mercury (Hg) compounds have been presented elsewhere (*1,11*).

Since the epidemic MeHg poisoning from contaminated fish consumption in Minamata, Japan, in the late 1950s (*12,13*), MeHg has been one of the most dramatic and best-documented examples of the bioaccumulation of toxins in the environment, particularly in the aquatic food chain (*14*). The neurologic symptoms induced by MeHg in the Minamata epidemic are still being observed 22 years after consumption of contaminated fish (*15*). MeHg attains its highest concentrations in edible tissues of long-lived predatory fish. It is an example of a toxic compound that is well absorbed from the diet despite having no demonstrated biologic requirement in humans (*9*), and the diet serves as the main source of exposure in human populations (*1*).

Daily intake of MeHg depends on its concentration in foodstuffs and on the dietary habits of the consumer. With increasing naturally present inorganic Hg in the hydrosphere and biosphere due to acid rain and industrial mining activities and the subsequent biomethylation of this Hg, the global exposure to MeHg in the 21st century is expected to increase (*16*). MeHg has been implicated as a neurotoxicant, a mutagen, and a teratogen in biologic organisms (*17*). Therefore, MeHg toxicity is becoming a global environmental health concern.

Currently, the Food and Agriculture Organization/World Health Organization (FAO/WHO) provisional tolerable weekly intake is defined as 3.3 μg/kg/week or 200 μg/week for adults and breast-fed infants, based on prevention of parathesia in adults and older children (*1*). Moreover, the fetus is particularly sensitive to MeHg even at levels that result in few, if any, signs of maternal clinical illness or toxicity. High levels of prenatal MeHg exposure can result in cerebral palsy, mental retardation, low birth weight, and early sensorimotor dysfunction (*18*). Therefore, scientists have focused on the reevaluation of reference doses for MeHg in view of its prenatal developmental effects, infant exposure, and the important objective of establishing the lowest level effects for human exposure (*19–23*).

Recently, results of two large controlled longitudinal studies of effects of prenatal Hg exposure from seafood consumption on child neurodevelopment have been published (*24,25*). These studies are considered references by many regulatory agencies because they use low-dose chronic exposure and state-of-the-art methodologies for measuring developmental effects. The first study was conducted in the Republic of Seychelles, an archipelago in the Indian Ocean, where 85% of the population daily consumes ocean fish (*3,24*). A cohort of 711 mother–child pairs was studied. The mean maternal hair total Hg level was 6.8 ppm and the mean child hair total Hg level at 66 months of age was 6.5 ppm. No adverse outcomes at 66 months were associated with either prenatal or postnatal MeHg exposure. The second study was conducted on a cohort of 1,022 consecutive singleton births during 1986 and 1987 in the Faroe Islands (*4,25*). At approximately 7 years of age, 917 of the children underwent detailed neurobehavioral examination. Clinical examination and neurophysiologic testing did not reveal any clear-cut Hg-related abnormalities. However, when a subsample of 112 children whose mothers had a hair Hg concentration of 10–20 ppm was compared to a subsample of children whose mothers had exposures below 3 ppm, mild decrements were observed, especially in the domains of motor function, language, and memory (*25*).

In response to this recently available epidemiologic data, Health Canada has proposed a provisional no observable adverse effect level of 10 ppm Hg in maternal hair (*26*). When converted to an equivalent daily intake from food and using a 5-fold uncertainty factor to account for interindividual variability, the provisional tolerable daily intake for women of reproductive age and infants was revised to 0.2 μg/kg body weight (bw)/day (*26*). The U. S. Environmental

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Protection Agency (U.S.EPA) took a similar approach and set the reference dose for MeHg at 0.1 μg/kg bw/day, using an uncertainty factor of 10 (*27*). Under these guidelines, the maximum weekly MeHg intake for a woman of average body weight (65 kg) should be less than 91 μg (Health Canada) or 45.5 μg (U.S. EPA). Assuming the average MeHg concentration in fish is 0.5 μg/g, a woman can only consume between half a fish (100 g) to a whole fish meal (200 g) per week. It is clear that a significant portion of the population, particularly the families of fishermen and aboriginal people, are exposed to MeHg beyond these guideline levels. The risk of dietary exposure to MeHg among the general public has to be better characterized.

Epidemiologic Evidence for Dietary Effects on MeHg Toxicity

An extensive review of epidemiologic data relating Hg exposure through the diet to nutritional parameters is presented in Table 1 (see Appendix for all tables). Fish and marine products are generally regarded as the major sources of MeHg exposure among the general public. Data collected by the Joint United National Environment Program (UNEP)/FAO/WHO Food Contamination Monitoring Program revealed that the MeHg contribution from fish and fish products varied from 20 to 85% among different populations and that drinking water, cereals, vegetables, and meat could also be significant contributors to MeHg burden (*46,47*). In addition, dietary practices such as chewing hard-boiled eggs, which decreased mercury vapor (Hg^0) release from dental amalgams (*48*), or chewing gum, which increased the release of Hg^0 from dental amalgams (*40*), may modify individual exposures to Hg. Thus, the conclusion that fish are a major contributor to the total intake of Hg is not necessarily justified for every population and is highly dependent on dietary habits (*46,47*).

Epidemiologic studies have been conducted on the exposure of humans to Hg through fish and marine mammal consumption in different geographical areas: the Seychelles (*21,24*), the Canadian North (*49,50*), the Amazon (*2*), the Faroe Islands (*25*), Papua New Guinea (*51*), and Sweden (*52*). There are inconsistencies in the toxic dose; for example, the populations in the Amazon appear to be more sensitive (*53*). It has been suggested that dietary practice may be a significant factor affecting the susceptibility to MeHg on the basis of the observation that more whale meat is consumed in the Faroe Islands and more fish in the Seychelles (*5*). The duration and timing of exposure are also critical factors. For example, effects of prenatal exposure were more significant than the effects of exposure through breast-feeding in mice (*54*).

Of all nutrients, selenium (Se), because of protective effects observed in animal studies, has received the most attention as a potential protector against MeHg toxicity in populations consuming seafood (*55*). Moreover, the main sources of Hg in the diet, such as fish and marine mammals, are also rich sources of Se (*56*). Thus, Se has been the main nutritional factor considered by epidemiologic and clinical studies to date (Table 1). Dewailly (*28*) and Grandjean et al. (*32*) reported a correlation between Se and Hg in the serum or plasma, but other researchers did not observe such a correlation (*34,45*). No epidemiologic studies, however, have shown a correlation between Se intake and the occurrence or absence of symptoms for MeHg intoxication. Inconsistencies were also observed in the protective effects seen in animal studies (*57*). The role of Se remains to be confirmed in MeHg intoxication.

Macronutrient intakes such as fat intake have also been correlated with MeHg toxicity. Meltzer et al. (*36*) observed a positive correlation between dietary Hg and low-density lipoprotein cholesterol. Unsaturated fatty acids were also correlated with Hg exposure in populations frequently consuming seafood and fish (*28,42*), but there was no evidence of beneficial or antagonistic effects (Table 1). Other diet-related conditions with symptoms similar to those of MeHg may exacerbate its intoxication. Farkas (*30*) suggested that thiamine deficiency in Northern Canadian Indians may often be concurrent with MeHg exposure and that the neurotoxicity symptoms may be additive. Alcoholism and the occurrence of fetal alcohol syndrome are also diet-related confounders of the symptoms of MeHg toxicity (*58*). Since most studies did not collect sufficient detailed dietary information, it is unclear how dietary modifications, besides decreased consumption of Hg-containing foods, can affect the risk of MeHg toxicity.

Roles for Nutrition in MeHg Toxicity

Even though there is little evidence of nutrient effects at the population level, there is plenty of evidence that nutrients interact with the metabolism of Hg at the physiologic level. Nutrients can affect bioavailability, toxico-dynamics, and transport to target organs, and influence the immunologic, biochemical, or cytologic functional responses to Hg. However, as in the limited understanding of the mechanisms of MeHg toxicity (*17,59,60*), the overall mechanisms of modification of MeHg toxicity by nutrients are not well understood. Review articles in this area of nutritional toxicology are scant; most focus on the modification of MeHg toxicity by Se (*57,61–63*), vitamin C (*64–66*), vitamin E (*64,65*), and essential minerals (*7,67*). Examples of foods, macronutrients, vitamins, minerals and other food-related compounds that cause alterations in the metabolism of Hg are summarized in Tables 2, 3, and 4.

Foods such as fish, milk, meat, and wheat bran (Table 2); minerals such as Se, zinc (Zn), copper (Cu), and magnesium (Mg) (Table 3); and vitamins such as vitamin C, vitamin E, and vitamin B complex (Table 4) have been implicated in the alteration of Hg metabolism. However, evidence for protective or antagonistic effects is often complex and highly dependent on metabolic conditions. With the exception of Se and vitamin E, evidence for other nutrients is derived mainly from results of one or two studies. Moreover, nutritional considerations in many of these studies were not the main objective of the study. To address the conflicting results of the recent epidemiologic studies, principal investigators of these studies and other experts in Hg toxicology were invited to participate in a workshop titled the "Scientific Issues Relevant to Assessment of Health Effects from Exposure to MeHg" held by the National Institute of Environmental Health Sciences in North Carolina (November 18–20, 1998) (*154*). Among other conclusions, it was agreed that dietary factors may affect MeHg toxicity, but due to inadequate data there is a need for an extensive review of factors that might influence chronic MeHg toxicity. In response, this review provides an overview of our current understanding of how dietary factors affect MeHg toxicity.

Nutrition–Mercury Interactions

Studies on the interactions of nutrients and MeHg fall into two major categories: effects of nutrients on Hg metabolism and effects of Hg on nutrient metabolism. Both types of interactions will be addressed. Most information is currently derived from animal research and thus implications for human populations consuming mixed diets can only be speculative at this time.

Absorption of MeHg

Studies on the effects of nutrients on MeHg absorption are summarized in Table 5. Such studies are few, and the inconsistent animal model, dose, and route of exposure make comparison of studies difficult. MeHg is absorbed throughout the intestine and absorption is possible through most biologic membranes (*158*). Up to 90% of MeHg is quickly absorbed across the intestinal membrane and binds *in vivo* to proteins (*158,159*) such as albumin and other sulfur-containing proteins (*104,160*). MeHg recycles through the enterophepatic system in adults (*159,161*) and is excreted primarily in the

feces (*88*). It has been suggested that nutritional factors influence the reabsorption rate of MeHg rather than its primary absorption (*96*). Several nutrients such as wheat bran may decrease the toxic effects of MeHg by inhibiting MeHg reabsorption in the gut after enterohepatic circulation. Wheat bran fiber (30% of diet) has been shown to alter the demethlyation rate of MeHg by intestinal flora in mice and thus influence the reabsorption and the excretion rate of Hg (*78*). Antibiotic treatment removed the differential effect of diet on Hg elimination in mice fed 0.6 mg Hg/kg body weight as methyl mercury chloride (MeHgCl) (*88*). It was also suggested that the speciation of Hg in some fish, such as tuna, may be less toxic to fish consumers than other fish or foods containing other forms of Hg (*55*), but it is unknown if this effect is due to decreased bioavailability of MeHg. An important factor not adequately addressed is the effect of pH on absorption of biologic forms of MeHg, although Endo et al. (*162*) observed that alkalinity of the bile promoted the absorption of mercuric mercury (Hg^{2+}) in rats.

Foods such as milk may also promote the absorption of MeHg (Table 5). Landry et al. (*85*) showed that a milk diet in mice enhanced the reabsorption of MeHg after enterohepatic circulation. They suggested that this was due to decreased demethylation of MeHg, as inorganic forms of Hg are less readily absorbed (*85*). It is likely that diet affects the absorption of organic and inorganic Hg by a combination of different mechanisms. For instance, the inhibition of Hg^{2+} absorption by a milk diet, unlike MeHg absorption, is thought to be due to its association with the milk triglycerides (*86*) rather than metabolism by intestinal flora. In addition, removal of the cecum decreased the excretion of Hg after exposure to Hg^{2+} in mice (*163*), but the significance of bowel resection to MeHg exposure in humans is not known.

The effects of MeHg on nutritional metabolism can be deleterious (Table 5). Mykkanen and Metsaniitty (*98*) studied the effect of MeHg on the absorption of Se and selenomethionine (Se–Met) in the duodenum of leghorn chicks and concluded that Hg reduced the transfer of selenite from the intestine to the body but not the transfer of Se–Met. This study suggested that the form of Se is a critical factor in the regulation of Se–Hg interactions. MeHg, not Hg^{2+}, is implicated in altering chloride (Cl^-) secretion in enterocytes (*133*), but Hg^{2+} such as that from MeHg demethylation also influences the absorption of nutrients. Mykkanen and Metsaniitty (*98*) suggested that a Se–Hg^{2+} complex may reduce the absorption of Se. The binding of Hg^{2+} to transmembrane thiol groups was implicated in the inhibition of the sugar–sodium (Na^+) phlorizin-sensitive cotransport system, and thus inhibition of the absorption of galactose in rats (*113*). Interestingly, cysteine (Cys) treatment post-Hg^{2+} exposure reversed this type of inhibition (*113*). Iturri and Nunez (*164*) observed that Hg^{2+} had no effect on the uptake of ferrous and ferric ions in mouse intestine.

Metabolism, Compartmentalization, and Kinetics

Nutrients have been shown to modulate the toxicokinetics and dynamics of MeHg metabolism. The following sections elaborate on the effects of nutrients on transport, distribution, and retention of MeHg, and the overall effects of MeHg on the metabolism of protein, carbohydrate, lipids, and other metabolites.

Nutrient effects on transport, distribution and retention of MeHg. FOODS AND MACRONUTRIENTS. In mice, MeHg is transported in blood, bound to serum proteins such as albumin and mercaptoalbumin (*104*), as stable conjugates to major organs such as kidney, liver, and brain, and also to the placenta and fetus in pregnancy. A significant fraction of MeHg, however, remains in erythrocytes and epithelial tissues (*165*). Although it is unknown whether certain foods could inhibit MeHg toxicity by influencing its transport, L-leucine, L-methionine, and 2-amino-2-norborane carboxylic acid may inhibit the uptake of MeHg through amino acid transport system L (*166*).

Cys is implicated as one nutrient that may increase MeHg neurotoxicity (Table 5). Studies with cultured calf brain capillary endothelial cells, an *in vitro* model of the blood–brain barrier, suggest that MeHg is transported to the brain as an L-Cys complex by amino acid transport system L (*167*), but MeHg may enter organs by any one of several transport systems, including the facilitated D-glucose transport system and the Cl^- ion transport system (*93*). Equilibrium constants of mercurials favor a link with thiol ligands (*57*). Association of MeHg with thiol compounds of small molecular weight promotes transport of MeHg both into and out of cells, providing access to specific membrane carriers through mimicry of natural substrates (*57*). For example, the observed MeHg–Cys complex was similar to Met, and the structure of two glutathione (GSH) molecules bound to Hg was similar to oxidized GSH (*168,169*).

Conversely, MeHg can also disturb nutrient transport such as the exchange of Met and Se through the blood–brain barrier (*170*). In pregnancy, Hg^{2+} can alter fetal uptake of nutrients such as Se, vitamin B_{12}, and Zn in mice (*171*), chickens (*98*), and humans (*172,173*). Hg^{2+} inhibited the Na^+-dependent L-alanine transport and L-lysine transport across human placenta (*172*), and Urbach et al. (*173*) showed that transfer of amino acids, but not glucose, across the placenta was affected. It is unknown whether competition occurs between serum protein-transported nutrients such as Cu and MeHg.

Hojbjerg et al. (*111,174*) and Rowland et al. (*78,88,175*) showed that diet composition affects the distribution of MeHg and its toxicity. Retention of Hg by various organs has been the prime concern of most studies on nutrient–Hg interactions (Tables 6–8). Whole-body Hg retention, organ Hg distribution and mortality rate are usually measured. Most studies, however, report effects of acute Hg exposure by injection rather than the more relevant chronic dietary exposure.

Seafood has received attention as a possible modifier of MeHg distribution in a way that protects organisms exposed to MeHg through the consumption of seafood. Eaton et al. (181) showed that cats receiving MeHg naturally in seal liver developed no signs of neurologic abnormalities after 90 days, unlike cats consuming beef liver with added MeHgCl. Thrower and Andrewartha (182) also reported that in rats, consumption of shark flesh naturally containing Hg and Se resulted in stimulated activities of GSH peroxidase, whereas Torula yeast diets with added Hg and Se did not. Ganther and Sunde (183) observed that MeHg exposure from a diet of tuna fish prolonged survival of Japanese quail compared to corn and soy diets containing similar levels of MeHg. Ohi et al. (72), however, also observed that Se in tuna fish was approximately half as efficient as selenite in the prevention of neurologic symptoms of MeHg exposure in rats.

The percentage of fiber in the diet also affects the retention of Hg. Rowland et al. (*78*) examined the effects of pectin, wheat bran, and cellulose compared to fiber-free diets on the toxicity of MeHg in mice and found that these alterations in the diet altered the ability of microflora to demethylate MeHg and thus affected the reabsorption rate of MeHg. As discussed earlier, wheat bran increased the excretion of Hg after MeHg exposure (*78*).

Protein level in the diet also affected the metabolism of MeHg; adequate protein intake prolongs survival after oral doses of MeHg (*69,87,89,257*). Specific amino acids such as Cys may detoxify MeHg by preventing inhibition of enzymes such as carnitine acyltransferase (*108*). However, Cys can act as a carrier for MeHg across the blood–brain barrier and thus alter Hg distribution by increasing Hg levels in the brain and increasing neurotoxicity (*76,82*).

Certain phytochemicals found in the diet reportedly protect against MeHg toxicity. Bala et al. (*75*) found that γ-linoleic acid reduced aberrations and sister chromatid exchanges caused by MeHg exposure in lymphocyte cultures. Tree barks containing tannins have been used industrially to decontaminate Hg in industrial sludge by adsorption (*194*). In addition, Cha (*73*) reported that rats consuming raw garlic as 6.7% of their diet decreased Hg accumulation in liver, kidneys, bone, and testes after exposure to 4 ppm MeHgCl in their drinking water for 12 weeks.

Foods such as milk and coconut oil appear to increase the retention of MeHg in organisms. Kostial et al. (*258,259*) suggested that milk diets may reduce Hg^{2+} retention compared to solid food diets in suckling rats. It is not clear how milk pre- and post-treatments affect the survival of laboratory animals of different ages exposed to MeHg or how this might be significant for human infants exposed to MeHg.

Increased coconut oil in the diet (5–50%) increased the whole-body retention of Hg in mice receiving single injections of 5 μmol MeHgCl, whereas increased cod liver oil in the diet (5–50%) did not affect the retention of MeHg (*111*). Mortality increased in Japanese quail with 15 ppm MeHgCl in their diet as the percentage of linoleic acid increased (*84*). However, these effects were only observed in birds that had not been receiving linoleic acid in their diets since hatching (*83*). It was shown that long-chain fatty acids interact with Hg *in vitro* (*260*), but how these interactions affect the toxicity of MeHg is unknown. Kling and Soares (*84*) suggested that increased levels of polyunsaturated fatty acids in the diet may increase susceptibility to Hg poisoning, but no results were presented to support this hypothesis.

Total Hg levels in mouse brain increased with a low-protein diet and the increase was further enhanced by sulfur amino acid supplementation (*69*). Hepatic, renal, blood, and plasma Hg levels also increased with a sulfur amino acid supplement to inadequate protein diets, likely because of changes in the neutral amino acid transport that altered the biochemical fate of MeHg (*69*). The one commonly consumed nonfood known to alter MeHg detoxification is alcohol. Ethanol appears to enhance the toxic effects and the mortality of MeHg (*185–187*). It enhances toxicity to the kidney by reducing activities of amino acid transferases and creatine phosphokinases (*79,188*).

MINERALS. Adequate intakes of Se and Zn may delay MeHg toxicity. Se has been suggested to counteract the toxicity of several heavy metals, including cadmium, Hg^{2+}, MeHg, thallium, and silver (*63*). The protective effect of Se against MeHg intoxication is less dramatic than that against sublimate intoxication (*57*), and Se in food at best delays but does not prevent MeHg intoxication (*57*). For both inorganic and organic Hg, Se has been implicated in the formation of the Hg–Se complexes GSH–Se–Hg and bis(methylmercuric) selenide, respectively (*115,237,249,261*). The protective effect of Se against MeHg toxicity does not appear to involve Hg absorption in the intestine or excretion of Hg in the urine or feces; Se also does not appear to affect the rate of MeHg demethylation (*57*). Sumino et al. (*201*) suggested that Se modifies the form of MeHg, thus altering its distribution by freeing MeHg from blood proteins.

The chemical speciation of Se is also an important factor. Nielsen and Andersen (*97*) observed that Se–Met, compared to selenite, fed to mice (3 μg/mL in drinking water) only slightly affected the toxicokinetics of MeHgCl in offspring. $HgCl_2$ given to rats caused a decrease in GSH reductase activity and δ-glutamyl Cys synthetase in the kidney (*262*). This decrease in enzyme activity was blocked if rats were given Se after Hg exposure (2:1 ratio of Hg to Se). Chmielnicka (*263*) reported that when selenite and Hg^{2+} were given jointly, the rise in urinary excretions of endogenous Cu^{2+} and Zn^{2+} due to Hg exposure were decreased. Several theories have been proposed for the protective effect of Se, including delayed onset of Hg toxicity, decreased severity of effects of inorganic or organic Hg, and the formation of an inert Hg–Se complex (*10,264*).

Studies on the effects of Zn^{2+} on Hg exposure have focused mainly on inorganic Hg rather than organic mercury. It is thought that Zn^{2+} may reduce lipid peroxidation by increasing the activities of enzymes such as GSH peroxidase to ameliorate signs of neurotoxicity (*125,265*). Zn^{2+} induction of metallothionein (MT) in rat astrocytes was protective of alterations in sodium and potassium ion flux due to MeHg exposure (*225*).

Iron appears to enhance MeHg toxicity. LeBel et al. (*266*) showed that the iron chelator deferoxamine inhibited MeHg-induced excess oxygen reactive species formation. Peckham and Choi (*267*) also observed that MeHg exposure to fetal mouse astrocytes disrupted ferritin along cell membranes.

VITAMINS. It is well established that active oxygen species (superoxide radical, hydroxyl radical, singlet oxygen, peroxides) are produced during the metabolism of MeHg (*114,268,269*). Vitamins E and C may modify MeHg toxicity due to their antioxidant properties. Vitamin E protected against neurotoxic effects such as ataxia, paralysis of hind limbs, and necrosis in brain in rat and hamster (*143,270*). Vitamin E alleviated toxicity due to organic Hg toxicity but not Hg^{2+} toxicity in Japanese quail (*84*). There is also some evidence that the protective effect provided by vitamin E extends from the parent to offspring (*208*). Vitamin E inhibited MeHg toxicity in a number of *in vitro* studies (*144,145,251*).

Studies of vitamin C treatment after exposure to MeHg showed contradictory results. Vijayalakshmi et al. (*180*) and Bapu et al. (*127*) examined the effects of vitamin C treatment after subcutaneous injections of MeHgCl for 7 days in mice and found improvements in recoveries of enzymes activities of α- and β-galactosidases and glycosidases. However, the recovery of enzymes was not complete and was organ dependent, thus highlighting a general problem in therapy of MeHg toxicity. A treatment that provides a beneficial decrease in the Hg burden in an organ such as the liver or the kidney may increase the Hg burden in another organ, such as the brain, stimulating symptoms of neurotoxicity (*103*). For example, exposure to vitamin C enhanced MeHg toxicity in cultured mouse neuroblastoma cells (*251*). In humans, Calabrese et al. (*44*) observed no change in Hg body burden of humans as measured by hair Hg after supplementation with ascorbic acid for 3 months.

Vitamin A was protective in cell culture (*255*) but enhanced MeHg toxicity in *in vivo* studies with rats (*148*). It is unknown if these effects are related to antioxidant/pro-oxidant activity of vitamin A or to some other factor of metabolism.

Several B vitamins have been implicated in the amelioration of MeHg toxicity, possibly because of their role in overall health and repair in organisms (*103*). Vitamin B_{12} has received the most attention because of its biologic role in methylation metabolism. For example, Met synthetase is inhibited by MeHg in rat organs, except liver (*95*), likely due to its nature as a sulfhydryl enzyme. No study has examined how this might affect B_{12} metabolism and folate metabolism in which Met synthethase plays a role (*271*), or how folate and B_{12} supplementation affect MeHg toxicity symptoms. Zorn and Smith (*147*) studied the effect of folate, vitamin B_{12} and ascorbate on Hg^{2+} methylation in guinea pigs. They concluded that doses of these vitamins can increase MeHg in the liver and in hair, and the combination of the vitamin C with vitamin B_{12} can increase MeHg in the brain.

COMBINED NUTRIENT EFFECTS. Information on how combinations of nutrients influence MeHg metabolism is scant, but several combinations of nutrients have been examined (Table 9). The protective effects of Se and vitamin E appear to be additive at low

Se concentrations (*202,204*), possibly because of the interaction between vitamin E and Se antioxidant mechanisms. Met competed with Hg for Cys-mediated transport across the blood–brain barrier (*82*), and the availability of other amino acids also affected this transport (*257*). There also appears to be a relationship between vitamin E and vitamin A effects on MeHg toxicity (*148*).

Effect of MeHg on protein metabolism. Mercury exposure results in inhibition of protein synthesis due to inactivation of enzymes, such as the inhibition of several aspartate and alanine amino acid transferases observed in fish exposed to Hg^{2+} (*277*). However, protein synthesis in the mitochondria appears to be stimulated in mice exposed to MeHg (*100*).

Induction of GSH with a Cys precursor (1 mmol L-2-oxothiazolidine-4-carboxylic acid) reduced MeHgCl-induced amino acid release from astrocytes (*278*). A general pattern of GSH enzyme (GSH reductase and GSH peroxidase) induction was observed in both liver and kidney of mice after dietary exposure to MeHg and sodium selenite (*224*). Buthionine, a specific inhibitor of GSH, reduced cystine-enhanced MeHg toxicity, suggesting that cystine may enhance MeHg toxicity indirectly by stimulating the synthesis of cellular GSH (*279*).

Effect of MeHg on lipid, carbohydrate, and energy metabolism. Mercury affects both lipid and carbohydrate metabolism. MeHg exposure decreased the incorporation of ^{14}C glucose in the brains of suckling rats (*280*). Janik (*281*) also showed that rats fed MeHgCl more than 3 weeks had altered levels of glycogen and lactic acid in their hearts and livers and Das and Scott (*282*) showed that offspring of mice injected with MeHgCl had abnormal glycogen deposits in their alveolar tubules. Rana and Sharma (*283*) showed that many enzymes in carbohydrate metabolism are inhibited by exposure to Hg^{2+}, including glucose-6-phosphatase, amylase, maltase, and lactase. Varghese et al. (*106*) reported that carbohydrate metabolism in crabs exposed to Hg^{2+} switched toward glycolysis and caused an initial increase in blood sugar levels upon exposure. Exposure to Hg also decreased the glycogen content in liver, muscle, brain, and kidney in fish (*103*).

Hg exposure can alter lipid profiles and fatty acid and cholesterol production (*284–287*). MeHg decreased triglycerides in the central nervous system of rats (*102*), possibly due to alterations in Mg^{2+}, adenosine triphosphate (ATP), or acetyl coenzyme A levels. MeHg, on the other hand, increased the levels of tocopherol in rat serum, possibly due to increased serum lipid levels (*254*). Kasuya (*77*) reported that the phospholipids sphingomyelin and phosphatidyl serine of cellular membranes prevented some of the toxic effects of organic Hg compounds in tissue culture. Hg^{2+} inhibited hepatic fatty acid synthetase and the stimulated mitochondrial fatty acid elongation in chickens (*110,152*). Other enzymes of lipid metabolism such as lipase (*283*) and carnitine acetyltransferase in the human placenta (*108*) were also inhibited. George (*288*) also reported that Hg affected fat cell response to insulin *in vitro*.

Perturbation of essential mineral metabolism by MeHg. Methyl mercury perturbs the metabolism of Zn, Cu, Mn, Cr, Ni, Fe (manganese, chromium, nickel, iron), and Se (*127*). Abdulla and Chmielnicka (*289*) suggested the analysis of elemental composition of body tissues and fluids be used as an indicator of the effect of MeHg on nutritional and pathologic status of humans. For example, Cu concentration in the kidney could be used an indicator of renal toxicity due to MeHg exposure. Bjorkman et al. (*290*) found that Se levels in the brain occipital pole and thalamus were lower in monkeys exposed to 50 µg MeHg/day for up to 18 months. Hg vapor can induce MT formation, which alters blood levels of metallic cations such as Cu^{2+} and Zn^{2+} (*291*), possibly due to the dissociation and mobilization of Cu^{2+} and Zn^{2+} from MT (*292*). Manganese is also mobilized from tissues (*127*), possibly due to the denaturation of enzymes that use it as a cofactor.

Interaction of MeHg with electrolytes. Mercury affects sodium and potassium ion channels, and some end points of Hg toxicity can be protected by pharmacologic ion-channel blockers (*225*). Some of these effects may be due to the inhibition of Na^+/K^+-ATPases (*136,293*).

Ca^{2+} metabolism was also perturbed by Hg, resulting in increased Ca^{2+} permeability and altered Ca^{2+} metabolism in muscle tissue (*294,295*). Sakamota et al. (*296*) observed that Ca^{2+}-channel blockers prevented a decrease in body weight and other neurologic symptoms in rats. Hg also affected Cl^- channels in rats (*297*).

Excretion of MeHg

Methyl mercury is normally excreted in bile as a GSH complex in rats (*298*), and it has been observed that some thiols can increase biliary excretion of MeHg (*299–301*). Nutrients can also influence the excretion of Hg after exposure to MeHg (Table 10). Rowland et al. (*78,88*) concluded that dietary fiber such as wheat bran increased the demethylation rate of MeHg by intestinal flora and increased the fecal excretion of Hg. Se may reduce (*199*) or increase (*302*) the excretion of Hg.

Nutritional factors may also decrease the excretion of Hg after MeHg exposure. A low-protein diet (7.5%) decreased the amount of Hg being excreted into the urine (*68*). Gregus et al. (*139*) found that injections of lipoic acid decreased MeHg excretion by competing for GSH. Interestingly, Hg^{2+} excretion into the bile was increased by the same treatment of lipoic acid.

Public Health Considerations

Problems Induced by Nutrient Deficiency

The health implications for human populations consuming MeHg through a mixed diet remain speculative. Loss of appetite, decreased food intake, decreased water intake, and loss of body weight are side effects associated with MeHg exposure (*303,304*). The implications of diet modification on these parameters, however, have not been examined in humans. Nutrient deficiencies may develop as a result of anorexia and may also develop in cases of chronic Hg intake. Yonemoto et al. (*233*) showed that MeHg exposure could stimulate the formation of toxic, volatile dimethylselenide, which causes loss of Se by exhalation. MeHg may also be associated with an increased requirement for vitamins E and B_1 (*103*) and vitamin C (*149*). Inorganic Hg has also been shown to alter the levels of nutrients such as vitamins C and E in the kidney (*124*).

Few studies have examined the effects of malnutrition on the metabolism and toxicity of Hg, but malnutrition in general has a deleterious effect. Inadequate protein increased MeHg-induced mortality in mice (*69*), and Met deficiency during MeHgCl exposure caused an increase in serum prostaglandins (*192*). Yamini and Sleight (*305*) reported that vitamin C deficiency in guinea pigs promoted toxicity of MeHg, and Nishikido et al. (*229*) found that Se deficiency exacerbated MeHg fetal lethality in mouse.

Is There a Case for Nutritional Therapy?

Current chelation therapies for the treatment of MeHg intoxication are thiol derivatives (*306*). Choices have included 2,3-dimercaptopropane-1-sulfonate (*307*) and *N*-acetylcysteine (*308*). However, an efficient and effective therapy that can be used for long-term chronic MeHg exposure in fish-eating populations is not available.

The search for therapies in chronic MeHg intoxication has led to the suggestion that vitamins or other dietary modifications may enhance the detoxification of MeHg. Megadoses of vitamin B_{12}, folic acid, or amino acids can affect Hg uptake and methylation, though sometimes not in a positive way. Zorn and Smith (*147*) reported that vitamin B_{12} administered alone or with folic acid increased methylation of Hg^{2+}, resulting in increased MeHg levels in the liver.

Megadoses of vitamin B_{12} administered with vitamin C after exposure to Hg^{2+} increased MeHg levels in the brain (*147*). The enhancement of Hg^{2+} toxicity by vitamin C treatment led to the suggestion that megadoses of vitamin C should be contraindicated among populations with high Hg exposure (*150*). Some researchers have suggested that certain types of fish should be preferred because of their high Se content (*309*), but others warn of the toxicity with high levels of Se (*205*). Another suggestion was to detoxify food containing Hg by food processing. For instance, Aizpurua et al. (*176*) used cysteine (0.5%) solution to remove Hg from shark muscle but concluded that the method was too inefficient to be of practical purpose.

The effect of cooking and preparation method on the concentrations of MeHg in seafood and fish has been examined (*310–312*), but these effects are minor compared to factors such as fish age and size.

It is important to encourage collaborations among toxicologists, nutritionists, and public health officials in risk assessment and risk management. Emphasis should be given to assessing overall dietary quality and identifying alternative food sources for replacing the nutrients provided by fish and seafood in the diet. Both the risks and the nutritional and sociocultural benefits of consuming these foods should be assessed before drastic interventions to discourage people from consumption are implemented. For example, among the aboriginal populations, the traditionally consumed fish and seafood often provide a rich source of nutrients such as protein, Fe, vitamins, and Ca^{2+} that may be less easy to obtain in expensive store-bought foods (*313*). Country foods are cheap, reliable sources of foods with high-quality protein, minerals, and vitamins (*314*). Increased physical activity that occurs during the procurement of these foods reduces the risk of diabetes, obesity, and loss of fitness (*315*). There is a continuing need for education among fish- and seafood-consuming populations. Fear or lack of understanding of contamination in animal and fish foods may lead to a drastic shift away from the traditional diet and may result in increased consumption of high-carbohydrate diets associated with health risks such as diabetes and obesity (*316*). Often only a slight modification in eating patterns or partial restriction of highly MeHg-contaminated foods for individuals identified with high exposure may decrease MeHg intake significantly. It may not be necessary to recommend complete removal of a food from a diet (*50,315–318*). The relationships between MeHg and trophic level or fish size can be explained so that the species with less MeHg can be promoted (*319*). The public must also be aware of the increased sensitivity of young children and women of childbearing age, especially pregnant women and nursing mothers, to MeHg. Moreover, it has been concluded that exposure to MeHg through breast milk does not outweigh the benefit of infant weight gain produced by breast-feeding (*320*). Therefore, continuation of breast-feeding is recommended despite the risk of MeHg exposure to the infant during lactation.

Conclusion

A wide variety of foods and nutrients alter MeHg metabolism, but the mechanisms of interaction often remain speculative. More studies designed specifically to address the role of nutrition in the metabolism and detoxification of MeHg are needed. Such studies must expand the understanding of the biologic mechanisms and the toxicokinetics to aid in making interspecies comparisons. In addition, hypotheses about the effect of nutrients on MeHg have sometimes been made on the basis of studies using inorganic Hg; these hypotheses should also be tested during chronic dietary exposure to MeHg.

Clarification of the effects of specific dietary lipids on MeHg toxicity is needed and is relevant for defining MeHg exposure in seafood-consuming communities with high intakes of polyunsaturated fatty acids and ω-3 fatty acids (*33,321*). In addition, understanding of how dietary supplementation of cofactors and coenzymes for enzymes that are inhibited by MeHg might alter MeHg toxicity is very limited and requires the focus of well-designed studies. Another interesting area not yet been explored is the effect of herbal foods and phytochemical agents on MeHg intoxication.

We hope that this review will stimulate interest and consideration of nutritional parameters in studies of MeHg intoxication and lead to further studies addressing mechanistic hypotheses. Currently, the epidemiologic links between exposure to MeHg and beneficial or detrimental effects of diet have not been established, but it is clear that dietary factors need to be better addressed in future epidemiologic and clinical studies. Emphasis should be given to assessing overall dietary quality, with appropriate recommendations, as needed, to reduce MeHg exposure.

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Appendix

Table 1. Nutrition and MeHg toxicity: epidemiologic data.

Population	*n*	Source of Hg	Hg exposure	Nutrient factor measured	Relationship	Ref.
Northern Canada	432	Marine food	71 nmol Hg/L in cord blood plasma	Se in plasma (4.2 μmol/L); ω-3 fatty acids (4.5% of phospholipids in plasma)	Positive correlation between blood concentrations of Se and Hg; ω-3 fatty acids and Hg	(*28*)
Northern Canada	448	Country food	100 ppb Hg in blood (16% of tests)	Eating habits (food consumption frequency and preferences)	Lake trout was a major contributor to Hg exposure; exposure may also be associated with a longer beluga harvest	(*29*)
Northern Canada	NA	Country food	NA	Thiamine deficiency	Similarities exist between the symptoms of Hg and thiamine neurotoxicity; a concurrence of thiamine antagonists and Hg exposure in the diet	(*30*)
Denmark	198	Environment	6.9 nmol Hg/L in blood	Serum Se, Ni, Cd, Al, Zn, Cu	Positive correlation between blood Se and Hg; correlation between Hg and fish intake	(*31*)
Faroe Islands	1,023	Maternal sea-food diet	24.2 μg Hg/L in cord blood (25% of tests exceeded 40 μg/L); 4.5 mg Hg/g in maternal hair	Whale and fish dinners	Whale meat and frequent fish consumption were associated with high blood Hg; correlation between blood Se and Hg	(*32*)
Finland	1,861	Fish	103 g fish/d	Intake of vitamin C, protein, ω-3 fatty acids, Se and salt and plasma antioxidants (α-tocopherol, γ-tocopherol, β-carotene)	Higher fish consumption was associated with higher Hg intake	(*33*)
Greenland	376	Country and marine food	14.9 μg Hg/L maternal blood; 21 μg Hg/L offspring blood	Number of meals of country food/wk	No effect of country food intake on gestational length or birth weight	(*20*)
Greenland	138	Marine food	86–186 μg Hg/L in blood	Blood Se	No correlation between Se and Hg by individuals, but in groups according to eating habits	(*34*)
Greenland	1	Diet	NA	Country food and beluga maktak (intake not evaluated)	Man stopped eating traditional diet and began to show symptoms of Hg poisoning; symptoms disappeared after eating maktak again	(*35*)
Norway	32	Fish	18 μg Hg/d	Lipids, Se (115 μg Se/d)	Positive correlation of dietary Hg with LDL-cholesterol; negative correlation with HDL-cholesterol	(*36*)
Japan	NA	Fish	NA	Ethanol	Ethanol was several times more common among residents of MeHg-polluted areas	(*37*)
Japan	NA	Fish	NA	Ethanol	Mortality from liver cancer, chronic liver disease, and cirrhosis was higher in verifed Minamata disease patients	(*38*)
Japan	575	Environment	NA	Se	Expression of Hg values in relation to urine Se is a good index in younger subjects as creatinine concentration changes with age	(*39*)
Sweden	18	Dental amalgam	27 nmol Hg/L in plasma; 6.5 nmol Hg/mmol creatinine in urine	Nicotine chewing gum	Chewing gum increases the release rate of Hg vapor from amalgam fillings	(*40*)
Turkey	95	Dialysis	NA	Se	Subjects on hemodialysis are subject to more toxic elements than transplantation patients	(*41*)
Sweden	395	Fish	6.7 ng Hg/g whole blood (at least two fish meals/wk)	Plasma Se	Plasma Hg was associated with ω-3 fatty acids in phosphatidylcholine; both plasma Se and Hg are positively associatied with fish intake	(*42*)
Sweden	30	Dental amalgam and fish	0.6 ng Hg/g breast milk; 2.3 ng Hg/g in blood; 0.28 μg Hg/g in hair 6 wk after delivery	Breast milk, fish intake	Blood Hg was positively correlated with number of amalgams and intake of fish; amalgam Hg was the main source of Hg in the milk	(*43*)
United States	52	Nonoccupational environmental exposure	1.05 ppm Hg in hair	Vitamin C supplementation	No effect of vitamin C on Hg body burden as measured by hair and blood Hg	(*44*)
Norway	49	Occupational exposure to Hg^0	NA	Se	Exposed group excreted more Se into urine; no significant correlation between Hg and Se excretion was found	(*45*)

Abbreviations: d, day, HDL, high-density lipoprotein; LDL, low-density lipoprotein; NA, not available; wk, week.

Table 2. Interactions between nutrients and Hg: foods and macronutrients.[a]

Nutrient/nutrition factor	Proposed type of interaction	Ref.
Protective effects		
Cysteine	Stimulates de novo synthesis of CoASH, which then exerts protective effect	(*68*)
Cystine	Decreases Hg deposition in kidney	(*69–71*)
Fish protein	Decreases toxicity symptoms of MeHg, presumably due to its Se content	(*70,72*)
Garlic	Promotes Hg excretion due to -SH and -SS- radicals that promote formation of Hg–sulfur compounds	(*73*)
Glutathione	Forms low molecular weight conjugate with Hg that can be extracted into kidneys and catabolized	(*74*)
γ-Linolenic acid	Allows the bypass of blocked linoleic acid production that occurs due to MeHg displacement of Zn ions from rate-determining enzymes	(*75*)
Neutral amino acids (e.g., leucine)	Inhibit uptake of Hg in brain because of competition for the neutral amino acid transport carrier with Hg–Cys complex; leucine has a greater affinity for the carrier	(*76*)
Phospholipids	Prevent toxic effect of MeHg	(*77*)
Wheat bran	Decreased the retention of orally administered MeHg in mice due to modification of metabolic activity of gut microflora	(*78*)
Enhanced toxicity		
Alcohol	Causes additive effect with MeHg on kidney pathology; may inhibit reoxidation of Hg vapor; may stimulate absorption of metals from the intestinal mucosa	(*80,81*)
Chewing gum	Increases Hg release from dental amalgams through mechanical action	(*40*)
Cysteine	Increases brain uptake of MeHg and Hg^{2+} in kidney by forming Cys–Hg complexes	(*76,81,82*)
Cystine	Increases brain MeHg	(*69–71*)
Glutamate	Interrupts transport by forming Hg–sulfide bridges between Cys and residues in protein; interactions result in neurotoxicity	(*83*)
Linoleic acid	May compete with Hg for the vitamin E antioxidant system and thus exacerbate the lethal effects of MeHg	(*84*)
Milk	Increases MeHg absorption from the intestinal tract; decreases fecal excretion; increases initial absorption due to binding of Hg to fatty acid from milk triglycerides	(*85,86*)
Protein	Low protein diet increases uptake of Hg in the brain because of involvement of neutral amino acid carrier; low protein diet may decrease urinary excretion of Hg; higher protein levels increase the susceptibility of the liver to Hg	(*69,87–89*)
Thiamine-related factors: high carbohydrate diet; intake of tea, raw fish; alcoholism	Clinical manifestation of thiamine deficiency may intensify clinical symptoms of Hg toxicity	(*30,90*)
Other effects		
Amino acids	Altered Hg uptake in kidney; renal uptake of Hg partially involves amino acid transport mechanisms acting on Hg–amino acid complexes	(*91,92*)
Cellulose	Alters metabolism of MeHg by intestinal flora	(*78*)
Glucose	Competes with Hg in use of the facilitated D-glucose transport system	(*93*)
Glutamine and glycylglycine	Serve as messengers in functional alterations in uptake of MeHg that occur through signaling pathways	(*94*)
Methionine	Increases brain MeHg; acts competively to inhibit Cys–Hg transport across the blood–brain barrier; Hg inhibits methionine synthase in brain because it is a sulfhydryl enzyme	(*69,82,95*)
Phytate	No effect on absorption of Hg	(*96*)
Seleno-L-methionine	Minimal effect on Hg distribution in offspring	(*97,98*)
Small aliphatic dicarboxylic acids (e.g., succinate)	Mechanism of Hg^{2+} uptake in the proximal tubule involves the activity of the organic anion transporter; affects renal uptake of Hg	(*99,100*)
Thiol compounds	Increase brain, liver, and kidney MeHg; decrease plasma MeHg; alter chelation and excretion of Hg	(*101–103*)
Effects of Hg		
Albumin	Hg alters free albumin availability; albumin shows preferential interaction with hydrophobic domains of the mercurial ligand; mercaptoalbumin forms stable complex with MeHg in serum	(*69,104*)
Carbohydrate	Hg acts through the endocrine system creating hormone/enzyme imbalance in carbohydrate metabolism; induces anaerobic stress that causes switch to glycolysis	(*93,105–107*)
Linoleic acid	May compete with Hg for the vitamin E antioxidant system and thus exacerbate the lethal effects of MeHg; Hg may catalyze lipid peroxidation of linoleic acid	(*84*)
Lipids	Inhibition of carnitine acetyltransferase occurs when Hg binds to enzyme sulfhydryl groups; Hg reacts with double bonds of fatty acid residues in phospholipids (major component of biomembranes)	(*108,109*)
Lipids	Inhibitory effect on hepatic fatty acid synthetase activity is mediated through interaction of Hg with sulfhydryl groups of the enzymes; Hg promotes oxidation of lipids; fat composition of diet affects toxicokinetics of Hg	(*110,111*)
Sugars	Hg inhibition of sugar absorption is ascribed to impairment of the sugar–Na phlorizin-sensitive cotransport; interacts with ligands of the transport proteins in the luminal membrane of enterocytes	(*112,113*)
Ubiquinol	MeHgCl induces alterations in electron transport in the ubiquinol–cytochrome *c* oxidoreductase region	(*114*)

Abbreviations: SH-, thiol; -SS-, oxidized thiol. [a]Table contains references to both inorganic and organic forms of Hg.

Table 3. Interactions between nutrients and Hg: minerals.[a]

Nutrient/nutrition factor	Proposed type of interaction	Ref.
Protective effects		
Phosphate ions (with ATP)	Decreased severity of inhibition of protein synthesis by Hg	(*93,100*)
Selenium	Alters GSH and GSH enzyme metabolism; forms precipitate with Hg; protective of toxic effects of MeHg and $HgCl_2$; protects kidneys by reducing their MeHg uptake (may be mechanism for protecting survival)	(*115–123*)
Zinc	Activates GSH-associated enzymes that thus increase GSH level in kidney; altered superoxide dismutase activity; reduction of oxidative stress; induces metallothionein and activities of enzymes (GSH peroxidase and G-6-P dehydrogenase) that inhibit lipid peroxidation	(*124–126*)
Enhanced toxicity		
Iron	May increase lipid peroxidation by MeHg	(*127–129*)
Manganese ions	Mn exacerbated Hg damage to bigenic amines in the central nervous system; Hg altered superoxide dismutase activity	(*126,127*)
Other effects		
Calcium	Binding of inositol 1,4,5-triphosphate and 1,3,4,5-tetrakisphosphate to cellular membranes is inhibited by Hg	(*130*)
Iodine	Increases gastrointestinal absorption of Hg	(*131*)
Effects of Hg		
Cations	Hg alters cation metabolism; related to renal toxicity and/or the synthesis of metallothionein in kidney	(*132*)
Chloride ion	Action by direct effect of Hg on epithelial cells and also mediated by prostaglandins and cholinergic and noncholinergic neurons	(*133,134*)
Cobalt	Fluctuates due to altered vitamin B_1 and B_{12} metabolism by Hg	(*127*)
Copper	Hg affects superoxide dismutase activity	(*126,135*)
Iron	Fluctuates due to lipid peroxidation by MeHg	(*127–129*)
Magnesium	Mg levels are altered due to alteration in GSH metabolism by Hg	(*127*)
Potassium ions	Hg disrupts the function of Na^+,K^+-ATPase; Hg altered permeability through antiporters	(*136,137*)
Sodium ions	Hg disrupts the function of Na^+,K^+-ATPase; Hg altered permeability through antiporters	(*136,137*)
Sulfur (sulfate, sulfite)	Hg reacts with sulfhydryl groups on proteins to form mercaptides; fluctuates due to altered vitamins B_1 and B_{12} metabolism by Hg	(*103,134,138*)
Trace metals	Fluctuate due to association of Hg with various macromolecules; Hg dissociates Cu and Zn from metallothionein	(*127*)

Abbreviations: ATP, adenosine triphosphate; G-6-P, glucose 6-phosphate. [a]Table contains references to both inorganic and organic forms of Hg.

Table 4. Interactions between nutrients and Hg: vitamins.[a]

Nutrient/nutrition factor	Proposed type of interaction	Ref.
Protective effects		
Lipoic acid	Decreases biliary excretion of MeHg and increases the biliary excretion of $HgCl_2$; protects against toxicity	(*139,140*)
Vitamin B complex	Aids in recovery of glycosidases injured by Hg; protects membrane and maintains cell stability during Hg toxicity	(*103,127*)
Vitamin E	Alleviates MeHgCl and $HgCl_2$ toxicity and neuronal degeneration; prevents lipid peroxidation due to Hg	(*127,141–145*)
Enhanced toxicity		
β-carotene	Alters fatty composition and hepatic GSH concentration; alters antioxidant defense mechanisms against MeHg-induced lipid peroxidation	(*144,145*)
Folate	Deficiency enhances the development of symptoms of Hg toxicity	(*147*)
Vitamin A	Increases toxicity of MeHg in rat; interaction not clear	(*148*)
Vitamin B_{12}	Increases MeHg uptake in liver	(*95,147*)
Vitamin B_1 (thiamine)	Deficiency enhances development of symptoms of Hg toxicity; possible ionic reaction similar to that with Cu and Cd	(*30,90,134*)
Vitamin C (ascorbate)	Enhances Hg absorption from intestinal tract; reducing agent of Hg^0	(*134,149,150*)
Other effects		
Vitamin D	Does not affect Hg uptake into tibia of chicks	(*151*)
Effects of Hg		
Biotin	Hg stimulates lipogenesis in biotin deficient state	(*152*)
Coenzyme A	Hg binds to CoA and interferes with CoASH function	(*68*)
NADPH	Hg forms a covalent complex with NADPH	(*153*)
Vitamin B_{12}	Hg inhibits Met synthesis in brain	(*95,147*)

Abbreviations: NADPH, nicotinamide adenine dinucleiotide phosphate. [a]Table contains references to both inorganic and organic forms of Hg.

Table 5. Effects of food and nutrients on the absorption of MeHg.

Food/nutrient	MeHg exposure	Nutrient dose	Animal model	Duration of experiment	Effects	Ref.
Protective effects						
Dried algae (phosphorus)	Hg from algae grown on wastewater	Phosphorous in algae	Chicken	NA	Decreased absorption of Hg	(*155*)
Enhanced toxicity						
Fish meal	Hg in polluted fish meal 1.4 g Hg/kg diet vs with commercial fish meal 0.3 g Hg/kg diet	Experimental fish diet vs commercial fish diet	Rat	12 d	Absorption of Hg was greater from the experimental fish meal diet	(*96*)
Vitamin C	8 mg MeHgI/kg bw/d, orally	Ascorbic acid	Guinea pigs	5 d	Increased absorption of organic Hg	(*150*)
Other effects						
Corn silage	Hg from corn grown in industrial area 0.2 g Hg/kg diet	Corn silage vs casein diet	Rat	12 d	No effect on absorption of Hg	(*96*)
Diet (with sludge from sewage plant)	Hg from sludge 5.5 g/kg diet	Sludge diet vs casein control diet	Rat	12 d	No effect on absorption of Hg; ingested amount of Hg from sludge diet was higher	(*96*)
Phytate, fish meal diet	1.4 g Hg from fish meal/kg diet	Phytate 2 g/kg experimental fish meal diet compared with experimental fish meal diet	Rat	12 d	No reduction in the absorption of Hg	(*96*)
Selenium	Hg in hen liver (hens fed 15–30 ppm MeHgCl in diet)	Se in hen liver (hen fed 0.6 ppm selenite in diet)	Japanese quail	NA	No effect on the availability of Hg; Hg was highly available	(*156*)
Selenium	0–1.0 mM MeHgCl, intraduodenal dose, 0.05 mL	Selenite, intraduodenal dose 0.01 mM, 0.05 mL	Leghorn cockerel	3 wk	No interaction between Se and Hg; Hg level is manyfold excess of Se, suggests effect not of great nutritional importance	(*98*)
Selenium	0.5 µmol MeHgCl in 0.2 mL s.c. injection or 1.25–5 µmol, injected by gastric gavage, 5 mL/kg bw	0.5 µmol selenite alone or in combination	Rat	48 hr	No delay in absorption of MeHg by simultaneous selenite administration	(*157*)

Table 6. Effects on the metabolism and distribution of methyl mercury: foods and macronutrients.

Nutrient	MeHg exposure	Nutrient dose	Animal model	Duration of experiment	Effects	Ref.
Protective effects						
ADP	10 or 50 nmol MeHgCl/g bw (i.p. injection)	ADP, 250 µM, 1-hr incubation	Mouse, *in vitro* rabbit lysate translation system	12 hr	Decreased elevation of mitochondrial protein synthesis	(*100*)
Cysteine	1–100 µM MeHg, 24 hr	0.8 mg Cys/mL, 24 hr	*In vitro* mouse neuron culture	24 hr	Blocked neurotoxicity	(*145*)
Cysteine	5–50 µM MeHgCl	Cys, 12-min preincubation 0.2–2 mM	*In vitro* human placental syncytiotrophoblast	90 min	Partially blocked inhibition of carnitine acyltransferase	(*108*)
Cysteine	0.95 µg Hg/g shark muscle	Cys, 0.5%	*In vitro* shark muscle	1–24 hr	Decreased Hg concentration but efficiency was not high enough to make process efficient	(*176*)
Cystine	25 ppm MeHg in diet	0.4% cystine in diet	Rat	10 wk	Prevented increase in SGPT and SGOT levels	(*177*)
Cystine	15–25 ppm MeHgCl in diet *ad libitum*	0.4% L-cystine in diet *ad libitum*	Rat	6–10 wk	Increased weight gain; slightly decreased kidney Hg; no effect on survival	(*70*)
Cystine	10 ppm MeHgCl in diet	0.3% cystine in diet	Japanese quail	16 wk	Improved egg production; no effect on survival	(*71*)
Fish protein	15–25 ppm MeHgCl in diet	10–20% fish protein in diet, *ad libitum* vs casein diet	Rat	6–10 wk	Improved weight gain and survival	(*70*)
Fish protein	Organic Hg, oral and parenteral dose (dose NA)	High fish protein vs low fish protein or caseinate diet	Mouse	NA	Reduced whole-body retention of Hg; oral dose increased liver deposition; no effect on relative organ distribution	(*174*)
γ-Linolenic acid	MeHgCl, 10^{-5} to 10^{-7} M	10^{-9} M γ-linolenic acid	*In vitro* human lymphocytes	72 hr	Reduced sister chromatid exchange	(*75*)
Garlic	4 ppm MeHgCl in drinking water	1.7–6.7% raw garlic in diet, p.o.	Rat	12 wk	Decreased brain, kidney levels of Hg; high level of garlic decreased severity of histologic damage	(*73*)
Glucose	MeHg–GSH 1 mmol MeHg/L packed erythrocytes	2 mM D-Glucose	*In vitro* rat erythrocytes	30 min	Inhibited MeHg uptake; MeHg uptake might use the passive D-glucose transport system	(*93*)
Glutathione	4 µM MeHgCl	0.6 mM GSH	*In vitro* rat hepatocytes	240 min	Reduced cellular uptake of MeHg from medium	(*74*)
Glutathione	1 mg/kg/d or 10 mg MeHgCl (i.m. injection, 0–7 d)	100 or 150 mg GSH/kg bw/d (i.m. injection, 7–14 d)	Rat	15 d	Allowed recovery of cholesterol concentration and duration-dependent recovery of triglyceride concentrations in areas of the CNS (cerebral hemisphere, cerebellum, medulla oblongata, spinal cord)	(*102*)
Glutathione	4 µmol MeHgCl/kg bw (single i.v. injection)	8 µmol Cys/kg bw (single i.v. injection pre-mixed with Hg)	Rat	4 hr	Increased uptake of Hg in kidney and decreased liver and blood content	(*74*)
High-protein diet	40 µmol/kg bw (injection)	24.8% protein diet	Mouse	16 d	Mice survived	(*89*)
Isoleucine	10 µmol MeHgCl (injection, with 100 µmol Cys/rat)	20 µmol L-isoleucine, (i.v. injection)	Rat	2 hr	Isoleucine inhibited the effect of L-Cys on increased brain uptake of MeHg	(*178*)
Leucine	50 µmol MeHgCl/hr for 1 hr (at 24, 48, and 72 hr) (continuous infusion to external jugular vein)	0.1 mmol L-leucine/hr, (continuous infusion to external jugular vein) 4 d	Rat (pregnant)	92 hr	Inhibited brain uptake of Hg in nonpregnant rats; did not alter Hg distribution between pregnant or nonpregnant rats	(*76*)
Low molecular weight thiols	1–50 µmol MeHgCl (i.v. injection)	Low molecular weight thiols (i.v. injection, equimolar, simultaneous)	Rat	60 min	Increased short-term accumulation of MeHg in liver, kidneys, cerebrum; decreased Hg in plasma	(*101*)
Marine mammal meat; Se	17.5 ppm MeHgCl in diet, in either sebastes or sperm whale meat	Marine mammal meat Se, 0.3–0.6 ppm in diet (either sebastes or sperm whale meat or sodium selenite)	Rat	12 wk	Sebastes meat protected growth (to an extent similar to selenite) and delayed neurologic signs (tail rotation, paralysis of hind limbs) for 7 wk (more protection than selenite); sperm whale meat was less effective; Se in organs was positively correlated with neurologic protection	(*179*)
Monothiols (glutathione, *N*-acetyl-DL-homocysteine thiolactone)	1 mg MeHgCl/kg bw/d (s.c. injection)	Monothiols (50 mg GSH/kg bw and 40 mg *N*-acetyl-DL-homocysteine thiolactone/kg bw)	Mouse	15 d	α-gal and β-gal activities recovered toward normal in brain and spinal cord; GSH recovered α-gal in liver and testes and β-gal in kidney and testes	(*180*)

(*Continued*)

Table 6. *Continued.*

Nutrient	MeHg exposure	Nutrient dose	Animal model	Duration of experiment	Effects	Ref.
Monothiols (glutathione)	1 mg MeHgCl/kg/d for 7 d (s.c. injection)	50 mg GSH/kg s.c. injection (for 7 d) after the 7 d MeHg treatment	Mouse	14 d	Showed recovery of α- and β-glycosidases activities enzymes in the CNS	(*103*)
Monothiols (glutathione, *N*-acetyl-DL-homocysteine)	1 mg MeHg/kg bw/d (7 d) s.c. injection	40 mg *N*-acetyl-DL-homocysteine thiolactone/kg bw, 50 mg GSH/kg bw for 7 d (8–14 d after Hg exposure)	Mouse	14 d	Mobilized Hg from all tissues except brain; decrease in Na, K, Mg, Mn, Cu, Zn, Cr, and Ni for most organs was restored toward normal, but recovery was not complete; decreased kidney Fe	(*127*)
N-acetyl-DL-homocysteine	1 or 10 mg MeHgCl mg/kg bw/d (i.m. injection, 0–7 d)	40 or 80 mg *N*-acetyl-DL-homocysteine/kg bw/d or 80 mg/kg bw, i.m. injection, 7–14 d	Rat	15 d	Allowed recovery of cholesterol and duration-dependent recovery of triglycerides in the CNS (cerebral hemisphere, cerebellum, medulla oblongata, spinal cord)	(*102*)
Ringed seal liver	About 3% of Hg was organic; equivalent to about 0.25 mg Hg/kg bw/d	Ringed seal liver vs MeHg-supplemented beef liver	Cat	90 d	Seal liver group had no neurologic symptoms; cats fed MeHg-supplemented beef liver developed neurologic symptoms of toxicity (convulsions, hind limb weakness); elevated brain levels of Hg in supplemented beef liver group	(*181*)
Shark flesh	0.02–2.0 ppm in diet from shark flesh	0.01–0.46 ppm Se in diet from shark flesh	Rat	56 d	Increased GSH–peroxidase in brain and liver with Se supplementation up to 0.3 ppm; no effect on ornithine transcarbamylase activity; fish diet yielded higher GSH-peroxidase activities than yeast diet with equivalent Se as selenite	(*182*)
Soy protein	Organic Hg, oral and parenteral dose	High-soy protein vs caseinate or low-soy protein	Mouse	NA	Reduction in whole-body retention of Hg; relative organ distribution not affected; oral dose increased liver deposition	(*174*)
Succinate	10 or 50 nmol MeHgCl/g bw (single i.p. injection)	150 μM succinate,1 hr incubation	Mouse	12 hr	Decreased elevated mitochondrial protein synthesis	(*100*)
Sulfur amino acids in low protein diet	20 μmol MeHg/kg bw orally (24 hr before death)	7.5% protein diet vs 24.8% protein diet plus 0.03% cysteine in diet and 1.1% methionine in diet, 5 d	Mouse	5 d	Increased Hg uptake to brain and liver more than low-protein diet; increased urinary Hg over normal-protein diet; decreased Hg in kidney, blood, and plasma	(*69*)
Synthetic liquid diet (high protein, low fat)	0.6 mg MeHgCl/kg bw, single dose, p.o.	Synthetic diet (high protein, low fat) *ad libitum* vs milk or pellet diet	Mouse	2 wk	Lowered Hg concentration in blood, brain, liver, kidneys; increased percent Hg^{2+} compared to mice on milk diet or pellet rodent diet; Hg^{2+} body burden was higher than rodent pellet diet; Hg burden of the gut was highest in the cecum	(*88*)
Tuna fish	MeHg (from tuna fish, 17% of diet)	17% tuna diet vs corn soya diet	Japanese quail	6 wk	Decreased MeHg toxicity and prolonged survival; decreased incoordination, mortality, growth inhibition	(*183*)
Wheat bran	5.0 mg Hg/kg bw (single dose, p.o., as MeHgCl)	5, 15, 30% wheat bran in diet compared to fiber-free diet	Mouse	104 d	Decreased Hg in blood, brain, small intestine with 30% diet; Hg elimination affected by dietary bran may reduce neurotoxic effects	(*78*)
Enhanced toxicity						
Cellulose	5.0 mg MeHgCl/kg bw, single dose, p.o.	5% cellulose in diet compared to fiber-free diet	Mouse	104 d	Increased Hg retention; did not alter percentage inorganic Hg	(*78*)
Chemically defined liquid diet	0.46 mg MeHgCl/kg bw, single dose, p.o.	GIBCO 116 EC *ad libitum* vs pellet rodent diet	Mouse	14 d	Organ Hg levels were increased	(*85*)
Coconut oil	5 μmol MeHgCl/kg bw (single oral dose after 3 wk)	Coconut oil, 5–50% of energy vs cod liver oil diet	Mice	5 wk	Increased whole-body, liver, and kidney retention of Hg; 50% diet decreased retention in liver and kidney	(*111*)
Cysteine	10 μmol MeHgCl, injection	100 μmol L-Cys, injection	Rat	1 hr	Increased brain uptake of MeHg	(*178*)
Cysteine	4 μM MeHgCl	0.08–0.8 mmol Cys	*In vitro* rat hepatocytes	240 min	Increased cellular uptake of MeHg from medium	(*74*)
Cysteine	0.05 mM MeHgCl, intracarotid injection	0.1 mmol L-Cys (simultaneous intracarotid injection)	Rat	15 s	Increased brain Hg uptake	(*82*)
Cysteine	4 μmol MeHgCl/kg bw (single i.v. injection)	Cys, 8 μmol /kg bw (single i.v. injection premixed with Hg)	Rat	4 hr	Increased uptake of Hg in kidney but decreased liver and blood content	(*74*)

(*Continued*)

Table 6. *Continued.*

Nutrient	MeHg exposure	Nutrient dose	Animal model	Duration of experiment	Effects	Ref.
Cysteine	50 µmol MeHgCl/hr for 1 hr (at 24, 48 and 72 hr), continuous infusion to external jugular vein	0.1 mmol L-Cys/hr (continuous infusion to external jugular vein), 4 d	Rat (pregnant, 17 d, vs non-pregnant)	92 hr	Increased brain Hg in both types of rat; did not alter Hg distribution between pregnant and nonpregnant states	(*76*)
Cysteine	MeHg–GSH, 1 mmol MeHg/L packed erythrocytes	Cysteine	Rat	30 min	Increased MeHg uptake; MeHg uptake might use the Cys-facilitated transport system	(*93*)
Ethanol	MeHg (dose NA)	Ethanol (dose NA)	Mouse	NA	Potentiated toxicity and mortality	(*184*)
Ethanol	MeHg (dose NA)	Ethanol (dose NA)	Human	NA	Associated with increased mortality from liver cancer, chronic liver disease, and cirrhosis among Minamata disease patients	(*38*)
Ethanol	1.5 mg MeHg/kg bw/d or 1.5 mg/d for 45 d (oral gavage)	2.0 g ethanol/kg bw/d, 45 d	Rat	NA	Increased renal weight; caused oliguria and increased blood urea nitrogen levels; impaired kidney function; decreased glucose in urine	(*185*)
Ethanol	5 mg MeHgCl/kg bw/d (10 consecutive days after d 7)	2.5–10% ethanol in drinking water	Rat	50 d	Increased mortality; potentiated neurologic manifestations; increased Hg in kidney and brain	(*186*)
Ethanol	2.5 mg MeHgCl/kg bw (s.c. injection)	50% ethanol (s.c. injection, 0.1 mL/200 g bw)	Rat	44 d	Decreased body weight; increased severity of hindlimb ataxia	(*187*)
Ethanol	0.5 mg MeHgCl/kg bw/d	8 g ethanol/kg bw/d, orally	Rat	14 wk	Decreased renal γ-glutamyltransferase; no effect on the distribution of MeHg and its inorganic metabolites or GSH in brain and kidney	(*188*)
Ethanol	1–2.5 mg MeHgCl/kg bw in water	5.0 mL/kg bw of 25% ethanol	Rat	7 wk	Increased Hg in kidney but not brain and blood levels; lowered activity of apartate amino transferase and increased creatine phosphokinase; increased kidney pathology; no effect on percentage inorganic Hg; no effect on neurotoxicity (ataxia, tail rotation, convulsion)	(*79*)
Glutamate	0.5–10 µM MeHg	100 µM glutamate, 4 or 8 min	*In vitro* (mouse astrocytes)	60 min	Hg inhibited amino acid uptake in astrocytes	(*189*)
Glutamate	0–10 µM MeHgCl	100 mM glutamate	*In vitro* mouse neonate astrocytes	14 min	Uptake of glutamate is inhibited in the presence of Ca^{2+}	(*83*)
High-protein diet	80 µmol MeHgCl/kg, injection	24.8% protein diet	Mouse	16 d	Killed mice within 16 d despite lower brain Hg than mice with a low-protein diet fed at a higher mercury dose; susceptibility to Hg was higher in normal-protein fed rats than low-protein–fed rats	(*89*)
High-protein diet	120 µmol MeHgCl/kg bw, injection	24.8% protein diet	Mouse	7 d	Killed mice within 7 d; plasma aspartate amino transferase and alanine amino transferase were higher than in low-protein group	(*89*)
Linoleic acid	15 ppm MeHgCl, in diet	1–3% linoleic acid in diet (remainder of fat was lard)	Japanese quail	15 d	Increased mortality as percentage linoleic acid increased in birds not receiving linoleic acid diets from hatching	(*84*)
Low-protein diet	20 µmol MeHg/kg, bw, orally (on d 0)	7.5% protein diet vs 24.8% protein diet	Mouse	7d	Increased Hg in brain, kidney, blood, and plasma	(*87*)
Low-protein diet	80 µmol MeHg/kg bw, orally	7.5% protein diet	Mouse	16 d	All mice died within 16 d but died earlier than mice with low-protein diets	(*89*)
Low-protein diet	120 µmol MeHg/kg bw, orally	7.5% protein diet	Mouse	7 d	Killed mice within 7 d	(*89*)
Low-protein diet	20 µmol MeHg/kg bw, orally (24 hr before death)	7.5% protein diet vs 24.8% protein diet, 5 d	Mouse	5 d	Increased Hg uptake to brain compared to mice on normal protein diets	(*69*)
Methionine	MeHg–GSH, 1 mmol MeHg/L packed erythrocytes	DL-Met	Rat erythrocytes	30 min	Stimulated MeHg uptake	(*93*)
Methionine	4 µM MeHgCl	0.6 mM GSH	*In vitro* rat hepatocytes	240 min	Increased cellular uptake of MeHg from medium	(*74*)
Milk	0.6 mg MeHgCl/kg bw, single dose, p.o.)	Evaporated whole milk, *ad libitum* vs rodent pellet diet	Mouse	2 wk	Increased Hg body burden; decreased percentage Hg^{2+}; burden in gut was small intestine > cecum > colon; Hg retention in blood, brain, liver, kidneys was increased	(*88*)

(*Continued*)

Table 6. *Continued.*

Nutrient	MeHg exposure	Nutrient dose	Animal model	Duration of experiment	Effects	Ref.
Milk	0.46 mg MeHgCl/kg bw, single dose p.o.	Evaporated whole milk diet *ad libitum* vs pellet rodent diet	Mouse	14 d	Increased Hg in whole body, brain, kidney, liver	(*85*)
Pectin	5.0 mg Hg/kg bw, single dose as MeHgCl	5% pectin in diet compared to fiber-free diet	Mouse	104 d	Increased percentage inorganic Hg in liver and brain	(*78*)
Soya oil	5 µM MeHgCl/kg bw, single oral dose after 3 wk	Soya oil, 20% of energy	Mouse	5 wk	Increased carcass Hg compared to cod liver oil diet; did not affect Hg in liver; decreased kidney Hg	(*111*)
Other effects						
Aspartate	0.05 mM MeHgCl (intracarotid injection)	0.1 mM L-Cysteine-L-aspartic acid (simultaneous intracarotid injection)	Rat	15 sec	No effect on Hg uptake across the blood–brain barrier	(*82*)
ATP	MeHg–GSH 1 mmol MeHg/L centrifuged erythrocytes	ATP	Rat	30 min	No effect on MeHg uptake (tests the active transport system)	(*93*)
Cholesterol	5×10^{-4} M MeHgCl, in buffer	NA	*In vitro*	NA	No effect on the flux of Hg across lipid membrane	(*190*)
Cod liver oil	5 µmol MeHgCl/kg bw (single oral dose after 3 wk)	Cod liver oil, 5–50% of energy	Mice	5 wk	No effect on whole-body retention of Hg; Hg retention was lower than with coconut oil diet	(*111*)
Cysteine	0.5 mg mercury cysteinide/kg bw (i.v. injection)	0.5 mg mercury cysteinide/kg bw (i.v. injection)	Mouse	14 d	No effect on distribution and excretion when compared to inorganic Hg	(*191*)
Cysteine	0.05 mM 0.5 mL MeHgCl (intracarotid injection)	0.1 mM D-Cys (simultaneous intracarotid injection, 0.5 mL)	Rat	15 sec	No effect on the rate of MeHg uptake in brain	(*82*)
Fiber	MeHgCl, oral, dose NA	Cellulose, pectin, oat, corn soy fiber, dose NA	Mouse	NA	No effect on whole-body Hg retention	(*174*)
Glutamate	10 µmol MeHgCl (i.v. injection, with 100 µmol Cys, 2 mL)	L-Glu 200 µmol (i.v. injection, 2 mL)	Rat	2 hr	No effect on brain Hg content	(*178*)
Glycine	4 µM MeHgCl	NA	*In vitro* rat hepatocytes	240 min	No effect	(*74*)
Glycine	MeHg–GSH 1 mmol MeHg/L centrifuged erythrocytes	Glycine	Rat erythrocytes	30 min	No effect on MeHg uptake; system glycine is not involved in MeHg uptake	(*93*)
Histidine	4 µM MeHgCl, i.v. injection	NA	*In vitro* rat hepatocytes	240 min	No effect	(*74*)
Kynurenine	MeHg 0.1–10 µM, 10 min	30 µM kynurenine, 2 min	*In vitro* mouse astrocytes	60 min	Hg inhibited amino acid uptake in astrocytes	(*189*)
Lysine	10 µmol MeHgCl (i.v. injection, with 100 µmol Cys 2 mL)	200 µmol L-Lysine, i.v. injection	Rat	2 hr	No effect on brain Hg content	(*178*)
Methionine	0.5–1.5 mg MeHgCl/kg bw/d oral gavage)	Met, 60, 100, 140% of sulfur amino acid requirement	Rat	5 wk	Serum thromboxane B_2 was affected; Met deficiency caused increase in serum prostaglandin E_1	(*192*)
Phenylalanine	10 µmol MeHgCl (i.v. injection, with 100 µmol Cys, 2 mL)	200 µmol L-Phenylalanine (i.v. injection)	Rat	2–12 hr	Phe inhibited the effect of L-Cys on increased brain uptake of MeHg	(*178*)
Seafood	121 nmol Hg/L in cord blood	Frequent whale meat dinners during pregnancy	Human	Birth cohort	Frequent ingestion of whale meat was associated with higher Hg in cord blood; blood Hg was correlated with blood Se	(*32*)
Soluble proteins	40 µM MeHgOH, aqueous	Soluble proteins 24 mg/mL protein, 1.4 mmol thiol groups, 1.5 mmol nonprotein thiol groups, in buffer	*In vitro* rat liver	1 hr	No effect on degradation of MeHg	(*193*)
Tannins	10–1,000 ppm Hg	Tree bark	*In vitro*		Tree barks were used in decontamination of industrial waste	(*194*)

Abbreviations: ADP, adenosine diphosphate; CNS, central nervous system; gal, galactosidase; i.m., intramuscular; i.p., intraperitoneal; i.v., intravenous; p.o., per os; s.c., subcutaneous, SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic–pyruvic transaminase.

Table 7. Effects of minerals on the metabolism and distribution of methyl mercury: minerals.

Nutrient	MeHg exposure	Nutrient dose	Animal model	Duration of experiment	Effects	Ref.
Protective effects						
Calcium ion	1×10^{-4} to 5×10^{-3} mg MeHg/L water	20–30 mg calcium/L	Algae	15 d	Inhibits MeHg toxicity; plays a more important role than Mg in the amelioration of MeHg toxicity	(*195*)
Chloride	MeHg–GSH 1 mmol MeHg/L centrifuged erythrocytes	Cl^-, dose NA	*In vitro*, rat erythrocytes	30 min	Cl^- inhibits MeHg uptake; uptake might use the Cl^- transport system	(*93*)
Copper	Hg, dose NA	Cu, dose NA	Rat	NA	Cu decreased whole-body retention of Hg by 50%; Cu decreased Hg:MT in the kidney	(*133*)
Magnesium ions	1×10^{-4} to 5×10^{-3} mg MeHg/L in water	20–30 mg/L magnesium in water	Algae	15 d	Had only a minor effect on severity of MeHg toxicity	(*195*)
Phosphate	1/3 of LD_{50} MeHgCl (single i.p. injection)	Pi buffer (i.p. injection, pretreatment)	Mouse	NA	Decreased severity of inhibition of protein synthesis and ATP synthesis	(*196*)
Phosphate	1×10^{-4} to 5×10^{-3} mg MeHg/L in water	20–30 mg/L phosphate	Algae	15 d	Ameliorated effect of MeHg, possibly due to effect on bioavailability; suggested that alkaline and hard eutropic waters might help protect fresh water organisms against heavy metal toxicity	(*195*)
Selenium	20 ppm MeHgCl in diet	8 ppm Se as selenite in diet	Chick	28 d	Decreased liver Hg; enhanced Hg depression of weight gain	(*197*)
Selenium	30 ppm MeHgCl in diet	Se, 0.4 ppm (type not mentioned) in diet	Cotournix quail	7 d	Se decreased elevated barbituate-induced sleeping time	(*198*)
Selenium	50 µmol MeHgCl/kg bw, p.o.	50 µmol selenite/kg bw, p.o.	Guinea pig	13 d	Se decreased concentration of Hg in major organs except brain; brain Hg was only lower after 7 d; organ and subcelluar distribution of Se was also altered to increase binding to insoluble nonhistone proteins	(*199*)
Selenium	15–30 ppm MeHgCl in diet	0.6 ppm selenite in diet	Hen	NA	At lower levels of Hg, less Hg is accumulated in liver and kidney	(*156*)
Selenium	4 µM MeHgCl	1, 3, 5 µM selenite	*In vitro* embryonic chicken neural retinal cells	24 hr	Provided protective effect on cell aggregation compared to MeHgCl alone	(*200*)
Selenium	3×10^{-6} M MeHgCl	1×10^{-7} to 3×10^{-5} M selenite	*In vitro* human blood	72 hr	Prevented the induction of sister chromatid exchange dose dependently when added simultaneously to Hg	(*117*)
Selenium	18 µg Hg/g/d in fish diet	115 µg Se/g/d in fish diet	Human	NA	Decreased bleeding time	(*36*)
Selenium	5 nM MeHgCl	5 nM selenite	*In vitro* human blood	2 hr	Released MeHg from blood proteins	(*201*)
Selenium	1×10^{-5} M MeHgCl	0.8×10^{-5} M selenate or 0.2×10^{-5} M selenite	*In vitro* rat (cerebellar tissues)	4 d	Both types of Se showed protection against toxicity	(*202*)
Selenium	5–15 ppm MeHgCl in diet, 7 d	1 ppm selenite in diet, 7 d	Japanese quail	9 d	Alleviated depression in weight gain and feed consumption; Se concentration in blood increased, but GSH–peroxidase activity in blood was not altered, suggesting that the Se remained unavailable	(203)
Selenium	20 ppm MeHgCl in corn oil	5 ppm selenite in water	Japanese quail	9 wk	Decreased percent mortality close to control; brain contained up to 40 ppm MeHg, but no symptoms of mortality occurred; increased Hg retention in liver, kidney, brain, eggs	(119)
Selenium	30 ppm MeHgC in diet	0.6 ppm selenite in diet	Japanese quail	28–34 d	Protected toxicity (altered hematocrit, decreased bond calcification, survival rate)	(*204*)
Selenium	5–30 ppm MeHgCl in diet	0.35–6 ppm selenite in diet	Japanese quail	20 wk	Survival increased with increasing Se in diet; lessened effects on egg hatchability, fertility, and production; Se alone resulted in toxic effects	(*205*)
Selenium	20 ppm MeHg in water	0.35–6 ppm selenite in diet	Japanese quail	67 d	Increased survival rate from 0 to 33% with 3 ppm Se	(*206*)
Selenium	25 ppm MeHgCl in diet	1 ppm selenite in diet	Japanese quail	15 d	Protected mortality	(*84*)
Selenium	32 ppm MeHgCl in diet	0.6 ppm Se in diet, 5 wk	Japanese quail	24 d	Prevented decrease SGOT levels in severe Hg toxicity; did not affect SGPT levels	(*207*)
Selenium	10 ppm MeHg in diet	0.6 ppm selenite in diet	Japanese quail	18 wk	Protected survival; effect was dose-dependent; protection extended from parents to offspring	(*208*)
Selenium	0.075–20 ppm MeHg from tuna or 0.075–20 ppm MeHgOH in diet	0.23–0.67 ppm Se from 17% tuna in diet	Japanese quail	6 wk	Decreased Hg intoxication; increased retention of Hg and Se	(*55*)
Selenium	10 ppm MeHgCl in diet	6 ppm selenium in diet	Japanese quail	16 wk	Prolonged survival time, improved egg production, improved fertility	(*71*)

(*Continued*)

Table 7. *Continued.*

Nutrient	MeHg exposure	Nutrient dose	Animal model	Duration of experiment	Effects	Ref.
Selenium	15, 30 ppm MeHg in diet	Selenite, 0.6 ppm in diet	Leghorn hen	35 d	Prevented rapid weight loss, improved egg laying and incidence of shell defects; prevented increased kidney weight by Hg; prevented change in SGOT; prevented increase in transaminase levels	(*177*)
Selenium	10 ppm MeHgCl in diet	Se, 10 ppm in diet	Mallard	10 wk	Combined treatment alleviated Hg-induced decreased activity for liver GSH peroxidase, brain G-6-PDH and liver GSSG. Plasma glucose was slightly increased and hematocrit was slightly decreased; increased Se retention in brain but decreased Hg retention in brain; increased Se uptake in liver	(*209*)
Selenium	10 ppm MeHgCl in diet	Sel-Met,10 ppm or 10 ppm Se in diet	Mallard	73 d	Prevented paralysis of the legs, but combination of Se and MeHG decreased reproductive stress over either alone, increased teratogenicity, and increased Se in tissues	(*210*)
Selenium	20 nmol MeHgCl/g bw, single injection on 6 consecutive d	10 nmol selenite,/g bw, simultaneous with or 30 min prior to MeHg, single injection (control dietary Se = 0.5 μg/g)	Mouse (Se deficient)	7 d	Reduced the MeHg-induced decrease in glutathione-*S*-transferase	(*120*)
Selenium	8 μC MeHg in lake water/vessel, dose NA	1–100 μg Se/L as selenite	Northern Pike	3–12 d	Reduced Hg contamination at low Se concentrations	(*211*)
Selenium	102 ng MeHg/d dry weight sediment	Se, 1.45 vs 0.28 mg/kg dry weight sediment or 0.5–50 mg Se/kg dry sediment as sodium selenite	Oligochaete worm	14 d	Higher doses of Se decreased MeHg uptake (25–86% reduction)	(*212*)
Selenium	7 mg MeHg/kg bw, single oral dose at 5 wk	0.03–5 ppm selenite (6–7 wk in diet	Pig	7 wk	Protected histologic signs of toxicity; decreased Hg in muscle, cerebrum, heart, liver,kidney, and blood; MeHg decreased Se in blood, liver, kidney, and muscle; clinical Se deficiency developed	(*213*)
Selenium	MeHg, dose NA	7.5 μM selenite or selenate (perfusion medium)	Rainbow trout		Increased uptake of MeHg across the gills	(*214*)
Selenium	15–25 ppm MeHgCl	Selenite, 0.6 ppm in diet *ad libitum*	Rat	6–10 wk	Improved weight gain and survival; slightly decreased kidney Hg	(*70*)
Selenium	1 μmol MeHgCl/kg bw, i.v. injection	5 μmol sodium selenite/kg bw, i.v. injection	Rat	5–60 min	Increased cerebral MeHg, decreased kidney MeHg (up to 60 min after treatment); lowered blood methyl mercury; did not alter binding of MeHg to GSH	(*215*)
Selenium	MeHg as panogen-42 (MeHg dicyandiamide) 25 ppm in diet	3 ppm selenite, in diet	Rat	4 wk	Enhanced liver and kidney organ accumulation of both Hg and Se when diets contain both but decreased Se retention; had beneficial effect on body weight and food consumption	(*216*)
Selenium	20 ppm MeHgCl in diet	3 ppm selenite in water	Rat	61 d	Protective effect was observed for growth and morbidity; Hg increased the accumulation of Se in organs (8-fold in kidneys)	(*157*)
Selenium	20 ppm MeHgCl in diet	0.5–1.5 ppm selenite or Se from tuna in diet	Rat	70 d	Both types of Se showed protection of survival rate, morbidity, and growth rate; tuna was half as effective as selenite in preventing neurologic manifestations; no correlation between Hg in brain and neurologic manifestations in groups with Se	(*72*)
Selenium	2.0 mg MeHgCl/kg bw/d, i.p. injection	2.0 mg sodium selenite/kg bw/d, i.p. injection	Rat	8 wk	Prevented crossing reflex of hind limbs, ataxicgait, weight loss, and reduction in glutathione peroxidase activity after 6 wk	(*217*)
Selenium	0.01 mmol MeHgCl/kg bw, s.c. injection	0.01 mol sodium selenite/kg bw, s.c. injection, 30 min before injection of Hg	Rat	1 hr	Increased Hg in blood, testes, brain; decreased Hg in kidney; did not affect liver, spleen, heart, or plasma	(*122*)
Selenium	10 mg MeHgCl/kg bw/d orally (for 8–10 d)	0.5 mg selenite/kg bw, s.c. injection daily at same time as Hg	Rat	15–17 d	Delayed weight loss and delayed onset of signs of neurotoxicity; accelerated accumulation of Hg in brain but shortened its retention	(*218*)
Selenium	20 μmol MeHgCl/kg, bw, i.p. injection	20 μmol selenite/kg bw (1 hr before or after Hg)	Rat	2 hr	Decreased Hg in liver and kidney and increased it in brain; increased benzene extractable Hg, which was present as bis(methylmercuric) selenide	(*219*)
Selenium	MeHgCl in diet, dose NA	Selenite	Rat		Showed protection against neurotoxicity	(*220*)

(*Continued*)

Table 7. *Continued.*

Nutrient	MeHg exposure	Nutrient dose	Animal model	Duration of experiment	Effects	Ref.
Selenium	0–40 ppm MeHgCl in diet	5 ppm selenite in diet	Rat	74 d	Protected weight gain at high MeHg, increased Hg in liver but decreased Hg-induced reduction in liver size and enlargement of kidney	(*221*)
Selenium	Bis(methylmercuric) selenide, dose NA	Se, dose NA			Less inhibition of glucose-6-phosphate dehydrogenase, catalase, and trypsin	(*222*)
Selenium	8 µC MeHg in lake water/vessel, dose NA	1–100 µg Se/L as selenite	White sucker	3–12 d	Reduced Hg contamination at low Se concentrations	(*211*)
Selenium	8 µC MeHg in lake water/vessel, dose NA	1–100 µg Se/L as selenite	Yellow Perch	3–12 d	Reduced Hg contamination at low Se concentrations	(*211*)
Selenium	10 nmol MeHg/g feed	8–50 nmol selenite/mL drinking water	Mouse	1–2 wk	Restored decrease in membrane fragility	(*223*)
Selenium	10–1,000 ppm MeHgCl, in diet	2–8 ppm sodium selenite in diet	Mouse	45 d	Protected damage at all doses; induced enzymes at high levels (100 ppm MeHg, 2–8 ppm Se) in liver and kidney; modified enzymes of GSH metabolism; suggests observations are a mixture of toxicity and repair	(*224*)
Selenium	1–100 µM MeHgCl	10–80 µM selenium	*In vitro* cerebral mouse neurons	1–24 hr	Blocked toxicity	(*145*)
Selenium	25 ppm MeHg in diet	0.6 ppm selenite	Rat	10 wk	Prevented increase in SGPT and SGOT levels	(*177*)
Zinc	10 µM MeHgl	100 µM $ZnSO_4$, 24-hr pretreatment	*In vitro* (rat astrocytes)		Increased MT protein levels and mRNA levels; provided resistance to MeHg-induced swelling; attenuated increased Na^+ uptake and K^+ release due to MeHg	(*225*)
Enhanced toxicity						
Halogens (Cl, nitrate, sulfate, phosphate, carbonate), sodium bromide, sodium iodide	100 µg Hg/L in water as MeHgCl	10^{-2} to 10^5 µM halogens	Fish (*Oryzias latipes*)	1–4 d	Cl^- significantly decreased hatchability of fish eggs; calcium chloride enhanced MeHg toxicity when present simultaneously; halides decreased survival time; chlorides reduced Hg content of whole embryos	(*226*)
Selenium	3 mg MeHgCl/kg bw, p.o., every 2nd d for 3 wk (10 doses)	Equimolar selenite	Guinea pig	28 d	Se decreased excretion of Hg in feces (2-fold) and in urine (7-fold); Se made a two-compartment model the best fit with half-lives for Hg of 8.7 and 40.8 d	(*227*)
Selenium	1×10^{-5} M MeHgCl	Selenate, 4×10^{-5} M and selenite, 1×10^{-5} M	*In vitro* rat (cerebellar tissues)	4 d	Enhanced toxicity	(*202*)
Selenium	20 ppm MeHgCl in diet	8 ppm Se in diet as selenite	Japanese quail	25 d	Increased liver Hg; no effect on weight gain	(*197*)
Selenium	10 µg MeHgCl/g in diet	2.5–10 µg sodium selenite/g diet	Japanese quail	21 d	Increased hepatic Hg levels; no change in hepatic GSH and GSSG; GSH transferase isozyme activities were modified; thioltransferase and GSH–peroxidase activity were stimulated	(*228*)
Selenium	15, 25, 35 µmol MeHgCl/kg bw/d on d 13, 14, and 15 of pregnancy (s.c. dose)	0.1, 0.2, 0.4 mg Se/kg diet as selenite, 5–7 wk	Mouse	8–10 wk	0.1 ppm Se in diet was enough to protect against fetolethality at 25 µmol/kg/d MeHgCl; GSH–peroxidase activity in mother was not affected; GSH–peroxidase activity in fetal liver was decreased and Se was increased, suggesting a decrease in Se bioavailability; Se supplementation increased Se in fetal liver	(*229*)
Other effects						
Calcium ion	1 mmol MeHg/L as MeHg–GSH	Ca^{2+}, dose NA	*In vitro* rat erythrocytes	30 min	No effect of Ca^{2+}-free buffer on MeHg uptake; Ca^{++} role may be via ATPase or signal transduction	(*93*)
Chloride ion	.5 µM MeHgCl in buffer	1–500 mM NaCl	*In vitro*	NA	Alters permeability of Hg across lipid membranes; suggests that Hg crosses the membrane in a neutral form	(*190*)
Magnesium ions	1 mmol MeHg/L as MeHg–GSH	Mg^{2+} (dose NA)	Rat erythrocytes	30 min	Mg^{2+}-free buffer had no effect on MeHg uptake; Mg^{2+} does not likely play an important role	(*93*)
Phosphate	1/3 of LD_{50} MeHgCl, single i.p. injection	Pi buffer, i.p. injection posttreatment	Mouse		Pi treatment was less effective in correcting already induced metabolic disorders	(*196*)
Potassium ions	0–1,000 µM MeHgCl	K^+	*In vitro,* rat astrocytes	30 min	MeHg inhibited uptake of Rb, a tracer for K^+	(*230*)
Selenium	Environmental, ocean	Se, environmental	Bowhead whale	NA	Positive correlation between Hg and Se; Hg:Se ratio was 1:40	(*231*)

(*Continued*)

Table 7. *Continued.*

Nutrient	MeHg exposure	Nutrient dose	Animal model	Duration of experiment	Effects	Ref.
Selenium	13 ppm phenyl Hg in seed	Se, dose NA	Chicken eggs	2 mo	MeHg was identified in the eggs, I-Hg was predominant in the yolk; Se level was higher than in normal eggs	(*232*)
Selenium	MeHg, dose NA	Selenite, dose NA	Fetus		MeHg increased the toxicity of selenite	(*233*)
Selenium	MeHg, dose NA	Selenite, selenomethionine, dose NA	Goldfish		NA	(*234*)
Selenium	0.3–0.9 nmol Hg/g wet weight	8.8–15.8 nmol Se/g	Human kidney	NA	Hg:Se in kidney is consistent with 1:1 ratio	(*235*)
Selenium	Hg, dose NA	Se and selenoprotein P, dose NA	*In vitro*		Hg–Se complex binds Seleno-protein P, but not Hg^{2+}	(*236*)
Selenium	10 nM MeHgCl	10 nM selenite	*In vitro* rabbit blood	30 min	Formation of bis(MeHg) selenide with the participation of GSH; MeHg transferred to the benzene fraction with molar ratio of 2:1	(*237*)
Selenium	10 μM MeHgCl	2.5 μM selenite	*In vitro* rat organs	30 min	Shows sulfhydryl groups of proteins and non-proteins are involved in interaction between protein-bound MeHg and selenite (GSH in liver and brain), Cys (in kidney); Cys in kidney may just be a breakdown product of GSH	(*238*)
Selenium	50 nM MeHgCl	50 nM selenite	*In vitro* rat blood	2 hr	Dereased Hg binding to egg albumin and to erythrocytes	(*201*)
Selenium	5–15 ppm MeHgCl, 7 d in diet	1 ppm selenite in diet, 7 d	Japanese quail	7 d	Se had no effect on Hg in kidney or brain but increased Hg in liver; Hg did not affect the level of Se in kidney, liver, or brain, but increased Se in the blood	(*239*)
Selenium	10 ppm MeHgCl in diet	0.3% selenite	Japanese quail	16 wk	No affect on survival of MeHg-fed quail	(*71*)
Selenium	0–1.0 mM MeHgCl, intraduodenal dose	0.01 mM Se as Se–Met, intraduodenal dose	Leghorn cockerels	3 wk	Lack of interaction between Se and Hg; note Hg level is manyfold excess of Se; suggests effect not of great nutritional importance	(*98*)
Selenium	0–1.0 mM MeHgCl, intraduodenal dose	0.01 mM selenite, intraduodenal dose	Leghorn cockerel	3 wk	No affect on selenite absorption; lack of interaction between Se and Hg; since Hg level is many fold excess of Se effect not of great nutritional importance	(*98*)
Selenium	10 nmol MeHg/g feed	0, 8, 20, 50 nmol selenite/mL drinking water	Mice		Selenite increased Hg in brain and liver, but decreased it in blood, kidneys, and spleen	(*223*)
Selenium	100 μg MeHgCl, s.c.	69 μg selenite, i.v. injection 1 wk after Hg	Mice	1 wk	Increased free MeHg in blood, liver and kidney, but not brain	(*201*)
Selenium	15, 25, 35 μM MeHgCl/kg bw/d, s.c. injection, to dams on d 13,14, and 15 of pregnancy	Se deficiency	Mouse	8–10 wk toxicity	Se deficiency exacerbated MeHg fetal lethal	(*229*)
Selenium	Bis(methylmercuric) selenide, i.v. injection, dose NA	Se, dose NA	Mouse		Decreased Hg retention in brain	(*240*)
Selenium	MeHg, dose NA	Se, dose NA	Mouse		Decreased Hg retention in brain	(*240*)
Selenium	1 nmol MeHgCl/mL in drinking water during pregnancy	3 μg Se–Met/mL in drinking water	Mouse (pregnant)	60 d	Increased Hg in offspring, decreased kidney Hg deposition in offspring	(*97*)
Selenium	20 mg MeHgCl/L in drinking water every second d	2 mg selenite/L in drinking water every second d	Rat	95 d	Increased mercury staining in cerebral cortex, thalamus, hypothalamus, brain stem nuclei, Purkinje cells, and white matter; increased Hg in nuclei of neurons; delayed functional toxicity (crossing of hind limbs, ataxia); did not delay malnourishment	(*241*)
Selenium	0.5 μmol MeHgCl, 0.2 mL, s.c. injection, or 1.25–5 μmol, injected by gastric gavage, 5 mL/kg bw	0.5 μmol, 0.2 mL, s.c. injection, selenite alone or in combination with MeHgCl	Rat	48 hr	Increased retention of Se but did not affect blood levels; retention was time dependent	(*157*)
Selenium	1–38 μmol MeHgCl/kg bw, i.p. injection	0.25–10 μmol selenite/kg bw i.p. injection	Rat	72 hr	Concurrent, equimolar injections protected slight decrease in GSH–peroxidase activity in brain; increased brain Hg uptake but did not alter Hg distribution	(*242*)
Selenium	0.01 mmol MeHgCl/kg bw	0.01 mmol selenite/kg bw	Rat		NA	(*122*)
Selenium	9 μmol MeHg/kg bw, oral intubation	Selenite 3–9 μmol/kg bw	Rat	16 hr	Hg was increased in all organs except kidney where Hg was decreased; effectiveness was Se–Met > Se–Cys > selenate > selenite	(*243*)

(*Continued*)

Table 7. *Continued.*

Nutrient	MeHg exposure	Nutrient dose	Animal model	Duration of experiment	Effects	Ref.
Selenium	Organic, inorganic Hg, dose NA	Se, dose NA	Rat	NA	NA	(*244*)
Selenium	MeHgCl injection, dose NA	Selenite injection, simultaneous, dose NA	Rat	NA	Gel chromatography of plasma showed that proteins derived from a pronase E digestion did not contain Hg and only low Se; the Hg–Se-rich fraction did not contain protein, but gel chromatography of serum showed that proteins derived from a pronase E digestion contained high Hg and Se; properties suggest a mercuric selenide colloid	(*245*)
Selenium	0.5 µmol MeHg, 5 mL	0.5 µmol selenite, 5 mL	Rat	7 d	Temporarily increases the concentration of MeHg in the brain; temporal separation of Hg and Se exposure alters MeHg distribution	(*246*)
Selenium	MeHg, dose NA	Selenite, dose NA	Rat		No significant effect on GSH–peroxidase activity in liver	(*247*)
Selenium	Hg in pike or trout 1:6 Hg:Se	3.4 mg Se–Met/kg fish meal	Rat		Se–Met increased both Hg^{2+} and MeHg in the blood	(*248*)
Selenium	Hg in Northern Pike or rainbow trout 1:6 Hg:Se	3.4 mg selenium dioxide/kg fish meal	Rat		Se decreased both inorganic Hg and MeHg in the blood and liver in rats fed Northern Pike	(*248*)
Selenium	16.6 µM MeHgCl	8.3 µM selenite	NA	10 min	Formation of bis(MeHg) selenide in benzene-soluble fraction	(*249*)
Sodium ions	MeHg-GSH 1 mmol MeHg/L centrifuged erythrocytes	Na^+, dose NA	Rat erythrocytes	30 min	Na^+-free buffer stimulated MeHg uptake; suggests a Na^+-dependent transport system exists for MeHg uptake	(*93*)
Zinc	Organic, inorganic Hg, dose NA	Zn, dose NA	Rat			(*244*)
Zinc	Hg, dose NA	Zn, dose NA	Rat		Zn slightly decreased whole-body retention of Hg; decreased Hg:MT in the kidney	(*135*)
Zinc	1×10^{-4} to 5×10^{-3} mg MeHg/L water	Zn, dose NA	Algae	15 d	NA	(*195*)

Abbreviations: GSSG, oxidized GSH; MeHgCl, methyl mercury chloride; MeHgOH, methyl mercury hydroxide; Se–Met, seleno-L-methionine.

Table 8. Effects on the metabolism and distribution of methyl mercury: vitamins and phytochemicals.

Nutrient	MeHg exposure	Nutrient dose	Animal model	Duration of experiment	Effects	Ref.
Protective effects						
Pantothine	80 ng Hg/mL as MeHgCl in tank water	10 µg pantothine/mL water in tank	Goldfish	24 hr	Decreased MeHg uptake by fish	(*250*)
Coenzyme A	80 ng Hg/mL as MeHgCl in tank water	0.6 µg coenzyme-A/mL water	Goldfish	24 hr	Protected fish against MeHg uptake	(*250*)
Vitamin B_{12}	1 mg MeHgCl/kg bw/d, 7 d, s.c. injection	2 mg/kg bw, s.c. injection for 7 d after 7-d MeHg treatment	Mouse	14 d	α- and β-Glycosidase activities recovered in brain, spinal cord; inhibtion of liver and kidney enzyme activities enhanced	(*103*)
Vitamin B_{12}	1 mg MeHgCl/kg bw/d, d 0–7, s.c. injection	2 mg vitamin B_{12}/kg bw/d, d 7–14, s.c. injection	Mouse	15 d	α-gal and β-gal activities recovered toward normal in brain and spinal cord; spinal cord had maximum recovery of β-gal; β-gal recovered in kidney and testes; α-gal recovered in kidney	(*180*)
Vitamin C	1 mg MeHgCl/kg bw/d, 7 d, s.c. injection	5 mg vitamin C/kg bw, s.c. injection for 7 d after 7-d MeHg treatment	Mouse	14 d	α- and β-Glycosidases activities recovered in brain, spinal cord; vitamin C showed maximum α-gal activity compared to other vitamins; inhibition of liver and kidney enzyme activies was enhanced	(*103*)
Vitamin C	1 mg MeHgCl/kg bw/d, d 0–7, s.c. injection	5 mg vitamin C/kg bw/d, d 7–14, s.c. injection	Mouse	15 d	α-gal and β-gal activities recovered toward normal in brain and spinal cord; β-gal recovered in kidney and testes; α-gal recovered in kidney but not in liver and testes	(*180*)
Vitamin E	10^{-5} M MeHgCl in buffer	$0.4–2.0 \times 10^{-5}$ M DL-α-tocopherol acetate	*In vitro* rat (cerebrallar tissues)	4 d	Inhibited toxic effect of MeHg on development of nerve fibers, glial cells, and fibroblasts	(*144*)
Vitamin E	10–40 mg MeHgCl/L in drinking water	10, 100 or 1,000 mg α-tocopherol/kg in diet	Mouse	2 wk	High tocopherol in diet protected against MeHg-induced lipid peroxidation in liver; deficient diet enhanced MeHg-induced lipid peroxidation; protected GSH–peroxidase activity	(*146*)
Vitamin E	4 µM MeHgCl	5, 7, and 10 µM DL-α-tocopherol acetate	*In vitro* embryonic neural retinal cells	24 hr	Provided protective effect on cell aggregation compared to MeHgCl alone; less effect than Se	(*200*)
Vitamin E	15 ppm MeHgCl in diet	0.05% all rac-α-tocopherol acetate in diet	Japanese quail	22 d –29 d	Protected against Hg-induced mortality	(*142*)
Vitamin E	30 ppm MeHgCl, in diet	500–1,000 IU vitamin E, in diet	Japanese quail	28–34 d	Protective effect was eventually overcome by toxic effect of Hg	(204)
Vitamin E	10–30 ppm MeHgCl, in drinking water	50–500 ppm vitamin E, in diet	Rat	6–13 wk	Fewer signs of toxicity and greater growth and survival over Hg alone	(*252*)
Vitamin E	20 mg MeHgCl/kg bw	2.0 ppm DL-α-tocopherol acetate/d, s.c. injection, 4 wk	Golden hamster	4 wk	Prevented signs of ill health: ataxia and paralysis of hind limbs as well as extensive lesions in cerebellum, loss of granule celles, glial fibers, necrosis, and active phagocytosis of debris	(*143*)
Vitamin E	2 ppm MeHg/d, injection type NA	2 ppm vitamin E/d, injection type NA	Hamster	4 wk	Prevented neurologic disturbances (degenerative changes in granule cells, morphologic changes)	(*253*)
Vitamin E	25 ppm MeHgCl in diet	50–500 mg/kg vitamin E in diet	Japanese quail	15 d	Protected mortality; high level had no additional protection compared to low level	(*84*)
Vitamin E	10 ppm MeHgCl in diet	700 mg/kg all rac-α-tocopheryl acetate in diet	Japanese quail	21 d	Did not affect GSH–peroxidase activity; Hg did not alter lipid peroxidation	(*141*)
Vitamin E	32 ppm MeHgCl in diet	Vitamin E (not given), dose NA	Japanese quail	24 d	Prevented decrease in SGOT levels in severe Hg toxicity; did not affect SGPT levels	(*207*)
Vitamin E	1 mg MeHg/kg bw/d, 7 d, injection	60 mg vitamin E/kg/d s.c. injection 7 d, after Hg exposure	Mouse	14 d	Restored decrease in Na, K, Mg, Mn, Cu, Zn, Cr, and Ni for most organs toward normal, but recovery was not complete; Fe decrease in brain and spinal cord did not recover; kidney Fe decreased	(*127*)
Vitamin E	1 mg MeHgCl/kg bw/d, 7 d, s.c. injection	60 mg vitamin E/kg bw, s.c. injection for 7 d after 7-d MeHg treatment	Mouse	14 d	α- and β-Glycosidase activities recovered in brain, spinal cord; vitamin E showed maximum recovery of β-glycosidases in the brain compared to other vitamins; liver and kidney enzyme activities inhibition was enhanced	(*103*)
Vitamin E	0.4 µM MeHgCl	10^{-5} to 10^{-2} M vitamin E	*In vitro* mouse neuroblastoma cells	3 d	Protected toxicity	(*251*)
Vitamin E	1 mg MeHgCl/kg bw/d, d 0–7, s.c. injection	60 mg vitamin E/kg bw/d, d 7–14, s.c. injection	Mouse	15 d	α-gal and β-gal activities recovered toward normal in brain and spinal cord; maximum recovery was in the brain; β-gal was further inhibited in kidney and testes; α-gal recovered in kidney but not in liver and testes	(*180*)

(*Continued*)

Table 8. *Continued.*

Nutrient	MeHg exposure	Nutrient dose	Animal model	Duration of experiment	Effects	Ref.
Vitamin E	10 ppm in drinking water	500 ppm vitamin E in diet with 0.1 ppm Se	Rat	Not given	Protected against toxicity (growth, neurologic symptoms, survival); suggests role of vitamin E is not just to spare Se	(*254*)
Vitamin E	10 ppm MeHg, in diet	100–500 mg D-α-tocopherol acetate, in diet	Japanese quail	18 wk	Protected survival; effect was dose dependent; protection extended from parents to offspring	(*208*)
Vitamin E	2 mg MeHg/kg bw, injection type NA	2 ppm α-tocopherol acetate in diet, injection type NA	Golden hamster	4 wk	Prevented toxic symptoms (neural damage, necrosis in cerebellum and calcarine cortex, ataxia, paralysis of hind limbs)	(*143*)
Vitamin E (γ-tocopherol)	15 ppm MeHgCl in diet	0.05% γ-tocopherol acetate in diet	Japanese quail	NA	Protected against Hg-induced mortality	(*142*)
Enhanced toxicity						
β-Carotene	10–40 mg MeHgCl/L in drinking water, 2 wk	1,000, 10,000, or 100,000 IU β-carotene/kg bw, in diet	Mouse	4 wk	Dietary excess of β-carotene enhanced MeHg-induced lipid peroxidation in brain, liver, and kidney	(*146*)
Vitamin A	10–15 ppm MeHgCl in drinking water	2,000–10,000 IU vitamin A/kg bw in diet	Rat	NA	Enhanced toxicity (growth, morbidity, mortality)	(*148*)
Vitamin C	20 μM MeHgOH, aqueous	0.4 mM ascorbate, aqueous	*In vitro* rat liver	10 min	Released Hg^0 and Hg^{2+}; Hg^{2+} release was proportional to ascorbate concentration	(*193*)
Vitamin C	0.4 μM MeHgCl	20–120 μg L-ascorbate/mL	*In vitro* mouse neuroblastoma cells	3 d	Enhanced toxicity	(*251*)
Other Effects						
Pantothenate	80 ng Hg/mL as MeHgCl in tank water	10 μg calcium pantothenate/mL water	Goldfish	24 hr	No effect on MeHg uptake by fish	(*250*)
Vitamin A	MeHg, dose NA	Vitamin A, dose NA	*In vitro* tissue culture	NA	NA	(*255*)
Vitamin C	0.4 μM MeHgCl	20–120 μg L-ascorbate/mL	*In vitro* rat glioma cells	3 d	No effect	(*251*)
Vitamin C	Nonoccupational environmental exposure	500 or 1,000 mg L-ascorbic acid/d for 3 months	Human	3 mo	No effect of vitamin C on Hg body burden as measured by hair and blood Hg	(*44*)
Vitamin C	80 ng Hg/mL as MeHgCl in water	10–1,000 times higher than Hg on a molar basis	Gold fish	24 hr	Reduction of MeHg toxicity was not consistent; possibly a role for vitamin C in the degradation of MeHg to Hg^{2+}; increased degradation increased mortality of fish	(*256*)
Vitamin E	0.4 μM MeHgCl	10^{-5} to 10^{-2} M vitamin E	*In vitro* mouse neuroblastoma cells	3 d	No effect	(*251*)
Vitamin E	13 ppm MeHgCl in drinking water	50 ppm vitamin E in diet compared to 275 ppm synthetic antioxidant DPPD	Rat	2 mo	DPPD decreased liver and brain Hg but increased kidney Hg compared to vitamin E	(*252*)
Vitamin E	20 ppm MeHgCl in drinking water	50 ppm vitamin E in diet compared to 275 ppm synthetic antioxidant DPPD	Rat (Se deficient)	7–9 wk	Vitamin E was not able to protect toxicity, but synthetic antioxidant DPPD did	(*252*)

DPPD, *N,N′*-Diphenyl-*p*-phenylenediamine.

Table 9. Effects of combined nutrients on the metabolism and distribution of MeHg.

Nutrient	MeHg exposure	Nutrient dose	Animal model	Duration of experiment	Effects	Ref.
Protective effects						
Cysteine and methionine	0.05 mM MeHgCl, 0.5 mL intracarotid injection	0.1 mM L-Cys, 0.1 mmol L-Met, 0.5 mL, intracarotid injection	Rat	15 s	Inhibited brain Hg uptake compared to cys alone	(*82*)
Cystine and selenium	15–25 ppm MeHgCl, in diet	0.4% L-cystine, 0.6 ppm selenite in diet, diet *ad libitum*	Rat	6–10 wk	Growth rate was similar to control diet; slightly decreased kidney Hg	(*70*)
Cystine and selenium	10 ppm MeHgCl, in diet	6 ppm selenite and 15 ppm cystine in diet	Japanese quail	16 wk	Prolonged survival time, improved egg production, improved fertility	(*71*)
Cystine and selenium	25 ppm MeHg, in diet	0.6 ppm selenite, 0.4% cystine of diet	Rat	10 wk	Prevented increase in SGPT and SGOT levels; effect was less than Se alone	(*177*)
Selenium and glutathione	0.3 μM MeHgCl	25 μM selenite and 5 mM GSH	*In vitro*	96 hr	Se and GSH decreased benzene-extractable Hg over time via cleavage of the Hg–C bond, but separately they did not; suggests reduction of selenite is needed for the degradation of MeHg	(272)
Selenium and methionine	10 ppm MeHgCl in diet	6 ppm selenite and 15 ppm Met in diet	Japanese quail	16 wk	Prolonged survival time, improved egg production, improved fertility	(*71*)
Selenium and vitamin E	1.4×10^{-5} M MeHgCl	1×10^{-5} M selenite; 1.0×10^{-5} M DL-α-tocopherol acetate	*In vitro* rat cerebrallar tissues	4 d	Protective effects of Se and vitamin E are additive	(*202*)
Selenium in tuna fish	0.05–20 ppm MeHgOH	0.49 ppm Se from tuna	Japanese quail	6 wk	Decreased MeHg toxicity and prolonged survival compared to corn, soya diet; decreased incoordination, mortality, growth inhibition	(*183*)
Selenium in tuna fish	20 ppm MeHgCl in diet	Tuna meal vs casein diet; natural Se in tuna or 0.5–1.5 ppm selenite	Rat	70 d	Se in tuna and selenite had same protective effect on growth; Se in tuna was half as effective as selenite in prevention of neurologic symptoms	(*273*)
Vitamin B complex	1 mg MeHgCl/kg bw/d, d 0–7, s.c. injection	20 mg vitamin B complex/kg bw/d, s.c. injection, d 8–14	Mouse	15 d	α-gal and β-gal activities recovered toward normal in brain and spinal cord; maximum recovery of α-gal was in spinal cord; α-gal recovered in kidney and testes; β-gal recovered in kidney but not liver and testes	(*180*)
Vitamin B complex	1 mg MeHg/kg bw/d, injection type NA, 7 d	20 mg vitamin B/kg bw/d complex, 7 days after Hg exposure, s.c. injection	Mouse	14 d	Mobilized Hg from all tissues; decrease in Na, K, Mg, Mn, Cu, Zn, Cr, and Ni for most organs was restored toward normal, but recovery was not complete; recovery of decreased Fe in brain and spinal cord but not kidney	(*127*)
Vitamin B complex	1 mg MeHgCl/kg bw/d, 7 d, s.c. injection	20 mg/kg bw, s.c. injection for 7 d after the 7-d MeHg treatment	Mouse	14 d	α- and β-Glycosidases activities recovered in brain, spinal cord; B-complex showed maximum recovery of β-glycosidase in the spinal cord; inhibition of liver and kidney enzyme activities was enhanced	(*103*)
Vitamin E and selenium	30 ppm MeHgCl in diet	0.05–0.6 ppm selenite and 10–500 IU α-tocopherol, in diet	Japanese quail	28–34 d	Vitamin E added to the protective effect of Se on mortality and clinical symptoms; vitamin E had a greater protective effect at low levels of Se; improved growth rate with larger effect attributed to vitamin E	(*274*)
Vitamin E and selenium	10–30 ppm MeHgCl in drinking water	50–500 ppm vitamin E diet and 0.1 ppm Se in diet for 8 wk	Rat	17–48 wk	Both Se and vitamin E protected signs of toxicity, growth and survival	(*252*)
Vitamin E, selenium	30 ppm MeHgCl in diet	500–1,000 IU α-tocopherol with 0.05–0.6 ppm selenite, in diet	Japanese quail	28–34 d	Protected toxicity (altered hematocrit, decreased bond calcification, survival rate); vitamin E provided little added protection at high levels Se	(*204*)
Vitamin E, selenium	10 ppm MeHg in diet	100–500 mg D-α-tocopherol acetate; 0.6 ppm selenite,in diet	Japanese quail	18 wk	Combined treatment offered more protection than either alone	(*208*)
Vitamins E and A	10–15 ppm MeHgCl in drinking water	50, 500 ppm vitamin E, 2,000–10,000 IU vitamin A/kg, in diet	Rats	NA	Protected toxicity at high vitamin E concentrations but not at low vitamin E concentrations (growth, morbidity, mortality)	(*148*)
Enhanced toxicity						
Methionine and protein	20 μmol Hg as MeHg/kg bw, oral administration	1% Met in diet to 7.5% or24.8% protein diet	Rat	NA	Met increased Hg in brain with low protein but not high protein diet; Met increased Hg in liver, plasma and decreased Hg in kidney	(*257*)

(*Continued*)

Table 9. *Continued.*

Nutrient	MeHg exposure	Nutrient dose	Animal model	Duration of experiment	Effects	Ref.
Vitamin C and copper	100 nM MeHg	10 μM copper sulfate with 100 μM L-ascorbate	*In vitro* (rat brain cells)	10 d	Increased oxygen reactive substances, and decreased activities of antioxidant enzymes, when effects were not observed with Hg alone	(275)
Other effects						
Selenium-L-methionine	1 nmol MeHgCl/mL, 5 wk, during and after pregnancy, in drinking water	3 μg Se–Met/mL in drinking water (diet already contains 0.9 ppm Se)	Mouse	9–10 wk	Percent Hg deposited in offspring *in utero* and during lactation was not influenced by Se–Met	(*276*)

Table 10. Evidence for the effect of nutrients on the excretion of MeHg.

Nutrient	MeHg exposure	Nutrient dose	Animal model	Duration of experiment	Effects	Ref.
Protective effects						
Chemically defined liquid diet	0.46 mg MeHgCl/kg bw, single dose p.o. on d 0	116 EC GIBCO diet *ad libitum* vs pellet rodent diet	Mouse	14 d	Increased elimination of whole-body Hg compared to rodent pellet diet; increased excretion of inorganic Hg	(*85*)
Cysteine	4 mmol MeHgCl/kg bw, single i.v. injection	8 mmol Cys/kg bw, single i.v. injection premixed with Hg	Rat	4 hr	Promoted biliary excretion of MeHg	(*74*)
Cysteine	4 mmol MeHgCl/kg bw, single i.v. injection	3 mmol cysteine/kg bw in 2 mL of water	Rat	300 min	Cys temporarily decreased biliary excretion of MeHg but then increased it as biliary excretion of Cys decreased	(*301*)
Cystine and selenite	15–25 ppm MeHgCl	0.4% L-cystine, 0.6 ppm selenite, in diet, *ad libitum*	Rat	6–10 wk	Reduced Hg toxicity; decreased excretion of Hg slightly and increased retention	(*70*)
Fish protein	15–25 ppm MeHgCl in diet, *ad libitum* vs casein diet	10–20% fish protein	Rat	6–10 wk	Increased urinary and fecal excretion compared to diets supplemented with selenite or cystine or the casein diet; slightly increased Hg in muscle	(*70*)
Glutathione	4 mmol MeHgCl/kg bw, single i.v. injection	8 mmol cysteine/kg bw, single i.v. injection premixed with Hg	Rat	4 hr	Promoted biliary excretion of MeHg	(*74*)
Lipoic acid	NA	NA	NA	NA	Protected Hg toxicity	(*140*)
Methionine	20 mmol Hg as MeHg/ kg bw	1–7.5% or 24.8% protein diet	Rat		Hg excretion in urine was increased but not fecal excretion	(*257*)
Selenium	6.5–13 ppm MeHgCl in diet	0.5–4 ppm selenite in diet	Chick	12 d	Increased Hg concentration in ileum; increased Hg excretion	(*302*)
Sulfur amino acids in low protein diet	20 mmol MeHg/kg, orally (24 hr before death)	7.5% protein diet vs 24.8% protein diet plus 0.03% cysteine and 1.1% methionine, 5 d	Mouse	5 d	Increased urinary Hg over normal protein diet	(*69*)
Synthetic liquid diet (high protein, low fat)	0.6 mg MeHgCl/kg bw (single p.o. dose)	Synthetic diet (high protein, low fat) *ad libitum*	Mouse	2 wk	Increased whole-body elimination of Hg compared to rodent pellet diet; antibiotic treatment reduced fecal Hg to zero and suppressed urinary Hg excretion	(*88*)
Wheatbran	5.0 mg Hg as MeHgCl/kg bw, single p.o. dose)	5, 15, 30% wheatbran in diet compared to fiber-free diet	Mouse	104 d	Increased rate of Hg elimination by 43%	(*78*)
Enhanced toxicity						
Lipoic acid	10 mmol/kg bw, i.v. injection	37.5–300 µmol lipoic acid /kg, i.v. injection	Rat	3 hr	Decreased biliary excretion of MeHg but increased GSH and inorganic Hg excretion	(*139*)
Low- protein diet	20 mmol Hg as MeHg/ kg bw, orally, on d 0	7.5% vs 24.8% protein diet	Mouse	7 d	Decreased urine Hg 3.7 times; did not affect fecal level	(*87*)
Low-protein diet	20 mmol Hg as MeHg/ kg,bw orally, 24 hr before death	7.5 vs 24.8% protein diet, 5 d	Mouse	5 d	Decreased Hg in urine	(*69*)
Methyl iodide	MeHg, dose NA	0.5 mmol methyl iodide/ kg bw, single i.v. injection	Rat	300 min	Decreased biliary excretion of MeHg	(*301*)
Selenium	50 mmol Hg as MeHgCl/kg bw, p.o.	50 mmol selenite/kg bw, p.o.	Guinea pigs	13 d	Decreased fecal excretion; fecal excretion was predominant excretion path	(*199*)
Other effects						
Cellulose	5.0 mg MeHgCl/kg bw, single p.o. dose	5% cellulose in diet vs fiber-free diet	Mouse	104 d	Did not affect Hg elimination	(*78*)
Cystine	15–25 ppm MeHgCl, in diet *ad libitum*	0.4% L-cystine, in diet, *ad libitum*	Rat	6–10 wk	Does not exert protective effect by increasing excretion	(*70*)
Ethanol	2.5 mg MeHgCl/kg bw, in water	5.0 mL/kg bw of 25% ethanol	Rat	7 wk	No effect on feces and urine levels of Hg	(*79*)
Milk	0.46 mg MeHgCl/kg (single dose p.o. on d 0)	Evaporated whole milk diet *ad libitum* vs pellet rodent diet	Mouse	14 d	Decreased elimination of whole-body Hg compared to rodent pellet diet; fecal excretion was less than pellet diet	(*85*)
Pectin	5.0 mg Hg as MeHgCl/kg bw, single p.o. dose	5% pectin in diet compared to fiber free diet	Mouse	104 d	No effect on Hg elimination	(*78*)
Selenium	15–25 ppm MeHgCl in diet	0.6 ppm selenite, in diet, *ad libitum*	Rat	6–10 wk	Reduced MeHg toxicity but did not accelerate elimination of Hg in urine or feces	(*70*)
Selenium-L-methionine	1 nmol MeHgCl/mL, 5 wk, during and after pregnancy, in drinking water (essentially nontoxic level)	3 mg Se–Met/mL in drinking water (diet already contains 0.9 ppm Se)	Mouse	9–10 wk	Rate of Hg excretion after birth was not affected by Se–Met	(*97, 276*)