The Influence of Nutrition on Methyl Mercury Intoxication

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Abstract

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) .

http://ehpnet1.niehs.nih.gov/docs/2000/suppl-1/29-56chapman/abstract.html

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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 pre-natal MeHg exposure can result in cerebral palsy, mental retardation, low birth weight, and early sensorimotor dysfunction (*18*). Therefore, scientists have focused on the re-evaluation 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 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 enterohepatic 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 I (*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 I (*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 γ-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 ß-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.

Appendix

(The Appendix contains tables 1-10 in a 193 K pdf file.) Individual tables can be reached through the following links.
Table 1 (97 K)
Table 2 (97 K)
Tables 3-4 (97 K)
Table 5 (97 K)
Table 6 (97 K)
Table 7 (97 K)
Table 8 (97 K)
Table 9 (97 K)
Table 10 (97 K)

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Last Updated: February 16, 2000