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Special Feature: Methylmercury

Original Contribution

Selenium Health Benefit Values as Seafood Safety Criteria

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Abstract: Selenium (Se) is absolutely required for activity of 25–30 genetically unique enzymes (selenoenzymes). All forms of life that have nervous systems possess selenoenzymes to protect their brains from oxidative damage. Homeostatic mechanisms normally maintain optimal selenoenzyme activities in brain tissues, but high methylmercury (MeHg) exposures sequester Se and irreversibly inhibit selenoenzyme activities. However, nutritionally relevant amounts of Se can replace the Se sequestered by MeHg and maintain normal selenoenzyme activities, thus preventing oxidative brain damage and other adverse consequences of MeHg toxicity. Findings of studies that seem contradictory from MeHg exposure perspectives are entirely consistent from MeHg:Se molar ratio perspectives. Studies that have reported dose-dependent consequences of maternal MeHg exposures on child development uniformly involved seafoods that contained much more Hg than Se. Meanwhile more typical varieties of ocean fish contain much more Se than Hg. This may explain why maternal MeHg exposure from eating ocean fish is associated with major IQ benefits in children instead of harm. Therefore, instead of being avoided, ocean fish consumption should be encouraged during pregnancy. However, the safety of freshwater fish consumption is less certain. In freshwater fish, MeHg bioaccumulation and toxicity are both inversely related to Se bioavailability. Their Se can be far lower than their MeHg contents, potentially making them more dangerous than pilot whale meats. Therefore, to provide accurate and appropriate regulatory advice regarding maternal consumption of seafoods and freshwater fish, Hg:Se molar ratios need to be incorporated in food safety criteria.

Keywords: brain selenium, seafood fish, mercury toxicity

Extremely high methylmercury (MeHg) exposures in Japan (Takeuchi and Eto, 1999; Tsubaki and Irukayama, 1977) and Iraq (Marsh et al., 1987) affected thousands of people and resulted in dose-dependent pathologies that ranged from barely perceptible to lethal. Maternal consumption of heavily contaminated foods in these catastrophes resulted in children being exposed to MeHg in utero. Children who were exposed during fetal development were particularly vulnerable to MeHg, frequently showing signs of severe neurologic damage, although their mothers were asymptomatic (Harada, 1968; Marsh et al., 1987). Based on the severe adverse effects of these disastrous MeHg exposures, a series of prospective human epidemiological studies were performed to evaluate the effects of MeHg exposure from seafood consumption during pregnancy. These studies were designed to test the hypothesis that ''Maternal MeHg exposures are directly associated with adverse child development outcomes.''

Major studies have been conducted to examine the effects of maternal MeHg exposure from fish consumption

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on child developmental outcomes in population groups from New Zealand (Crump et al., 1998), Faroe Islands (Grandjean et al., 1997), Seychelle Islands (Myers et al., 1998, 2000), United Kingdom (Hibbeln et al., 2007), United States (Lederman et al., 2008), and most recently, Denmark (Oken et al., 2008). Evidence from these epidemiological studies have variously reported clinically relevant harmful effects on child health outcomes (New Zealand, Faroes), no harmful effects on child outcomes (Seychelles, United Kingdom, United States, Denmark), or substantial beneficial effects on child neurodevelopment and IQ (United Kingdom, United States, Denmark). Therefore, the results of these studies do not consistently support the conventional hypothesis. Instead, the findings of the largest, most complete, and most appropriate studies directly conflict with the hypothesis and seem to disprove it. However, based on observations in the catastrophic poisoning episodes and generally consistent findings of dose-dependent adverse effects related to maternal MeHg exposures (Clarkson and Magos, 2006; Watanabe et al., 1999a, b) and in animal studies (Ralston et al., 2008), the conventional hypothesis is not likely to be completely wrong, but only seems wrong because it is incomplete.

Misleading and mistaken impressions provided by the media have induced many mothers to avoid or excessively limit their seafood intake during pregnancy in an effort to protect their unborn children. Widespread misunderstandings of regulatory advice have even led some physicians to recommend their pregnant patients completely avoid seafood consumption. Unfortunately, the focus on potential harms from MeHg exposure often has completely overshadowed consideration of the beneficial effects of nutrients present in ocean fish. In response to this unbalanced perspective, the Joint Expert Committee on Food Additives (2003) has recommended that "nutritional benefits be weighed against the possibility of harm when limits on the MeHg concentrations in fish or on fish consumption are being considered." Ocean fish are particularly rich in Se and omega-3 fatty acids (USDA National Nutrient Database, 2009). Therefore, fish consumption improves intakes of these beneficial nutrients, which are particularly important during pregnancy. Similarly, the summary statement of the International Bioindicators Roundtable recommended that Hg:Se molar ratios must be evaluated to interpret effects of Hg exposures and identify susceptibilities (Henshel et al., 2007). Consideration of the balance of relative amounts of Hg and Se in food safety issues seems to clarify many aspects and remove the inconsistencies in effects of MeHg exposure in studies designed to examine the conventional hypothesis.

Metabolism of Dietary Selenium

Selenium (Se) is a nutritionally essential element that is present in all foods, but is particularly abundant in ocean fish. In a survey of 1,100 foods (USDA National Nutrient Database, 2009), seafoods comprised 17 of the top 25 dietary sources of Se. The molecular forms of Se that predominate in foods (Fig. 1) are the amino acids selenocysteine (Sec) and selenomethionine (SeMet). Dietary Sec, SeMet, and other less abundant organic forms of Se in the diet must be degraded to the inorganic selenide form before their Se can be used in protein synthesis (Fig. 1). Selenite often is used in nutrition studies because it is well absorbed and readily forms selenide (Hsieh and Ganther, 1977), the precursor required for Se incorporation into Sec (Fig. 1).

Although inorganic Se, Sec, and SeMet are all readily absorbed in the digestive tract and directly or eventually provide the inorganic Se needed to support intracellular metabolic cycles of Sec synthesis, there are important distinctions between the processes governing the metabolism of Sec that is synthesized in animal tissues and the SeMet that is synthesized in plants. In contrast to other amino acids, Sec is not readily recycled for subsequent incorporation in new proteins, but is instead degraded to release the inorganic Se that is needed for de novo synthesis of Sec just before its insertion into new selenoproteins. Because selenite is already in an inorganic form when it arrives in the cell, it only needs to be reduced to selenide before its incorporation in newly formed Sec.

In contrast to the rapid incorporation of Se from selenite and Sec, SeMet tends to be a "slow release" form of Se for Sec synthesis. Because protein synthesis cycles do not differentiate between SeMet and methionine (Met), SeMet tends to be nonspecifically incorporated into proteins and the rate of SeMet degradation is linked to rates of Met degradation. This results in a relatively slow rate of release of its Se for de novo Sec synthesis in animal cells. As a result, SeMet may engage in many cycles of protein synthesis as a methionine equivalent (Fig. 1) before it is eventually degraded and releases Se for Sec synthesis.

The biochemical and physiological importance of Se is primarily through the activities of Sec, the 21st proteinogenic amino acid that is cotranslationally inserted into proteins at UGA codons in coordination with SECIS (Sec

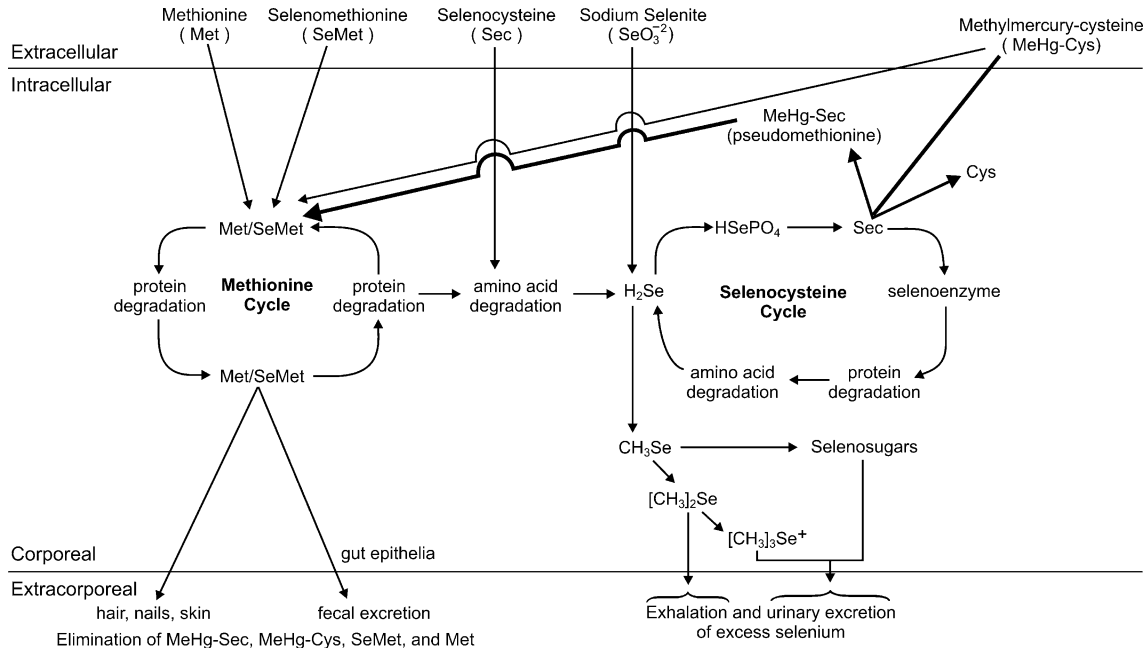

Figure 1. Metabolic cycles of selenomethionine, selenocysteine, inorganic selenium, and the proposed mechanism of MeHg dose-dependent disruption of the Se biosynthetic pathway.

insertion sequence) elements during synthesis of these unique proteins (selenoproteins). Selenoprotein occurrence and distribution vary between tissues, but most known eukaryotic selenoproteins are represented in the mammalian genome and relatively consistently between mammalian orders. Many selenoproteins have cysteine (Cys) orthologues, but the Se of the Sec in selenoenzymes performs biochemical functions that are beyond the capacity of the sulfur of Cys. Whereas the thiol of Cys is protonated at physiological pH, the Se of Sec is ionized, thus more highly interactive in its molecular environment. The redox range of Sec also is more extensive than that of Cys, enabling catalytic functions beyond the reaction potentials of Cys. The enzyme activities of the 25–30 selenoproteins distinguished by genetically directed incorporation of Sec in their primary structure are becoming increasingly well defined. All of the enzyme activities that have been characterized thus far employ the extensive redox potential of the Sec strategically positioned in their active sites to perform their catalytic functions.

Several selenoenzymes, including but not limited to, phospholipid glutathione peroxidase and the thioredoxin reductases, perform important antioxidant functions (Chen and Berry, 2003; Schweizer et al., 2004; Whanger, 2001; Kohrle, 2000) and are expressed with tissue-specific occurrence and distributions throughout the body, but seem to be particularly indispensable in the brain. Selenoprotein P, the most abundant selenoprotein in the plasma, contains 9–10 Sec/molecule, and seems to be a preferentially absorbed vehicle for Se distribution across placental and brain membrane barriers (Kasik and Rice, 1995; Hill et al., 2004). Newly described selenoenzyme functions (Ferguson et al., 2006; Novoselov et al., 2007; Dikiy et al., 2007) include redox control of an abundant class of brain proteins. Essentiality of these functions may explain why forms of animal life that possess nervous systems also selectively express and/or preferentially preserve selenoenzyme activities in brain and neuroendocrine tissues (Behne et al., 2000; Sun et al., 2001; Kohrle et al., 2005).

Mercury Interactions with Selenium

Selenium-dependent protective effects against Hg intoxication have been recognized in all forms of animal life that have been investigated (Cuvin-Aralar and Furness, 1991; Chapman and Chan, 2000). Methylmercury readily crosses placental and blood–brain barriers—in the form of a cysteine adduct (MeHg–Cys) that biochemically resembles methionine (Taylor et al., 1975) and is taken up by the LAT1 amino acid transporter (Simmons-Willis et al., 2002). This may occur because MeHg–Cys is a molecular mimic of Met (Bridges and Zalups, 2005; Aschner and Clarkson, 1989) or because amino acid transport by LAT1 tends to be non-

specific in its transport activities (George, et al., 2008). At low exposures, MeHg–Cys participates in the methionine cycle without pathological consequence; however, at higher exposures MeHg induces toxic effects. At all levels of exposure, MeHg exchanges partners to form covalent associations with chemical species of equal or greater affinities. Because the binding affinities between Se and Hg are approximately a million times greater than those between sulfur and Hg (Dyrssen and Wedborg, 1991), mass action effects support selective sequestration of Se in association with MeHg. When MeHg–Cys encounters the ionized Se of Sec at the active site of a selenoenzyme, its MeHg moiety exchanges its association with the sulfur of Cys for the higher affinity Se group of Sec, resulting in a direct exchange that results in formation of MeHg–Sec.

MeHg exposure cause diminishments to 43% of normal brain Se in weanling rats raised on low-Se diets (Ralston et al., 2008), a value well below the 60% level that may define the minimum for health. High maternal Hg exposures are known to diminish transport of Se across the placenta, diminishing the amount of Se supplied to the fetus by more than 50% (Parizek et al., 1971) and high maternal MeHg diminished fetal brain Se and brain selenoenzyme activities to ~30% (Watanabe et al., 1999a, b). Increasing exposure to MeHg will inevitably lead to increasing sequestration of Sec as MeHg–Sec. Just as MeHg–Cys appears biochemically similar to SeMet and Met, MeHg–Sec would be expected to similarly form a molecular mimic of Met. As a result of this case of mistaken molecular identity, MeHg–Sec distributions would become indistinguishable from those of Met/SeMet. Therefore, the MeHg–Sec adduct has been termed "pseudomethionine" (Ralston et al., 2008) to indicate its expected diversion into the methionine cycle (Fig. 1). The Se of pseudomethionine that is cycled into proteins indiscriminately from Met/SeMet is unavailable for participation in the selenocysteine metabolic cycle (Fig. 1). Because a portion of the Se present in blood and tissues is in the form of MeHg–Sec, the actual amounts of bioavailable Se in these cases is actually much lower than the total amount present.

Because intracellular Se is usually present in substantial excess of Hg, brain cells can normally maintain sufficient free Se to support optimal rates of selenoenzyme synthesis and activity. However, when the concentration of MeHg in the cells exceeds that of Se, the amount of biologically available Se for normal selenoenzyme synthesis diminishes. Therefore, the protective effect of supplemental Se may occur because additional dietary Se is able to offset the Se sequestered by Hg (Watanabe et al., 1999a, b) as pseudomethionine (Ralston et al., 2007, 2008) and maintain selenoenzyme activities.

The biochemical definition of an irreversible inhibitor is a molecule that covalently modifies an enzyme. In the proposed mechanism, MeHg binds with the Sec moiety at the selenoenzyme active site. Because the binding affinity between Hg and Se is extraordinarily high, MeHg is by definition a highly specific irreversible selenoenzyme inhibitor. However, the proposed inhibitor–enzyme complex not only abolishes the activity of the inhibited selenoenzyme, it also restricts Se release from the MeHg–Sec complex, severely limiting or effectively abolishing the bioavailability of the bound Se for participation in future intracellular cycles of Sec synthesis. The proposed mechanism coincides with expectations based on the preponderance of findings regarding Hg/Se interactions at the molecular, cellular, organism, and population levels. Contrary to previous expectations, Hg does not seem to cause oxidative damage directly (Seppanen et al., 2004). Instead, MeHg appears to cause increased oxidative damage as a result of inhibition of selenoenzyme activities that normally detoxify free radicals formed during normal cell metabolism. Selenium's ability to counteract toxic effects of high Hg exposures have been recognized since 1967 (Parizek and Ostadolova, 1967) and subsequent studies increasingly confirm that organic and inorganic forms of Se prevent or ameliorate otherwise toxic consequences of Hg exposure (Iwata et al., 1973; Ohi et al., 1976; Beijer and Jernelov, 1978; El-Begearmi et al., 1982; Whanger, 1992; El-Demerdash, 2001; Ralston et al., 2007, 2008). Maternal Hg exposures compromise redistribution of maternal Se to the fetus (Parizek et al., 1971; Watanabe et al., 1999a, b) and dose-dependently diminish selenoenzyme activities in fetal brain (Watanabe et al., 1999a, b; Stringari et al., 2008). However when maternal Se status is enhanced by feeding rich Se diets, diminishments in total Se and selenoenzyme activities in brains of the exposed offspring were Se dose-dependently prevented and neurological signs of fetal MeHg intoxication were alleviated (Watanabe et al., 1999a, b).

Studies demonstrating Se-dependent amelioration of MeHg toxicity have included Se from yellowfin tuna (Ohi et al., 1976; Ganther et al., 1972), menhaden (Stillings et al., 1974), swordfish (Freidman et al., 1978), and rockfish (Ohi et al., 1980). Therefore, the organic forms of Se present in ocean fish are bioavailable and effective in counteracting MeHg toxicity. It is important to note that the protective effects of Se are less obvious when slow-release forms of Se, such as SeMet, are used (Beyrouty and Chan, 2006) or

when Hg:Se molar ratios remain disproportionate, particularly during fetal exposures. Studies of maternal MeHg exposure need to pay particular attention to blood Hg:Se molar ratios because the developing fetus is entirely dependent on uninterupted delivery of Se across the placenta. In maternal exposures, it seems that Se supplementation cannot counteract adverse outcomes from MeHg exposures if the total dietary Hg:Se ratio is greater than 1:1. As these ratios are approached, the biovailabilities and rate of Se release from food sources become increasingly important aspects. Animal studies demonstrate that dietary Hg:Se ratios will need to be significantly lower than 1:1 to ensure that maternal export of Se to the fetus is unimpaired to prevent adverse neurodevelopmental outcomes in the offspring (Newland et al., 2006; Reed et al., 2006; Reed et al., 2008). High maternal exposures to MeHg causes increased oxidative damage as measured by F_2-isoprostane levels in fetal brain (Stringari et al., 2008), apparently as a consequence of Hg dose-dependent diminishments in brain selenoenzyme activities (Watanabe et al., 1999a, b; Seppanen et al., 2004; Stringari et al., 2008). Prenatal MeHg exposure did not only diminish selenoenzyme activities during fetal development. Although Hg contents in brains of prenatally exposed mice had diminished to near basal levels by postnatal day 21, selenoenzyme activities remained diminished, indicating that prenatal exposure to toxic amounts of MeHg had lasting effects (Stringari et al., 2008).

Although it is clear that MeHg dose-dependently affects selenoenzyme activities and Se dose-dependently counteracts development and reversal of signs of MeHg toxicity, it currently remains unknown whether selenoenzyme inhibition/Se-sequestration are the exclusive causes of MeHg toxicity, or whether other molecular mechanisms also contribute to its pathological syndrome. However, because Se-dependent therapeutic reversal of MeHg-dependent growth inhibition, cessation of declines in motor function, and prevention of lethality were virtually equivalent regardless of whether toxic dietary MeHg was continued (Ralston 2008, unpublished data, 2008), any other effects of MeHg toxicity would be expected to be relatively minor compared with etiologies secondary to selenoenzyme inhibition/Se-sequestration mechanisms.

Selenium Health Benefit Values

To simplify assessment of Se-specific nutritional benefits in relation to potential MeHg exposure risks associated with seafoods, the Se Health Benefit Value (Se-HBV) was proposed by Kaneko and Ralston (2007). The Se-HBV incorporates consideration of both the absolute and the relative amounts of Se and Hg in the diet to provide an index that is easily interpreted. The sign of the calculated Se-HBV indicates the expected health benefits (if positive values are obtained) or health risks (if negative values result) and the magnitude of the obtained values are proportional to the expected benefits or risks. Because it is vitally important to evaluate the Hg:Se stoichiometric relationship, molar concentrations (μmol/kg) are used in the Se-HBV calculation. The Hg:Se and Se:Hg molar ratios are calculated by direct division of the individual molar concentrations, and respectively multiplied times their absolute molar concentrations as follows:

$$\text{Se-HBV} = [(\mu\text{mol Se/kg}) \times (\text{Se/Hg})] - [(\mu\text{mol MeHg/kg}) \times (\text{Hg/Se})]$$

The current iteration of the Se-HBV uses total Hg/Se and Se/Hg molar ratios because total elemental concentrations are more readily available. However, a more sophisticated evaluation can be achieved through use of MeHg instead of total Hg and Sec instead of total Se. In fish fillets, the MeHg concentrations usually tend to represent the bulk of total Hg, but there are instances in which this is not the case. In the case of Se, the total Se in animal proteins includes a significant fraction as SeMet. Although SeMet is well absorbed and readily incorporated into proteins, its far slower rate of release of inorganic Se makes it a long-term Se source, but Se for synthesis of new Sec is more readily available from inorganic forms of Se or Sec in the diet. The degradation rates of SeMet may need to be integrated to enable a time-dependent SeMet Se-release factor to be included in more exacting versions of the equation.

Human Studies

Concurrent maternal exposure to potentially harmful effects of toxicants and beneficial effects of essential nutrients in seafoods is a classic example of statistical confounding. Because both occur together in seafoods, but affect developmental outcomes in opposing directions, it is essential to address potential confounding effects by identifying and differentiating the discrete adverse effects caused by MeHg exposure in distinction from the beneficial effects of the increasing nutrient intakes. Otherwise, these confounding effects will inexorably, although inadvertantly, bias the data

and diminish the statistical robustness and the reliability of the findings. Although the findings of the major epidemiological studies appear to conflict with one another, it is only because the conventional hypothesis, "Maternal MeHg exposures are directly associated with adverse child development outcomes" (Hypothesis 1) does not include consideration of Se. From the more informed perspective that incorporates consideration of Se physiology, the updated version of the hypothesis states, "Maternal MeHg exposures *in excess of Se intakes* are directly associated with adverse child development outcomes" (Hypothesis 2). The current evaluation compares the findings of the human epidemiological studies as tests of the conventional and updated hypothesis.

A number of epidemiological studies of the effects of maternal MeHg exposure on child development outcomes are presented below in their approximate chronological order. Basic descriptions of the study and whether the findings support hypothesis 1 and hypothesis 2 are provided along with characterization of the dietary Se-HBV of the MeHg exposure sources for each study. The results of these descriptions are collected and reported in Table 1 for ease of comparison.

Minamata Bay, Japan

Widespread MeHg poisoning occurred in Minamata, Japan, during the late 1950's. After an industrial plant had discharged many tons of Hg waste directly into the waters of a small bay, MeHg bioaccumulated to extremely high levels in ocean fish that occupied the bay. Because these fish were a major food source for the local population, >2,000 cases of MeHg poisoning developed. Acute MeHg poisoning was characterized by gross disturbance of the central nervous system, which was lethal in some cases, whereas others became comatose and/or developed permanent disabilities with severe symptoms resulting from widespread brain damage. In cases with less severe poisoning, symptoms included motor control and sensation disturbances (Takeuchi and Eto, 1999). Patients who died displayed severe brain atrophy, cerebral and cerebellar lesions, and pathologic changes in cytoarchitecture. Symptoms of MeHg poisoning were characterized by silent latency. In some cases, symptoms did not appear until more than 5 years after high MeHg exposure ceased. Awareness of fetal sensitivity to MeHg neurotoxicity arose when children of asymptomatic mothers displayed disturbances in motor control, mental retardation, and related symptoms. Brain pathology of congenital MeHg poisoning included cortex atrophy/hypoplasia and dysmyelination of the pyramidal tract. In the cerebellum, hypoplasia and degeneration of the granular cell layer and other layers were observed (Harada, 1968). Fish in Minamata Bay were heavily contaminated with MeHg, occurring in concentrations up to ~250 μϖ mol/kg; ~50 mg Hg/kg in the meats of certain fish (Takeuchi and Eto, 1999). Although Se was not measured

Table 1. Hypothesis testing

Study location	Hypothesis 1[a]				Hypothesis 2[b]			
	Development outcomes[c]	Study supports	Does not support	Study conflicts	Calculated ~Se-HBV[d]	Study supports	Does not support	Study conflicts
Minamata	Harmed	Yes	No	No	144 to −5,000	Yes	No	No
Iraq	Harmed	Yes	No	No	−800	Yes	No	No
New Zealand	Harmed	Yes	No	No	144 to −123	Yes	No	No
Faroe Islands	Harmed	Yes	No	No	40 to −83	Yes	No	No
Peru	Not harmed	No	Yes	No	84	Yes	No	No
Seychelle Islands	Not harmed	No	Yes	No	173	Yes	No	No
United Kingdom	Benefitted	No	Yes	Yes	202	Yes	No	No
United States	Benefitted	No	Yes	Yes	144	Yes	No	No
Denmark	Benefitted	No	Yes	Yes	202	Yes	No	No

[a]Hypothesis 1: maternal MeHg exposures are directly associated with adverse child development outcomes.
[b]Hypothesis 2: maternal MeHg exposures *in excess of Se intakes* are directly associated with adverse child development outcomes.
[c]Effects of maternal seafood (MeHg) exposure on child development outcomes.
[d]Approximate Selenium Health Benefit Values of MeHg-containing food sources were calculated using best available data.

in fish from Minamata Bay, it has been established that Se levels in fillet portions from commonly consumed varieties of Pacific Ocean fish range between 5 and 20 μmol Se/kg (Kaneko and Ralston 2007), and in species other than blue marlin, Se contents of fillet do not increase with increasing MeHg levels (Ralston and Kaneko, unpublished data, 2008). The Se content of Pacific Ocean fish other than blue marlin assessed in that study were 9.77 (95% confidence interval (CI), 6.99–12.55) μmol Se/kg. Using this mean value as an approximation of the amount of Se expected to have been present in these fish, the calculated Se-HBV for fish from Minamata Bay would be estimated to have been −5,000 (Table 1). Ocean fish that had only recently entered the bay before being caught would have had much lower MeHg contents and would have retained positive Se-HBVs until they had bioaccumulated significant amounts of MeHg. The intermittent presence of Se-rich fish would have delayed onset of MeHg toxicity and extended the silent latency period before onset of clinical symptoms in this population. Harmful child development outcomes tended to occur in direct association with increasing MeHg exposure. Therefore, the findings of this study support Hypothesis 1. Because the Se-HBVs of the MeHg source were extremely negative, the observation of these severely harmful effects also are consistent with Hypothesis 2.

Iraq Outbreak

In 1971, MeHg-treated seed grain was imported into Iraq during a time of famine. Because there was a food shortage, the seed grain was baked into bread and consumed by malnourished Iraqi villagers. There are no reliable estimates of how many developed toxicity, but within 2 months, there were thousands of hospital admissions and hundreds of hospital deaths from MeHg ingestion. Children of pregnant women exposed in utero manifested severe motor and sensory impairments and delayed mental development (Amin-Zaki et al., 1974). MeHg dose-dependent relationships on adverse effects in offspring exposed in utero are described in a series of reports by Amin-Zaki et al. (1974, 1976, 1979) and Marsh et al. (1980, 1987). Symptoms closely resembled those recorded in Minamata, Japan, but the period of latency was far shorter. Adults developed paresthesia after a latent period of only 16 to 38 days after initiation of exposure. Those who were severely afflicted developed ataxia, motor, and sensory difficulties. Lethality resulted from failure of the central nervous system (Bakir et al., 1973). Concentrations of MeHg in the wheat flour ranged from 4.8–14.6 (mean, 9.1) μg/g (∼45 μmol Hg/kg). The Se content of wheat varies depending on the Se content of the soil in which it is grown, and it was not measured in the wheat consumed in Iraq. However, it is reasonable to assume that it would have been in the medium range of ∼0.2 μg/g (∼2.5 μmol Se/kg) for the sake of the current approximation. Using these values, the calculated Se-HBV of the bread consumed in Iraq at the time of the disaster would have been in the range of −800. The findings of this study support Hypothesis 1, because adverse effects on children generally increased in severity in direct association with increasing maternal MeHg exposure. Because the Se-HBV of the MeHg source was in the harmful range, these increasingly adverse effects also are consistent with Hypothesis 2.

Peru

A study (Marsh et al., 1995) of maternal MeHg exposure on child development outcomes was conducted in Mancora, Peru, between 1981 and 1984. The study site was selected because marine fish were a large source of dietary protein, resulting in high maternal MeHg exposures. Participants consisted of 131 mother-infant pairs analyzed for hair MeHg content. The geometric mean hair level was 7.05 (range, 0.9–28.5) ppm. The peak maternal hair MeHg levels during pregnancy ranged from 1.2 to 30 (geometric mean, 8.3) ppm. This study found no relationship between MeHg exposures and measures of infant development or neurological signs. The authors suggested that because marine fish contain Se, the toxicity of MeHg was reduced and prevented adverse neurological consequences. The mean Se-HBV for ocean fish consumed by the population of Mancora is estimated at approximately 84, using the mean values established by Kaneko and Ralston (2007) for the varieties of Pacific ocean fish expected to have been consumed by this population. Because no harms were noted in association with increasing MeHg exposure, the findings of this study do not support Hypothesis 1. However, because the Se-HBV of the MeHg source was in the beneficial instead of the harmful range, no harms would have been expected. Therefore, the results are consistent with Hypothesis 2.

New Zealand

The effect of MeHg on children exposed in utero from maternal fish consumption was studied between 1982 and

1983. Of ~11,000 mothers who were initially questioned, less than 1,000 had consumed fish more than three times per week during 9 months of pregnancy. Maternal hair Hg concentrations were assessed in these groups and were used as a means of selection. Higher hair Hg during pregnancy was consistently associated with decreased performance in tests of neurodevelopment. The authors concluded that MeHg exposure led to developmental delays and deficits in psychological tests. Crump et al. (1998) performed a reanalysis of the results and no associations between MeHg exposure and children's test scores were identified, unless the results from one child whose mother's hair Hg level was four times higher than for any other mother was omitted. When that outlier was omitted, multiple tests were dose-dependently associated with maternal hair MeHg concentrations. The seafood consumed in this study was primarily "fish and chips" prepared from varieties of fish, including shark. The MeHg contents of shark meats collected from the seas surrounding New Zealand can be very high: average 0.72 (ranging up to 4.4) mg Hg/kg; 3.58 and 22 μmol Hg/kg, respectively (Mitchell et al., 1982). Because Se in shark meats do not increase in the presence of increasing MeHg (Kaneko and Ralston 2007), the ~Se-HBV calculated for a shark with 22 μmol Hg/kg would be –123. Normal varieties of ocean fish with Se-HBVs estimated at approximately 84 (Kaneko and Ralston 2007) would also be expected to have been consumed by this population. It is important to recognize that the New Zealand population had a notoriously poor Se status at the time of this study (Robinson 1988), a factor that would have greatly accentuated their vulnerability to MeHg exposure (Ralston et al., 2008). The findings of this study are consistent with Hypothesis 1, and, because sharks with highly negative Se-HBVs were consumed, the harms noted are also consistent with Hypothesis 2.

Seychelles Islands

The first Seychelles study consisted of a cohort of 779 mother–infant pairs that were selected between 1989 and 1990. This population eats on average ~12 fish meals per week, which is far more than what is typical in the United States. However, no negative effects were found in association with high fish consumption and MeHg exposure (Davidson et al., 1998; Myers et al., 1998, 2000). Average maternal hair Hg levels during the entire pregnancy (range, 0.5–26.7 (median, 5.9) ppm) were used as the marker of fetal Hg exposure. The cohort was evaluated at ages 6.5, 19, 29, and 66 months (Marsh et al., 1995; Myers et al., 1995) and at age 9 years (Myers et al., 2003). Children were repeatedly assessed using multiple sensitive standardized measures of cognitive development and neurological endpoints. Using maternal hair-Hg levels as the independent variable, prenatal MeHg exposure from fish consumption in Seychellois children was not associated with adverse effects. The Seychelles study found that no adverse neurological outcomes in Seychellois children during a 9-year period were associated with prenatal MeHg exposures from maternal consumption of ocean fish (Myers et al., 2000, 2003). A recent report from this population suggests that MeHg effects on psychomotor development are detectable after controlling for polyunsaturated fatty acids (Davidson et al., 2008; Strain et al., 2008) but did not indicate that harmful effects accompanied fish consumption. To the contrary, certain developmental outcomes of prenatally exposed children indicated beneficial effects that correlated with Hg exposures during pregnancy. The authors indicated that the presence of micronutrients in fish provided a plausible explanation for these findings (Clarkson and Strain 2003). The fish consumed in the Seychelles have been assessed for both Hg and Se contents. The average of the observed Hg and Se concentrations in these 16 fish species were 0.34 ± 0.23 μmol Hg/kg and 3.73 ± 1.64 μmol Se/kg (mean ± 95% CI). The mean and 95% CI of the Se-HBVs for these 16 fish species was 173 ± 148 for the various fish types. Because no harms were noted in association with increasing MeHg exposure, the findings of this study do not support Hypothesis 1. However, because the Se-HBV of the MeHg source was in the beneficial instead of the harmful range, benefits instead of harms would have been expected, therefore, the results do support Hypothesis 2.

Faroe Islands

The Faroes Islands studies examined the influence of MeHg exposure from maternal consumption of pilot whale and cod fish on child development outcomes. Seafood constitutes a major part of the diet in the Faroe Islands (Grandjean et al., 1992a, b); >90% of their MeHg exposure arises from consumption of pilot whale, and the majority of dietary Se is from consumption of codfish (Grandjean et al., 1997). Increased Hg in maternal hair and umbilical cord blood were directly related to maternal consumption of pilot whale. At age 12 months, 583 children were evaluated for developmental milestones. Infants who reached milestone criteria early had significantly higher hair Hg than those who did

not. Neurobehavioral tests were used to assess 914 children at age 7 years (Dahl et al., 1996). Higher prenatal MeHg exposure was associated with difficulties on cognitive measures (Grandjean et al., 1997, 1998). The most pronounced difficulties were in the areas of language, attention, and memory, and to a lesser extent sensory and motor functions. The codfish eaten in the Faroes contain small amounts of MeHg, are good sources of Se (Hall et al., 1978), and have a reasonably good Se-HBV of 18 as a result. In contrast, the pilot whale meats consumed in the Faroes are highly contaminated with Hg. Using data from the 1977 collection study (Julshamn et al., 1987) cited by Grandjean et al. (1992a), pilot whale meat contained 3.3 mg/kg, 16.45 μmole Hg/kg, blubber contained 0.7 mg/kg, 3.49 μmole Hg/kg, and kidney contained 18 mg/kg, 89.74 μmole Hg/kg. The average Se concentrations in the meat, blubber, and kidney were 3.17, 1.52, and 16.46 μmole Hg/kg, resulting in Se-HBVs of −85, −7, and −486 respectively, in these tissues. Kidney was being distributed along with meat and blubber throughout the Faroes at the time of the study, but it is not clear whether, or how much, kidney was actually consumed. For this reason, only the cod and whale meat Se-HBVs are listed in Table 1. Pilot whale blubber has unusually high contamination levels with polychlorinated biphenyls (PCBs) resulting in high exposures in the Faroese population, which may present further confounding factors. However, the study authors concluded that they did not recognize effects from the concomitant PCB exposure that indicated any influence on Hg-associated effects.

Most interestingly, the adverse effects that were dose-dependently associated with cord blood Hg were equally proportional to cord blood Hg:Se molar ratios (P. Grandjean personal communication, 2008) in an analysis performed in association with, but not reported in, the article by Choi et al. (2008). Blood Hg:Se molar ratios approached and exceeded 1:1 molar stoichiometry in the cord bloods of children most affected by Hg exposure. Because the association between MeHg toxicity and blood Hg:Se molar ratios has been observed to be more reliable than associations based on blood Hg (Ralston et al., 2008), it seems likely that using cord blood Hg:Se molar ratios will provide a superior basis for analysis of outcomes. This is in sharp contrast to what is expected in populations exposed to MeHg exclusively from ocean fish. It is not expected that cord blood Hg:Se molar ratios will approach 1:1 molar ratios, but should generally be less than 1:3 or 1:5 in most populations (Ralston unpublished data, 2008). The findings of this study support Hypothesis 1 because the adverse effects on child outcomes increased with increasing maternal MeHg. Because the adverse effects also increased in proportion to Hg:Se molar ratios, and the Se-HBV's major source of maternal MeHg exposure was negative, the findings also are completely consistent with Hypothesis 2.

United Kingdom

The Avon Longitudinal Study of Parents and Children (ALSPAC) study examined rates of ocean fish consumption by 11,875 women during pregnancy and assessed effects on developmental, behavioral, and cognitive outcomes in their children from aged 6 months to 8 years (Hibbeln et al., 2007). The study was adjusted for 28 potential confounders to eliminate potential influences of social distinctions. Children of mothers who consumed little or no seafood per week had an increased risk of being in the lowest quartile for verbal intelligence compared with children of mothers who ate more than the EPA recommended amount of seafood. Low maternal seafood consumption was associated with increased risk of suboptimum outcomes for social behavior, fine motor, and communication scores. For each outcome, the lower the mother's intake of seafood was during pregnancy, the greater the risk of suboptimum development in their children. The children of mothers who had not consumed ocean fish were estimated to be at a ∼6 IQ point disadvantage relative to children whose mothers had consumed more than 340 g of fish per week (J. Hibbeln personal communication, 2008). The average Se-HBV for the varieties of white fish (87), oily fish (288), and shell fish (233) are uniformly beneficial, with a group mean of ∼202 for seafoods consumed in the United Kingdom (Ralston unpublished data, 2008). The study's findings that increasing maternal seafood consumption (and increasing MeHg exposure) resulted in improved child outcomes do not support, but directly conflict with, Hypothesis 1. Because seafood have positive Se-HBVs, benefits rather than harm would be expected, and therefore the results are in accord with Hypothesis 2.

World Trade Center (United States)

Prenatal exposure to elemental Hg vapor evolving from debris remaining after the World Trade Center (WTC) disaster was assessed in relation to effects on fetal growth and child development (Lederman et al., 2008). Maternal and umbilical cord blood total Hg of 329 women who delivered at term in lower Manhattan after September 11, 2001 were

assessed. Cord and maternal blood Hg levels were not higher for women residing or working within 1 or 2 miles of the WTC compared with women who lived and worked further away. Cord blood Hg levels were more than twice maternal levels, and blood Hg levels in cord and maternal blood samples were both higher in women who reported eating fish/seafood during pregnancy. Log cord Hg was inversely associated with full IQ scores in the children (b = − 3.8, $p = 0.002$) at age 48 months after controlling for fish/seafood consumption and other confounders. However, fish/seafood consumption during pregnancy was associated with a 5.6-point increase in Verbal and Full IQ scores. The ocean fish consumed in this study would be expected to conform with the Se-HBV of 144 calculated as the average for U.S. fish (Ralston unpublished data, 2008). The study found that maternal seafood consumption (and greater MeHg exposure) was associated with improved child outcomes. Therefore, the findings of this study do not support, but directly conflict with, Hypothesis 1. Because the seafood have positive Se-HBVs, benefits rather than harm were expected and were seen. Therefore, the results of this study are in accord with Hypothesis 2.

Denmark

The Danish National Birth Cohort prospective population-based cohort study examined rates of ocean fish intake by 25,446 women (Oken et al., 2008). Mothers reported child development through a standard interview, which was used to generate developmental scores at aged 6 and 18 months. Higher maternal fish consumption was associated with improved child development (odds ratio, 1.29; 95% CI, 1.2–1.38) for the highest vs. lowest quintile of fish intake) in 18 month old children and similar results were observed at 6 months of age. The authors conclude that maternal fish consumption during pregnancy was associated with improved early child development, rather than harmful effects. The fish consumed in Denmark would be expected to be the same or similar to those consumed in the United Kingdom with a calculated average Se-HBV of 202 (Ralston unpublished data, 2008). The study's findings that increasing maternal seafood consumption (and increasing MeHg exposure) improved child outcomes do not support, but directly conflict with, Hypothesis 1. Because the seafood consumed had positive Se-HBVs, benefits rather than harm were expected and were seen. Therefore, the results of this study are in accord with Hypothesis 2.

Discussion

The most important aspect of the Se-HBV is the positive or negative sign before the value. Foods with a negative sign contain Hg in excess of Se and should be completely avoided during pregnancy. If the Se-HBV of a type of fish has a positive sign, maternal consumption should be encouraged rather than limited. The more positive the value, the more beneficial the expected effects, and the more negative the value, the more harmful. The relationships shown in Table 1 suggest that the Se-HBV is a seafood safety indicator that is consistent with the results of the existing human and animal studies, and along with the preponderance of data available from animal studies, demonstrate the importance of dietary Se in counteracting the potential pathological effects of high MeHg exposures.

Further factors that need to be considered when assessing potential effects of maternal fish consumption include the form and amounts of other important nutrients, such as omega-3 fatty acids in the seafoods consumed. It is conceivable that future iterations of the Se-HBV will incorporate omega-3/omega-6 ratios (as well as other nutrient relationships) and simply become Health Benefit Values. Furthermore, the interactions between Se and other nutrients in the background diet of the exposed population are very significant. Vitamins C and E (May et al., 1998; Beyrouty and Chan 2006) are both involved in Se-dependent redox cycling, and the abundance of these nutrients should be considered when evaluating the importance of dietary Se from fish consumption. The greatest benefits of maternal seafood consumption on child outcomes would be expected to be observed when maternal Se-status is raised from low to normal, but dietary benefits also increase as dietary Se-status increases toward Se-rich (Rayman 2000).

Food safety criteria need to incorporate more sophisticated approaches to evaluating risks related to MeHg exposure from maternal consumption of ocean and fresh water fish. If not the Se-HBV, then some other means of more accurately evaluating risk associated with MeHg exposure from fish consumption needs to be developed to incorporate consideration of Se contents and Hg:Se ratios. Decision makers and agencies responsible for protecting public health need research information that will enable them to provide advice that not only protects the public from harm, but also improves maternal nutrition to optimize child development. Risk evaluations associated with

maternal MeHg exposure need to concurrently determine the relative and absolute amounts of MeHg and Se present in these food sources and employ these as components of their assessments. Until these steps are taken, studies reporting Hg levels in fish and blood of populations that eat fish and without concurrently measuring Se will simply be reporting MeHg exposures, but not providing any meaningful indications of associated risks.

In 2005, Trasande and colleagues suggested that the subtle loss of IQ that they attributed to MeHg exposure from ocean fish consumption (instead of pilot whale consumption) resulted in a cost of $8.7 billion per year for harms due to loss of ~0.1 IQ points per child for ~450,000 exposed children. As we now understand the issue, mothers with elevated blood Hg levels seem to represent the fraction of mothers who actually ate enough seafood to provide IQ benefits to their children. Assuming that the $8.7 billion estimate of Trasande and colleagues was correct, applying their results to the loss of 5.6 IQ points (Lederman et al., 2008) per child for ~3,500,000 children whose mothers did not eat robust amounts of fish, the harms to the U.S. economy from inadequate fish consumption during pregnancy would be expected to result in losses of tens of trillions of dollars to the nation per year.

It is essential to note that MeHg exposures that are unlikely to cause harm in populations that eat Se-rich ocean fish may still be harmful among populations exposed to MeHg without a rich dietary source of Se. Because the Faroes population consumed large amounts of ocean cod, their Se status was very good. However, using this Se-rich population as an indication of risks of MeHg exposure may not provide an accurate estimate of risks of MeHg exposures in populations with a low Se status. The Se levels in freshwater fish are exclusively dependent on the status of their waters of origin. Therefore, the Hg:Se ratios in freshwater fish will be far more variable and instances of disproportionately high MeHg concentrations relative to Se may be characteristic of top predator fish from Se poor regions (Luten et al., 1980; Peterson et al., 2009). Therefore, populations that consume fish from lakes in low Se regions may be at greater risk than is currently anticipated.

The prime directive of professionals in all areas of public responsibility should be, "Primum non nocere" (First, do no harm). Risk assessments based on neurodevelopmental harms from maternal consumption of pilot whale and shark meats with disproportionately high Hg:Se molar ratios (~5:1) and highly negative Se-HBVs seem to have resulted in gross overestimates of the risks associated with MeHg exposure from eating ocean fish. The unbalanced approach of only examining risks resulted in regulatory advisories that emphasized restrictions to minimize MeHg exposure, but overlooked the more substantial positive effects of ocean fish consumption during pregnancy. Maternal consumption of typical seafoods with highly positive Se-HBVs seems not only to be harmless but remarkably beneficial to healthy child development. Exaggerations of the risks of MeHg exposure have caused women to avoid eating ocean fish during pregnancy. Following such misguided advice may have inadvertently caused far more damage to children than the worst possible risks that were supposedly being avoided.

To resolve this issue, it seems that using the Se-HBV or a similarly balanced criterion for assessing seafood safety will alleviate many current misunderstandings of advisories regarding maternal seafood consumption. Using the Se-HBV as an environmental indicator that distinguishes health-promoting from hazardous fish will provide a basis for developing urgently needed regulatory protections against hazardous Hg:Se ratios that may be present in freshwater fish. Seafood safety criteria that include a balanced consideration of nutrients and toxicants will protect and improve public health by properly limiting hazards while encouraging maternal consumption of seafoods that enhance development of healthy children.

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References

Amin-Zaki L, Elhassani S, Majeed MA, Clarkson TW, Doherty RA, Greenwood M (1974) Intrauterine methylmercury poisoning in Iraq. *Pediatrics* 54:587–595

Amin-Zaki L, Majeed MA, Elhassani SB (1979) Prenatal methylmercury poisoning. Clinical observations over five years. *Am J Diseases of Child* 133:172–177

Amin-Zaki L, Elhassani S, Majeed MA (1976) Perinatal methylmercury poisoning in Iraq. *Am J Dis Child* 130:1070–1076

Aschner M, Clarkson TW (1989) Methylmercury uptake across bovine brain capillary endothelial cells in vitro: the role of amino acids. *Pharmacol Toxicol* 64:293–297

Bakir F, Damluji SF, Amin Zaki I (1973) Methylmercury poisoning in Iraq: an interuniversity report. *Science* 181:230–241

Behne D, Pfeifer H, Rothlein D, Kyriakopoulos A (2000) Cellular and subcellular distribution of selenium and selenium-containing proteins in the rat. In: *Trace Elements in Man and Animals 10*, Roussel AM, Favier AE, Anderson RA (editors), New York: Kluwer Academic/Plenum, pp 29–34

Beijer K, Jernelov A (1978) Ecological aspects of mercury–selenium interaction in the Marine environment. *Environ Health Perspect* 25:43–45

Beyrouty P, Chan HM (2006) Co-consumption of selenium and vitamin E altered the reproductive and developmental toxicity of methylmercury in rats. *Neurotoxicol Teratol* 28:49–58

Bridges CC, Zalups RK (2005) Molecular and ionic mimicry and the transport of toxic metals. *Toxicol Appl Pharmacol* 204:274–308

Budtz-Jørgensen E, Grandjean P, Weihe P (2007) Separation of risks and benefits of seafood intake. *Environ Health Perspect* 117:323–327

Chapman L, Chan HM (2000) The influence of nutrition on methylmercury intoxication. *Environ Health Perspect* 108:29–56

Chen J, Berry MJ (2003) Selenium and selenoproteins in the brain and brain diseases. *J Neurochem* 86:1–12

Choi AL, Budtz-Jørgensen E, Jørgensen PJ, Steuerwald U, Debes F, Weihe P, Grandjean P (2008) Selenium as a potential factor against mercury developmental neurotoxicity. *Environ Res* 107:45–52

Clarkson TW, Magos L (2006) The toxicology of mercury and its chemical compounds. *Crit Rev Toxicol* 36:608–662

Clarkson TW, Strain JJ (2003) Nutritional factors may modify the toxic action of methyl mercury in fish-eating populations. *J Nutr* 133:1539–1543

Crump KS, Kjellstrom T, Shipp AM, Silvers A, Stewart A (1998) Influence of prenatal mercury exposure upon scholastic and psychological test performance: benchmark analysis of a New Zealand cohort. *Risk Analysis* 18:701–713

Cuvin-Aralar ML, Furness RW (1991) Mercury and selenium interaction: a review. *Ecotoxicolol Environ Safety* 21:348–364

Dahl R, White RF, Weihe P, Sørensen N, Letz R, Hudnell HK, et al. (1996) Feasibility and validity of three computer-assisted neurobehavioral tests in 7-year-old children. *Neurotoxicology and Teratology* 18:413–419

Davidson PW, Strain JJ, Myers GJ, Thurston SW, Bonham MP, Shamlaye CF, et al. (2008) Neurodevelopmental effects of maternal nutritional status and exposure to methylmercury from eating fish during pregnancy. *Neurotoxicology* 29:767–775

Davidson PW, Myers GJ, Cox C, Axtell C, Shamlaye C, Sloane-Reeves J, et al. (1998) Effects of prenatal and postnatal methylmercury exposure from fish consumption on neurodevelopment: outcomes at 66 months of age in the Seychelles Child Development Study. *J Am Med Assoc* 280:701–707

Dikiy A, Novoselov SV, Fomenko DE, Sengupta A, Carlson BA, Cerny RL, et al. (2007) SelT, SelW, SelH, and Rdx12: genomics and molecular insights into the functions of selenoproteins of a novel thioredoxin-like family. *Biochemistry* 46:6871–6882

Dyrssen D, Wedborg M (1991) The sulfur–mercury(II) system in natural waters. *Water Air Soil Pollut* 56:507–519

El-Begearmi MM, Ganther HE, Sunde ML (1982) Dietary interaction between methylmercury, selenium, arsenic, and sulfur amino acids in Japanese quail. *Poult Sci* 61:272–279

El-Demerdash FM (2001) Effects of selenium and mercury on the enzymatic activities and lipid peroxidation in brain, liver, and blood of rats. *J Environ Sci Health* 36:489–499

Ferguson AD, Labunskyy VM, Fomenko DE, Araç D, Chelliah Y, Amezcua CA, et al. (2006) NMR structures of the selenoproteins Sep15 and SelM reveal redox activity of a new thioredoxin-like family. *J Biol Chem* 281:3536–3543

Freidman MA, Eaton LR, Carter WH (1978) Protective effects of freeze-dried swordfish on methylmercury Chloride toxicity in rats. *J Environ Contam Toxicol* 19:436–443

Ganther H, Goudie C, Sunde M, Kopeckey M, Wagner S, Hoekstra W (1972) Selenium: relation to decreased toxicity of methylmercury added to diets containing tuna. *Science* 175:1122–1124

George GN, Pickering IJ, Doonan CJ, Korbas M, Singh SP, Hoffmeyer RE (2008) *Inorganic Molecular Toxicology and Chelation Therapy of Heavy Metals and Metalloids Advances in Molecular Toxicology*, vol 2. B.V., Elsevier, pp. 124–148

Grandjean P, Weihe P, Jorgensen PJ, Clarkson T, Cernichiari E, Videro T (1992a) Impact of maternal seafood diet on fetal exposure to mercury, selenium and lead. *Archives Environ Health* 47:185–195

Grandjean P, Nielsen GD, Jorgensen PJ, Herder M (1992b) Reference intervals for trace elements in blood: significance of risk factors. *Scand J Clin Lab Invest* 52:321–337

Grandjean P, Weihe P, White RF, Debes F, Araki S, Murata K (1997) Cognitive deficit in 7-year old children with prenatal exposure to methylmercury. *Neurotoxicol Teratolol* 19:417–428

Grandjean P, Weihe P, White R, Debes F (1998) Cognitive performance of children prenatally exposed to safe levels of methyl mercury. *Environ Res* 77:165–172

Grandjean P, White RF, Weihe P, Jorgensen PJ (2003) Neurotoxic risk caused by stable and variable exposure to methylmercury from seafood. *Ambulatory Pediatr* 3:18–23

Hall RA, Zook EG, Meaburn GM (1978) National Marine Fisheries Service Survey of Trace Elements in the Fishery Resource. NOAA Technical Report MNFS SSRF–721

Harada Y (1968) Congenital (or fetal) Minimata disease. In: *Minamata Disease*. Study Group of Minamata Disease. Kumamoto University, Japan, pp. 93–117

Henshel D, Aschner M, Basu N, Bowerman W, Echeverria D, Gilbertson M, et al. (2007) New bioindicators for mercury toxicological assessment: recommendations from the first international bioindicators roundtable. *Environ Bioindicators* 2:183–207

Hibbeln JR, Davis JM, Steer C, Emmett P, Rogers I, Williams C, et al. (2007) Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. *Lancet* 69:578–585

Hill KE, Zhou J, McMahan WJ, Motley AK, Burk RF (2004) Neurological dysfunction occurs in mice with targeted deletion of the Selenoprotein P gene. *J Nutr* 134:157–161

Hsieh HS, Ganther HE (1977) Biosynthesis of dimethyl selenide from sodium selenite in rat liver and kidney cell free systems. *Biochimica et Biophysica Acta* 497:205–217

Iwata H, Okamoto H, Ohsawa Y (1973) Effect of selenium on methylmercury poisoning. *Research Commun Chem Pathol Pharmacol* 5:673–680

Joint Expert Committee on Food Additives (2003) Sixty-First Meeting, Summary and Conclusions. Available at ftp://ftp.fao.org/es/esn/jecfa/jecfa61sc.pdf

Julshamn K, Anderson A, Ringdal O, Morkore J (1987) Trace elements intake in the Faroe Islands, I. Element levels in edible parts of pilot whales (*Globicephalus meleanus*). *Sci Total Environ* 65:53–62

Kaneko JJ, Ralston NVC (2007) Selenium and mercury in pelagic fish in the central North Pacific near Hawaii. *Biol Trace Element Res* 119:242–254

Kasik JW, Rice EJ (1995) Selenoprotein p expression in liver, uterus and placenta during late pregnancy. *Placenta* 16:67–74

Kohrle J, Brigelius-Flohe R, Bock A, Gartner R, Meyer O, Flohe L (2000) Selenium in biology: facts and medical perspectives. *Biol Chem* 381:849–864

Kohrle J, Jakob F, Contempré B, Dumont JE (2005) Selenium, the thyroid, and the endocrine system. *Endocrine Reviews* 26:944–984

Lederman SA, Jones RL, Caldwell KL, Rau V, Sheets SE, Tang D, et al. (2008) Relation between cord blood mercury levels and early child development in a World Trade Center cohort. *Environ Health Perspect* doi:10.1289/ehp.10831. Available at http://dx.doi.org/

Luten JB, Ruiter A, Ritskes TM, Rauchbaar AB, Riekwel-Body G (1980) Mercury and selenium in marine and freshwater fish. *J Food Sci* 45:416–419

Marsh DO, Myers GJ, Clarkson TW (1980) Fetal methylmercury poisoning: clinical and toxicological data on 29 cases. *Ann Neurol* 7:348–353

Marsh DO, Clarkson TW, Cox C, Myers GJ, Amin-Zaki L, Al-Tikreti S (1987) Fetal methylmercury poisoning. *Relationship between concentration in single strands of maternal hair and child effects. Arch Neurol* 44:1017–1022

Marsh DO, Turner MD, Crispin Smith J, Allen P, Richdale N (1995) Fetal methylmercury study in a Peruvian fish-eating population. *NeurotToxicology* 16:717–725

May JM, Cobb CE, Mendiratta S, Hill KE, Burk RF (1998) Reduction of the ascorbyl free radical to ascorbate by thioredoxin reductase. *J Biol Chem* 273:23039–23045

Mitchell JW, Kjellstrom TE, Reeves RL (1982) Mercury in takeaway fish in New Zealand. *N Z Med J* 95:112–114

Myers GJ, Davidson P, Cox C, Shamlaye CF, Tanner MA, Marsh DO, et al. (1995) Summary of the Seychelles child development study on the relationship of fetal methylmercury exposure to neurodevelopment. *Neurotoxicology* 16:711–715

Myers GJ, Davidson PW (1998) Prenatal methylmercury exposure and children: neurologic, developmental, and behavioral research. *Environ Health Perspect* 106:841–847

Myers GJ, Davidson PW, Cox C, Shamlaye C, Cernichiari E, Clarkson TW (2000) Twenty-seven years studying the human neurotoxicity of methylmercury exposure. *Environ Res* 83:275–285

Myers GJ, Davidson PW, Cox C, Shamlaye CF, Palumbo D, Cernichiari E, et al. (2003) Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study. *Lancet* 361:1686–1692

Newland MC, Reed MN, LeBlanc A, Donlin WD (2006) Brain and blood mercury and selenium after chronic and developmental exposure to methylmercury. *Neurotoxicology* 27:710–720

Novoselov SV, Kryukov GV, Xu XM, Carlson BA, Hatfield DL, Gladyshev VN (2007) Selenoprotein H is a nucleolar thioredoxin-like protein with a unique expression pattern. *J Biol Chem* 282:11960–11968

Ohi G, Nishigaki S, Seki H, Tamura Y, Maki T (1976) Efficacy of selenium in tuna and selenite in modifying methylmercury intoxication. *Environ Res* 12:49–58

Ohi G, Nishigaki S, Seki H, Tamura Y, Maki T, Minowa K, et al. (1980) The protective potency of marine animal meat against the neurotoxicity of methylmercury: its relationship with the organ distribution of mercury and selenium in the rat. *Food and Cosmetics Toxicol* 18:139–145

Oken E, Osterdal L, Gillman MW, Knudsen VK, Halldorsson TI, Strom M, et al. (2008) Associations of maternal fish intake during pregnancy and breastfeeding duration with attainment of developmental milestones in early childhood: a study from the Danish National Birth Cohort. *Am J Clin Nutr* 88:789–796

Parizek J, Ostadalova I (1967) The protective effect of small amounts of selenite in sublimate intoxication. *Experientia* 23:142–143

Parizek J, Ostadalova I, Kalouskove J, Babicky A, Pavlik L, Bibr B (1971) Effect of mercuric compounds on the maternal transmission of selenium in the pregnant and lactating rat. *J Reprod Fertil* 25:157–170

Peterson SA, Ralston NVC, Peck DV, Sickle JV, Robertson JD, Spate VL, et al. (2009) How might selenium moderate the toxic effects of mercury in stream fish of the Western USA? *Environ Sci Technol* (in press)

Ralston NVC (2008) Dietary selenium alleviates methylmercury toxicity. Proceedings of the 25th International Neurotoxicology Conference. Environmental Etiologies of Neurological Disorders: Scientific, Translational and Policy Implications (pdf of presentation available upon request)

Ralston NVC, Blackwell JL, Raymond LJ (2007) Importance of molar ratios in selenium-dependent protection against methylmercury toxicity. *Biol Trace Element Res* 119:255–268

Ralston NVC, Ralston CR, Blackwell JL III, Raymond LJ (2008) Dietary and tissues selenium in relation to methylmercury toxicity. *Neurotoxicology* 29:802–811

Rayman M (2000) The importance of selenium to human health. *Lancet* 356:233–241

Reed MN, Banna KM, Donlin WD, Newland MC (2008) Effects of gestational exposure to methylmercury and dietary selenium on reinforcement efficacy in adulthood. *Neurotoxicology and Teratology* 30:29–37

Reed MN, Paletz EM, Newland MC (2006) Gestational exposure to methylmercury and selenium: effects on a spatial discrimination reversal in adulthood. *Neurotoxicology* 27:721–732

Robinson MF (1988) The New Zealand selenium experience. *Am J Clin Nutr* 48:521–534

Schweizer U, Bräuer AU, Köhrle J, Nitsch R, Savaskan NE (2004) Selenium and brain function: a poorly recognized liaison. *Brain Res Rev* 45:164–178

Seppanen K, Soininen P, Salonen JT, Lotjonen S, Laatikainen R (2004) Does mercury promote lipid peroxidation? An in vitro study concerning mercury, copper, and iron in peroxidation of low-density lipoprotein *Biol Trace Element Res* 101:117–132

Simmons-Willis TA, Koh AS, Clarkson TW, Ballatori N (2002) Transport of a neurotoxicant by molecular mimicry: the methylmercury-L-cysteine complex is a substrate for human L-type large neutral amino acid transporter (LAT) 1 and LAT2. *Biochem J* 367:239–246

Stillings BR, Lagally H, Bauersfield P, Soares J (1974) Effect of cystine, selenium, and fish protein on the toxicity and metabolism of methylmercury in rats. *Toxicol Appl Pharmacol* 30:243–254

Strain JJ, Davidson PW, Bonham MP, Duffy EM, Stokes-Riner A, Thurston SW, et al. (2008) Associations of maternal long-chain polyunsaturated fatty acids, methyl mercury, and infant development in the Seychelles Child Development Nutrition Study. *Neurotoxicology* 29:776–782

Stringari J, Nunes AKC, Franco JL, Bohrer D, Garcia SC, Dafre AL, et al. (2008) Prenatal methylmercury exposure hampers glutathione antioxidant system ontogenesis and causes long-lasting oxidative stress in the mouse brain . *Toxicol Appl Pharmacol* 227:147–154

Sugiura Y, Tamai Y, Tanaka H (1978) Selenium protection against mercury toxicity: high binding affinity of methylmercury by selenium containing ligands in comparison with sulfur containing ligands. *Bioinorganic Chem* 9:167–180

Sun Y, Ha PC, Butler JA, Ou BR, Yeh JY, Whanger PD (2001) Glutathione peroxidase activity and selenoprotein W levels in different brain regions of selenium-depleted rats. *J Nutr Biochem* 12:88–94

Takeuchi T, Eto K (1999) *The Pathology of Minamata Disease. A Tragic Story of Water Pollution*, Higashi-ku Fukuoka, Japan: Kyushu University Press Hakozaki

Taylor NJ, Wong YS, Chieh PC, Carty AJ (1975) Syntheses, X-ray crystal structure, and vibrational spectra of L-cysteinato(methyl) mercury(II) monohydrate. *J Chem Soc Dalton Transactions* 5:438–442

Trasande L, Landrigan PJ, Schechter C (2005) Public health and economic consequences of methyl mercury toxicity to the developing brain. *Environ Health Perspect* 113:590–596

Tsubaki T, Irukayama K (1977) *Minamata disease. Methylmercury poisoning in Minamata and Niigata*, Kodansha Japan, Tokyo: Japan

U.S. Department of Agriculture National Nutrient Database for Standard Reference, Release 17. Selenium, Se (μg) Content of selected foods. Available at: http://www.nal.usda.gov/fnic/foodcomp/. Accessed March 2009

Watanabe C, Yin K, Kasanuma Y, Satoh H (1999a) In utero exposure to methylmercury and Se deficiency converge on the neurobehavioral outcome in mice. *Neurotoxicol Teratol* 21:83–88

Watanabe C, Yoshida K, Kasanuma Y, Kun Y, Satoh H (1999b) In utero methylmercury exposure differentially affects the activities of selenoenzymes in the fetal mouse brain. *Environ Res* 80:208–214

Whanger PD (1992) Selenium in the treatment of heavy metal poisoning and chemical carcinogenesis. *J Trace Elem Electrolytes–Health Dis* 6:209–221

Whanger PD (2001) Selenium and the brain: a review. *Nutr Neurosci* 4:81–97