

Chapter 2

Epidemiological Evidence on Methylmercury Neurotoxicity

Jordi Julvez, Takashi Yorifuji, Anna L. Choi, and Philippe Grandjean

Abstract Methylmercury neurotoxicity has been gradually recorded over several decades. Designs of recent epidemiologic studies have improved to focus their assessments in developmental neurotoxicity. The developing brain, due to rapid physiologic changes and a protective system under development, is particularly vulnerable to the exposure to environmental insults. This chapter aims to systematically review and discuss the state-of-the-art epidemiological studies published up to the present days. We also describe and discuss some of the methodological problems. For example, the uncertainties (confounding) derived from a situation in which an association between an exposure and an outcome is distorted because it is mixed with the effect of a confounding variable. A majority of the studies have demonstrated that methylmercury exposure is neurotoxic to adults and children, but stronger adverse effects would result if negative confounding derived from the nutritional factors of seafood is taken into consideration in the data analyses. The EU and US decision to take preventive measures occurred at a substantial delay following the discovery of these neurotoxic effects.

Introduction

Scientific discoveries about the toxic effects of methylmercury have been gradually recorded over several decades, but the recognition of the public health impact of methylmercury toxicity has been sluggish, despite the severity of adverse effects.

J. Julvez, PhD • A.L. Choi, ScD • P. Grandjean, PhD, MD (✉)
Department of Environmental Health, Harvard School of Public Health,
401 Park Drive, Landmark Center East, Boston, MA 02215, USA
e-mail: pgrand@hsph.harvard.edu; pgrand@health.sdu.dk

T. Yorifuji, MD, PhD
Department of Epidemiology, Okayama University Graduate School of Medicine,
Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama, 7008558, Japan

As a result of the inertia, exposed adults and children have suffered as their symptoms were not recognized or acknowledged in a timely fashion, and prevention was delayed. Imprecision in exposure assessment and other forms of uncertainty tended to cause an underestimation of methylmercury toxicity, but the response was more often a call for more research rather than intervention.

After several major poisoning incidents involving methylmercury had occurred, it became evident that while methylmercury toxicity can be serious enough in adults, for children, especially those who are prenatally exposed, the effects can be detrimental to their development, in particular, in regard to nervous system functions. Development of the human fetal brain is the result of complex processes that already begin by end of the third week of gestation (Wilson 1980). During the third trimester, pathways for nervous system functions are being formed, and the brain appears to be particularly vulnerable at this stage to the transplacental transfer of neurotoxic chemicals, such as metal compounds (Bellinger 2009). The outcome of developmental neurotoxicity may not be immediately apparent at birth or during the first few years of postnatal development, but deficits will become evident as the brain matures, and such deficits tend to be long-standing or irreversible dysfunctions (Grandjean and Landrigan 2006).

The epidemiological evidence suggests that methylmercury exposures are more hazardous prenatally than postnatally, as a likely result of the increased vulnerability during early development. Still, the adverse effects due to prenatal exposures may have been underestimated, as adjustment for protective cofactors, such as essential nutrients in fish, seems to reveal even greater impacts by developmental neurotoxicity by methylmercury. Thus, as additional cohort studies have been carried out, and extended follow-up has taken place, the long-term effects have become better understood. Although epidemiologists are often cautious in making conclusions about causal relations, methylmercury is an example that such caution in science may result in adverse effects on public health due to the lacking use of precaution regarding a serious environmental pollutant.

Review Strategy

The review strategy utilized PubMed literature databases to identify epidemiological studies on the effects of environmental exposure to methylmercury and the neurobehavioral consequences in children and adults. Language was not specified, although English was preferred. The keywords used were exposure, pregnancy, prenatal, uterine period, postnatal period, early life, adulthood, methylmercury, behavior, neurobehavior, neuropsychological function, cognitive abilities, mental health, and neurodevelopment. These terms were first used separately and then, in a second step, were combined (e.g., exposure+methylmercury+neurobehavior). Otherwise, the search strategy followed the one described in a previous review (Grandjean and Landrigan 2006). Reference lists in the articles selected were also scrutinized so as to identify older studies that might satisfy the search criteria.

Developmental Neurotoxicity

Already in the nineteenth century, the toxic effects of methylmercury compounds in adults were documented (Edwards 1865). The clinical picture included sensory disturbance of the lower legs, lower arms, and face; visual field constriction (“tunnel vision”), deafness, ataxia, and dysarthria; and noted the “unique character of their symptoms, which do not resemble those produced by any known disease.” For many years, methylmercury poisoning in adults was due to occupational exposures or some ill-advised pharmaceutical uses (Grandjean et al. 2010). However, the first reports about neurotoxicity in children exposed to methylmercury during pregnancy were published in the 1970s, following two important poisoning incidents involving methylmercury poisoning in Japan (1950s) and Iraq (1972) (Amin-Zaki et al. 1981; Harada 1995). The name Minamata disease was coined after many cases of children with severe neurological disease were observed in the Minamata area of Kyushu Island, Japan. This poisoning event was caused by an affluent from an acetaldehyde plant, which contaminated the Minamata Bay and affected the local fish and water supply. The methylmercury was then transmitted to the population, including pregnant women mainly through the ingestion of fish (Harada 1995).

The Iraqi poisoning incident was triggered by the ingestion of bread made with wheat that was contaminated by methylmercury fungicide. Similarly to Minamata disease, children from affected pregnant women suffered severe neurodevelopment impairments (Amin-Zaki et al. 1981). Since then, several environmental studies have assessed the effects of methylmercury in developmental neurotoxicity. The target populations were primarily children because early-life exposures have been found to be more harmful than those occurring during adulthood. The intense activation of the neurodevelopment processes during this period of life causes the human brain to be like an open window that enhances fast learning, but at the same time it is vulnerable to insults of any kind, including methylmercury exposure (Grandjean and Landrigan 2006) (see Table 2.1).

Twenty-seven large epidemiological studies (>100 subjects) were conducted over the last 30 years: 14 were longitudinal and 13 cross-sectional (see Table 2.1). Most of the studies were based on communities with high fish intakes (Boucher et al. 2010; Cordier et al. 2002; Crump et al. 1998; Davidson et al. 1995, 1998, 2006b, 2010; Debes et al. 2006; Despres et al. 2005; Grandjean et al. 1995, 1997, 1999, 2001; Julvez et al. 2010; Lynch et al. 2010; Marsh et al. 1995; McKeown-Eyssen et al. 1983; Murata et al. 1999a, b, 2004a, b; Myers et al. 1995a–c, 1997, 2003; Saint-Amour et al. 2006; Steuerwald et al. 2000; Stokes-Riner et al. 2010; Strain et al. 2008; Suzuki et al. 2010; Tavares et al. 2005). A small number of studies aimed to assess the neurotoxic effects in populations exposed to comparatively low doses. In these cases, the subject samples were representative of general populations in the USA and in Poland (Cao et al. 2010; Jedrychowski et al. 2007; Stewart et al. 2003; Surkan et al. 2009). The most important cohort studies with the largest sample sizes, repeated assessments, and high participation rates at follow-up were based on the Seychelles Islands (Davidson et al. 1995, 1998, 2006b, 2010; Myers et al. 1995a,

Table 2.1 Description of the epidemiological studies assessing the developmental neurotoxicity of environmental exposure to methylmercury (from 1981 to 2011)

Country (reference)	Number (age of testing)	Exposure biomarker (average)	Outcome(s) and prenatal exposure	Outcome(s) and postnatal exposure
Brasil (Grandjean et al. 1999) ^a	354 (7–12 years) ^b	Child hair (11 µg/g)	Not reported	↓ Finger tapping ↓ Santa Anna test (motor coord.) ↓ Digit span (WISC) ↓ Stanford-Binet copying ↓ Stanford-Binet memory = Neurological development
Brasil (Tavares et al. 2005) ^a	75 vs. 134 (3–7 years)	Child hair (5 µg/g) vs. (2 µg/g)	Not reported	Not reported
Canada (McKeown-Eyssen et al. 1983) ^a	234 (12–30 months) ^b	Maternal hair (6 µg/g)	↓ Some neurological outcomes	
Canada (Despres et al. 2005; Saint-Amour et al. 2006) ^c	110 (5 years) ^b PCBs, OCs, lead ^d	Cord blood (16 µg/L) Child blood (6 µg/L) Child hair (2 µg/g)	= Neurological development = Motor development ↑ Visual evoked potentials (VEPs) (P100) Results were unchanged after controlling for cord and child selenium and <i>n</i> 3-PUFA	= Neurological development ↓ Motor development (only on action tremor during pointing movements) ↓ VEPs (N75 and P100) Results were unchanged after controlling for cord and child selenium and <i>n</i> 3-PUFA
Canada (Boucher et al. 2010) ^c	110 (11 years) ^b PCBs, OCs, lead ^d	Cord blood (16 µg/L) Child blood (5 µg/L)	Auditory oddball protocol (↓ scores of information processing and ↑ latencies of event-related potentials) Results were unchanged after controlling for cord and child selenium and <i>n</i> 3-PUFA	No associations found

Faroe Islands (Steuerwald et al. 2000) ^a	182 (2 weeks) ^b PCBs and OCs ^d	Cord blood (20 µg/L) Maternal hair (4 µg/g)	↓ Neurologic optimal score	Not reported
Faroe Islands (Grandjean et al. 1995) ^c	582 (12 months)	Cord blood (24 µg/L) Maternal hair (4 µg/g) Child hair (1 µg/g)	= Earlier milestone development	↑ Earlier milestone development ↑ Long-term breastfeeding
Faroe Islands (Grandjean et al. 1997, 2001; Murata et al. 1999b) ^c	917 (7 years) ^b PCBs ^d	Cord blood (23 µg/L) Maternal hair at parturition (4 µg/g) Child blood (9 µg/L) Child hair (3 µg/g)	↓ Attention ↓ Language ↓ Memory ↓ Motor speed ↓ Visuospatial ↑ Brainstem auditory-evoked potential latencies (BAEP) peaks III and IV (<i>N</i> = 382) = Contrast sensitivity performance The results were unchanged after controlling for whale and/or fish intake during pregnancy	No associations after adjusting for prenatal exposure
Faroe Islands (Debes et al. 2006; Julvez et al. 2010; Murata et al. 2004a) ^c	882 (14 years) ^b PCBs, lead ^d	Cord blood (23 µg/L) Maternal hair at parturition (3 µg/g) Child blood (4 µg/L) Child hair (1 µg/g)	↑ BAEP peaks III and IV and the inter-peak interval I-III = Audiometric data ↓ Attention ↓ Language ↓ Motor speed The results were unchanged after controlling for whale and/or fish intake during pregnancy	↑ BAEP inter-peak interval III-V = Audiometric data No associations with neuropsychological tests

(continued)

Table 2.1 (continued)

Country (reference)	Number (age of testing)	Exposure biomarker (average)	Outcome(s) and prenatal exposure	Outcome(s) and postnatal exposure
French Guiana (Cordier et al. 2002) ^a	230 (5–12 years) ^b	Maternal hair (3 groups) (12 µg/g; 7 µg/g; 3 µg/g)	↓ Stanford-Binet copying test ↓ McCarthy scales (coordination legs)	No association when adjusting for maternal hair
Madeira (Murata et al. 1999a) ^a	149 (7 years) ^b	Child hair (not reported) Maternal hair (10 µg/g)	↑ Deep tendon reflexes ↑ BAEP peaks III ↑ Pattern-reversal visual evoked potentials	No associations
Japan (Murata et al. 2004b) ^a	210 (7 years) ^b	Child hair (1 µg/g) Maternal hair (2 µg/g)	= Neuropsychological tests = BAEP = Neurobehavioral tests	Not reported
Japan (Suzuki et al. 2010) ^c	499 (neonates) ^b PCBs and lead ^a	Maternal hair 2 days after delivery (2 µg/g)	↓ Neonatal behavioral assessment-motor cluster (NBAS) before and after controlling for fish intake during pregnancy	Not reported due to neonate subjects
New Zealand (Crump et al. 1998) ^a	237 (6–7 years) ^b	Maternal hair (4 µg/g)	↓ Academic attainment ↓ Test of language development (TOLD) ↓ McCarthy scales ↓ Wechsler intelligence scale for children (WISC) 6 of 26 outcomes were negatively associated when a child with the highest exposure level was omitted (20 µg/g)	Not reported

Peru (Marsh et al. 1995) ^a	131 (not stated, early childhood) ^b	Maternal hair (8 µg/g)	= Neurologic and milestone development	Not reported
Poland (Jedrychowski et al. 2007) ^c	374 (12, 24, and 36 months) ^b	Cord blood (1 µg/g)	↓ Bayley mental scale (only 12 months) ↓ Bayley motor scale (only 12 months)	Not reported
Seychelles Islands (Pilot) (Myers et al. 1995c) ^a	789 (5–109 weeks) ^b	Maternal hair (7 µg/g)	= Denver developmental screening test-revised	Not reported
Seychelles Islands (Pilot) (Myers et al. 1995b) ^a	217 (66 months) ^b	Maternal hair (7 µg/g)	= McCarthy scales = The preschool language scale (↓ auditory comprehension subscale) = Letter word identification = Woodcock-Johnson tests of achievement	Not reported
Seychelles Islands (study 1) (Myers et al. 1995a) ^c	740 (6 months) ^b	Maternal hair during pregnancy (6 µg/g)	= Denver developmental screening test-revised = Testing of visual recognition memory and visual attention	Not reported
Seychelles Islands (study 1) (Davidson et al. 1995; Myers et al. 1997) ^c	738 (19 months) ^b 736 (29 months) ^b	Maternal hair during pregnancy (6 µg/g)	= Neurological examination = Bayley mental scale (both ages) = Bayley motor scale (both ages) = Bayley infant behavior scale (29 months) = Developmental milestones	Not reported

(continued)

Table 2.1 (continued)

Country (reference)	Number (age of testing)	Exposure biomarker (average)	Outcome(s) and prenatal exposure	Outcome(s) and postnatal exposure
Seychelles Islands (study 1) (Davidson et al. 1998) ^e	711 (66 months) ^b PCBs and lead ^d	Maternal hair during pregnancy (7 µg/g) Child hair (6 µg/g)	= McCarthy scales	No associations and some positive tendencies
			= Preschool language scale	
			= Bender gestalt	
			= Woodcock-Johnson tests of Achievement	
Seychelles Islands (study 1) (Myers et al. 2003) ^e	643 (9 years) ^b	Maternal hair during pregnancy (7 µg/g) Child hair (6 µg/g)	= Child behavior checklist	No associations
			= Wechsler intelligence scale for children (WISC-III)	
			= Woodcock-Johnson tests of achievement	
			= California verbal learning test (CVLTC)	
			= Wide-range assessment of memory and learning (WRAML)	
			= Finger tapping	
			= Trail making test	
			= Grooved pegboard	
			= Bruininks-Oseretsky test of motor proficiency	
			= Boston naming	
			= Beery-Buktenica developmental test of visual-motor integration	
			↓ Connor's continuous performance test (only hyperactivity outcome affected)	

Seychelles Islands (study 1) (Davidson et al. 2006b, 2010) ^c	643 (11 years) ^b	Maternal hair during pregnancy (7 µg/g)	Maternal hair during pregnancy = Similar tests than 9-year-olds	No associations
Seychelles Islands (study 2) (Lynch et al. 2010; Stokes-Riner et al. 2010; Strain et al. 2008) ^c	229 (9 and 30 months) ^b	Child hair (9 years) (6 µg/g) Maternal hair during pregnancy (6 µg/g)	= Scholastic achievements ↓ Bayley motor scale (both ages) = Bayley mental scale (both ages) After controlling for <i>n</i> -3 and <i>n</i> -6 LCPUFA	Not reported
USA (Stewart et al. 2003) ^c	212 (38 and 54 months) ^b PCBs and lead ^d	Maternal hair during pregnancy (<1 µg/g)	↓ General cognitive of McCarthy scales with higher prenatal exposure (only 38 months)	Not reported
USA (Surkan et al. 2009) ^a	355 (6–10 years)	Child hair (<1 µg/g)	Not reported	= Wechsler intelligence scale for children (WISC-III) = Wechsler individual achieve- ment test (WIAT) = Wide-range assessment of visual motor ability (WRAVMA) = Wide-range assessment of memory and learning (WRAML) = Wisconsin card scoring test (WCST) = Stroop test = Trail making test = Finger tapping

(continued)

Table 2.1 (continued)

Country (reference)	Number (age of testing)	Exposure biomarker (average)	Outcome(s) and prenatal exposure	Outcome(s) and postnatal exposure
USA (Cao et al. 2010) ^a	780 (2.5, 5 and 7 years) ^b lead ^d	Child blood (<1 µg/L)	Not reported	= Bayley mental scale (2.5 ages) = Bayley motor scale (2.5 ages) = A developmental neuropsychological assessment (NEPSY) (5 and 7 years) = Conners rating scales-revised (CPRS-R) (5 years) = Continuous performance task (CPT) (7 years) = California verbal learning test (CVLTC) (7 years) = Woodcock language proficiency Battery (WLPB-R) (7 years) = Sequential movements (NESS) (7 years) = Behavior assessment system for children (BASC) (7 years)

Sample size <100 excluded

^aCross-sectional study

^bAdjusted for covariates

^cLongitudinal study

^dAdjusted or controlled for other contaminants

= Parameter not changed

→ Parameter increased

↑ Parameter decreased

1997, 2003) and the Faroe Islands (Debes et al. 2006; Grandjean et al. 1997; Julvez et al. 2010; Murata et al. 1999b, 2004a). Both cohort studies began with examinations during the children's uterine life, while most of the neurodevelopment assessments occurred between birth and the beginning of school age. The Faroe Islands study has also published reports on the functional effects at adolescence (Debes et al. 2006; Julvez et al. 2010; Murata et al. 2004a). Although greater emphasis should be placed on prospective studies, the cross-sectional studies showed similar characteristics relative to the children's ages (see Table 2.1).

The methylmercury exposures in cohort studies were measured by mercury analysis of biological samples, such as maternal blood and hair sampled during pregnancy, at parturition or later on, in cord blood or cord tissue; all of them as indicators of prenatal exposure levels. Children's hair and blood mercury concentrations were used to assess postnatal exposures. Cross-sectional studies used maternal hair samples to estimate background concentrations during pregnancy and children's hair and blood samples to assess current exposures. Twenty-two of the studies focused on prenatal exposure as a main objective, whereas postnatal exposure was reported in half of the studies. The most common biological sample used was maternal hair due to its consistency as a biomarker of toxicity and relatively long-term retention (as compared to other biomarkers) as well as its noninvasive collection, easy storage, and transport. However, cord blood measurements were better indicators of methylmercury concentrations, as they appeared to be the most sensitive markers of methylmercury neurotoxicity as reflected by the stronger associations of cord blood with the outcomes than other mediums, i.e., maternal hair mercury concentration (Budtz-Jorgensen et al. 2007). The communities with a higher frequency of fish and seafood intake, such as the Faroe Islands, Seychelles Islands, Madeira, French Guiana, some areas of Peru, Canada, and Brazil, and to a lesser degree Japan and New Zealand, reported higher levels of methylmercury concentrations than communities in the USA and Poland, as expected (see Table 2.1). In addition, the communities with higher average intakes usually covered a wide range of exposures and therefore provided stronger information on the shape of the dose-response curve.

Among the youngest children (<6 years), the neurobehavioral outcomes primarily assessed were neurological, cognitive, and motor development. Whereas, for the older children, more specific neuropsychological functions such as motor speed, reaction time, attention, language, visuospatial, and memory functions were employed. Some studies also assessed neurophysiologic indicators such as visual and auditory evoked potential latencies. The studies utilized a wide array of tests and showed substantial variability between the studies so that a common test battery could not be identified for meta-analysis purposes. Nevertheless, some tests were repeatedly applied, such as Bayley, McCarthy, and WISC Scales. Greater disparity was observed in relation to specific neuropsychological tests, though versions of the Continuous Performance Test and the Finger Tapping Test were fairly common. Sixty percent of the studies reported clear negative associations between prenatal exposures to methylmercury and neurodevelopment, while 20% reported associations with exposures assessed postnatally (usually without adjustment for prenatal exposure levels). Cohort and cross-sectional studies showed similar percentages of

prenatal negative associations. The neuropsychological domains most often associated with prenatal methylmercury exposures were attention, language, motor, and visuospatial functions. Though less frequently investigated, evoked potentials and simple reaction time were consistently affected, as indicated by longer latencies at higher exposures. The neurodevelopmental deficits linked to postnatal exposure were less clear, but seemed to indicate a reduction of motor speed (see Table 2.1).

The covariate adjustments in most of the cases included a large range of socio-demographical covariates. Some studies also controlled for the effects of other environmental contaminants such as polychlorinated biphenyls (PCBs), other organochlorine compounds (OCs), and lead. Similar to methylmercury, OCs accumulate in the marine food chain and are known to be neurotoxic as well. However, it seems that co-exposure to other neurotoxicants has little effect on the methylmercury-associated deficits. Interestingly, negative confounding from protective substance has appeared as a much more important problem. Recent studies have analyzed the modification of methylmercury effects by controlling for fish intake frequencies and blood levels of polyunsaturated fatty acids (PUFAs) during pregnancy. PUFAs are essential nutrients for the neurodevelopment and have been observed in high concentrations in fish. The negative associations with prenatal exposure to methylmercury increase in strength when these cofactors were taken into account in multivariate models. The most remarkable findings were described by three recent reports from the Seychelles study (Lynch et al. 2010; Stokes-Riner et al. 2010; Strain et al. 2008). The first reports that the absence of methylmercury-associated neurotoxicity had not been adjusted for the benefits associated with fish intake, while including adjustment for postnatal methylmercury exposure. A new cohort study in the same community showed similar levels of hair methylmercury concentration during pregnancy, but now reported negative associations to Bayley Motor Scales when the beneficial effects of maternal PUFA levels during pregnancy were taken into account, which had not been investigated in the former analyses. The new findings thereby confirmed an explanation for the absence in the Seychelles of the negative associations otherwise found in more than seven different settings: Nutrients from the high fish intake at the Seychelles may have counterbalanced some of the neurotoxic effects due to methylmercury exposure (see Table 2.1).

In summary, 36 original articles have been published on 27 large epidemiological studies on adverse neurotoxic effects in children exposed to environmental methylmercury. The majority of the publications describe neurodevelopment impairments, particularly when the exposure was measured during uterine life. The biological samples used to assess methylmercury were mostly based on maternal and child hair, but cord blood samples were also used and seemed to show greater sensitivity to methylmercury neurotoxicity. A large range of different neurobehavioral scales and tests were utilized with a low degree of agreement as to a common test protocol among the studies. Adjusting the methylmercury effects with regard to socio-demographic and nutritional cofactors and other contaminants did not attenuate the results. On the contrary, in some populations, nutrients from fish and seafood seemed to counterbalance the real extent of developmental neurotoxicity due to methylmercury (see Table 2.1). Thus, in such cases, some of the neurotoxicity could be interpreted as obstructing important beneficial influences of essential nutrients.

Neurotoxicity in Adults

Organic mercury compounds were first used in chemical research in the mid-nineteenth century, later on as therapeutics, and from the early twentieth century as seed dressings—all of these uses were associated with adverse effects (Hunter et al. 1940). Soon after the first use of di-methylmercury in 1860s, two laboratory technicians in London suffered from poisoning and serious central nervous system signs, such as paresthesias of the hands, deafness, poor vision, ataxia, and dysarthria (Hunter et al. 1940). These symptoms were replicated numerous times later on, e.g., by poisoning cases in a factory where fungicidal dusts were manufactured. Severe generalized ataxia, dysarthria, and gross constriction of the visual fields were present in the severe cases, with memory and intelligence apparently being unaffected (Hunter et al. 1940). When one of the cases died many years later, a detailed report was produced on the pathology of central nervous system damage due to methylmercury (Hunter and Russell 1954). Following these case reports, it was obvious that organic mercury compounds are very toxic and that they cause neurological signs in adults (Von Oettingen 1952).

The first large-scale poisonings due to environmental contamination came to the forefront in Minamata, Japan, in the 1950s (Harada 1995). In Minamata, the poisoning occurred due to long-term exposure (more than 15 years) through the ingestion of fish contaminated by methylmercury, which was discharged from a local chemical factory (Harada 1995). Early epidemiological studies pointed to the cause of the disease, i.e., contaminated fish (Kitamura et al. 1957). In 1971, 3 years after the discharge of wastewater was stopped, the first population-based cross-sectional study of neurological signs was conducted by doctors at the local university (Tatetsu et al. 1972; Yorifuji et al. 2008). The investigation demonstrated that residents in the high and medium exposure areas manifested paresthesias, ataxia, dysarthria, constriction of the visual field, and hearing difficulties more frequently than those in the control area. Although exposure information for the majority of the participants in a separate investigation conducted in 1960 is not available, the median hair mercury concentration among fishermen was 30 $\mu\text{g/g}$ in the highly exposed area and 22 $\mu\text{g/g}$ in the medium-exposed area (Yorifuji et al. 2009). A 1971 investigation also demonstrated increased prevalence of psychiatric symptoms (e.g., impairment of intelligence and mood and behavioral dysfunction) in the highly exposed area (Yorifuji et al. 2011). Moreover, this study suggested that an increased prevalence of neurological signs, especially perioral paresthesias, was found among residents with hair mercury content below 50 $\mu\text{g/g}$, which had previously been thought to constitute a safe limit (Yorifuji et al. 2009). Another study showed that paresthesias remained even 30 years after cessation of methylmercury exposure (Ninomiya et al. 2005). As noted above, a considerable number of children were born during this period with conditions resembling cerebral palsy, the so-called congenital Minamata disease patients (Harada 1978).

In 1964, a similar incident of methylmercury food poisoning occurred in Niigata, Japan. The polluting factory operated in the same way as the facility in Minamata and thus discharged methylmercury into the local river. Although the exposed residents

manifested neurological signs characteristic of methylmercury poisoning, a follow-up study revealed a much larger number of residents having mild symptoms (e.g., only paresthesias) (World Health Organization 1976). In Niigata, the mercury content of hair samples from 30 initially identified patients ranged from 52 to 570 $\mu\text{g/g}$ (Tsubaki 1968, 1972, 1979).

Another major poisoning incident occurred in Iraq in the early 1970s (Bakir et al. 1973). In this case, the exposure occurred over several months through the consumption of homemade bread made from wheat seed that had been treated with a methylmercury fungicide. The exposures were more acute than those at Minamata Bay. The residents manifested similar neurological signs characteristic of methylmercury. In general, paresthesias appeared first, followed by ataxia, dysarthria, and hearing defects at increasing body burdens (Bakir et al. 1973). The threshold for paresthesias in Iraq was thought to be between 240 and 480 $\mu\text{g/L}$ blood (Bakir et al. 1973). In another study in Iraq, mild cases of methylmercury poisoning occurred at peak hair mercury concentrations as low as 120 $\mu\text{g/g}$ (Shahristani et al. 1976).

Based on evidence from Niigata and Iraq, the WHO concluded in 1990 that the effects of methylmercury in adults become detectable in the most sensitive individuals at blood mercury concentrations of 200–500 $\mu\text{g/L}$ and hair concentrations from 50 to 120 $\mu\text{g/g}$ (World Health Organization 1976, 1990). However, recent studies of chronic exposure to methylmercury in the Amazon (Yokoo et al. 2003) and Minamata (Yorifuji et al. 2009) suggest that exposures below 50 $\mu\text{g/g}$ in hair samples may not be innocuous, as also suggested by the National Research Council in 2000 (National Research Council (U.S.). Committee on the Toxicological Effects of Methylmercury 2000). In the Amazon, where gold mining and deforestation lead to methylmercury pollution (Dolbec et al. 2000), several studies have shown neurotoxic effects in adults below 50 $\mu\text{g/g}$ hair mercury content, with significant dose–effect associations between mercury exposure and motor, visual, and/or cognitive functions (Passos and Mergler 2008). For example, Lebel et al. (1998) targeted 91 adult inhabitants whose hair mercury concentration was lesser than 50 $\mu\text{g/g}$ and demonstrated positive associations of hair mercury concentration with visual contrast sensitivity and manual dexterity (Lebel et al. 1998). The same research group also showed that increased hair mercury concentrations were associated with diminished psychomotor performance as assessed by the Santa Ana manual dexterity test, the Grooved Pegboard Fine motor test, and finger tapping motor speed test among 84 subjects whose median hair mercury concentration was 9 $\mu\text{g/g}$ (Dolbec et al. 2000). Moreover, Yokoo et al. conducted a cross-sectional study in the Pantanal region of Brazil and demonstrated hair mercury concentration was associated with deficits in neurocognitive function (such as attention, fine-motor function, learning, and memory) in 129 subjects whose hair mercury concentration ranged from 0.56 to 13.6 $\mu\text{g/g}$ (median: 3.7 $\mu\text{g/g}$) (Yokoo et al. 2003). Besides, paresthesias were reported among Amazonian fishermen, whose hair mercury concentration was below 20 $\mu\text{g/g}$ (Harada et al. 2001).

Several studies were conducted in other fishing populations. Data from a 1977 cross-sectional study on 302 Quebec Cree adults (Canadian aboriginal population) for whom fish is a dietary staple showed hair mercury concentrations from 0.5

to 46 µg/g. In a reanalysis of these data, hair mercury was associated with increased prevalence of tremor in adults under 40 years of age, but there was no association with other outcomes considered (Auger et al. 2005). In Europe, 22 habitual consumers of tuna fish at a Mediterranean island (with hair mercury concentration from 1.4 to 34.5 µg/g) were compared with 22 controls in a cross-sectional design; the blood concentration of organic mercury was associated with decreased neurological performance in regard to reaction time and motor coordination (Carta et al. 2003).

Thus, the possible effects due to low-level exposure to methylmercury in the general population are of considerable concern. For example, in a US study, 474 randomly selected subjects with median blood mercury concentration of 2.1 µg/g (range: 0–16 µg/g) did not show any clear mercury-related deficits on 20 scores from 12 neurobehavioral tests (Weil et al. 2005). Further studies are required to elucidate the dose–response relationship at low exposure levels.

In summary, the evidence so far indicates that methylmercury is highly toxic, causing central nervous signs in adults (at higher exposures than those causing developmental neurotoxicity). High-level exposure, as observed in Minamata and Iraq, induces apparent neurological signs, such as paresthesias, ataxia, dysarthria, constriction of the visual field, hearing difficulties, and psychiatric symptoms. The least severely affected persons manifest paresthesias as the most persistent neurological sign. Moreover, even low-level exposure to methylmercury (e.g., below 50 µg/g of mercury in hair samples) can cause more subtle neurotoxic effects and lead to deficits in neurobehavioral or cognitive functions. However, the evidence on the effects of methylmercury exposure in the general population is still inconclusive.

Uncertainties

Confounding refers to a situation in which an association between an exposure and an outcome is distorted because it is mixed with the effect of a confounding variable. The confounding variable is related to both the exposure and the outcome, and it is not an intermediate step in the causal pathway between the exposure and the outcome (Rothman and Greenland 1998). Mercury toxicity might have been overestimated due to possible association of mercury intake with exposure to other neurotoxic pollutant(s), nutritional deficiencies, and other types of residual confounding (NIEHS 1998). The best protection against confounding problems is to select a study setting where such concerns are unlikely and, if relevant, may be adjusted for appropriately. Thus, a homogenous society with limited differences in socioeconomic and cultural factors should be preferred. Although the existence of residual confounding can never be fully excluded, careful attention should be paid to the inclusion of relevant covariates such that biologically plausible associations between methylmercury exposure and adverse effects may be identified without being exaggerated or explained away. Confounding is often assumed to occur in the same direction as the toxicant exposure, as in the case of multiple risks associated with a toxicant exposure. However, the concomitant occurrence of benefits and risks from

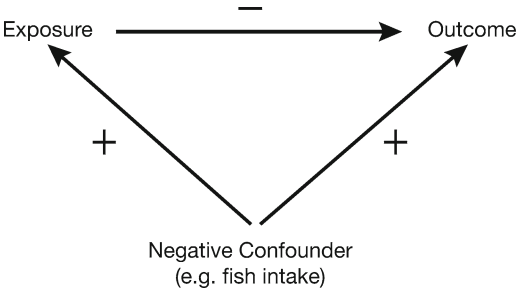


Fig. 2.1 Negative confounding: fish intake (a negative confounder) is positively associated with both methylmercury (exposure) and neurodevelopment or cardiovascular health (outcome), and the exposure has adverse effects on the outcome. Failure to adjust for fish intake would result in underestimation of both mercury toxicity and fish benefits (Choi et al. 2008a, b)

Table 2.2 Mercury effects on neurobehavioral tests at 7 and 14 years of age, as determined in structural equation analysis with covariate adjustment before and after addition of the frequency of maternal fish dinners during pregnancy (Budtz-Jorgensen et al. 2007)

Age/test group	Mercury without adjustment for fish intake		Mutual adjustment Fish intake		Mercury	
	Effect ^a	p-value	Effect	p-value	Effect	p-value
7 years						
Motor	-9.74	0.034	25.1	0.010	-12.2	0.0092
Verbal	-10.4	0.0018	3.62	0.61	-10.8	0.0017
14 years						
Motor	-7.41	0.033	19.9	0.006	-9.37	0.0082
Attention	-8.40	0.029	12.2	0.13	-9.54	0.016
Spatial	2.60	0.50	17.3	0.031	1.04	0.79
Verbal	-5.97	0.080	9.85	0.16	-6.87	0.049
Memory	-2.86	0.39	3.15	0.64	-3.05	0.37

^aEffect of true exposure doubling expressed in percent of SD of latent response

consumption of fish and seafood is an example of negative confounding. The exposure to methylmercury occurs from fish and seafood which are at the same time associated with beneficial nutrients that may counteract the development of mercury toxicity (Fig. 2.1). In this case, without adjustment for the confounding, both methylmercury toxicity and the benefits from the nutrients present in fish will be underestimated (Choi et al. 2008a).

Only a small number of studies have examined the effects of both nutrient and contaminant intakes at the same time as predictors of developmental outcomes. In the first Faroese birth cohort, adjustment for the benefits conferred by maternal fish intake during pregnancy resulted in an increased effect of the prenatal methylmercury exposure as compared to the unadjusted results (Budtz-Jorgensen et al. 2007) (Table 2.2). Similar results were reported in other studies (Oken et al. 2005;

Strain et al. 2008). These considerations also regard toxicity in adults, as well illustrated by epidemiological studies of cardiovascular parameters. When adjusted for fatty acid intakes, an increased methylmercury exposure was associated with increased risk of acute coronary events and cardiovascular mortality, so that mercury seemed to attenuate a protective effect of fish intake on cardiovascular health (Rissanen et al. 2000; Virtanen et al. 2005). Fish and seafood are a good source of selenium, a trace mineral that is essential to health and may bind to methylmercury. However, selenium generally occurs in substantial surplus in comparison with methylmercury, and adjustment for cord-blood selenium concentrations in the Faroe Islands did not have any impact on mercury-associated neurobehavioral deficits (Choi et al. 2008b; Steuerwald et al. 2000).

Established predictors such as sex, age, and maternal intelligence may cause confounding and should be included in the data analysis to obtain a more precise estimate of the mercury effect. Socioeconomic conditions vary substantially between three major prospective studies on the neurotoxicity of methylmercury—New Zealand (Kjellström et al. 1986, 1989), the Faroe Islands (Debes et al. 2006; Grandjean et al. 1997), and the Seychelles (Davidson et al. 2006a; Myers et al. 2003)—as well as several cross-sectional studies. Within each study, socioeconomic differences may also be important and may be associated with mercury exposures and therefore should be included in the confounder adjustment. For example, high intakes of methylmercury have been reported in certain ethnic groups (Innis et al. 2006; Schantz et al. 2010) and in social strata with a high sushi intake (Hightower and Moore 2003). As an additional concern, vulnerability to contaminant effects may differ between socioeconomic groups.

Other potential confounders include the family and home environment, which are documented as important determinants of childhood development (Bellinger 2009). In the New Zealand study, low social class and non-English home language resulted in reduced scores on some tests, and more than 6 months of breastfeeding increased the score on some tests (Kjellström et al. 1989). These variables were accounted for in the analysis. Although such covariates may not necessarily cause any confounding, adjustment may result in a more precise estimate of the methylmercury toxicity.

Exposure to other toxicants should also be considered. The Faroese, e.g., are exposed to PCBs from eating whale blubber (Grandjean et al. 1997). However, due to the scattered association with mercury, no important impact of PCB exposure on the neurotoxicity outcomes was shown from detailed analyses of the Faroes data (Budtz-Jorgensen et al. 2010; Steuerwald et al. 2000). The relative importance of PCB and mercury was assessed in structural equation analysis taking into account the imprecision in both variables. The inclusion of PCB exposure attenuated the mercury effect, but mercury remained statistically significant, while PCB definitely was not (Budtz-Jorgensen et al. 2010). In New Zealand and Seychelles, the ocean fish consumed is unlikely to be contaminated by PCB, and the same would be the case with freshwater fish in the Amazon Basin (Grandjean et al. 1999).

Discussion

Over a century and a half ago, it was discovered that methylmercury is toxic to adults. Initial discoveries demonstrated the severe toxicity of acute exposures to this organic metal compound. Poisoning events and population-based studies later on proved that chronic low-level exposure is also hazardous. Only relatively recently exposure limits have been addressed and established by governmental and multinational organizations. For example, the WHO concluded that the effects of methylmercury in adults become detectable in the most sensitive individuals at hair levels above 50 $\mu\text{g/g}$ (World Health Organization 1976, 1990). However, recent studies suggest that hair levels below 50 $\mu\text{g/g}$ may not at all be innocuous. In 2000, a safe limit corresponding to a hair mercury concentration of 1 $\mu\text{g/g}$ was thought to protect against developmental toxicity, but additional research was recommended to define the lower portion of the dose–response curve (National Research Council (U.S.). Committee on the Toxicological Effects of Methylmercury 2000). More recently, the validity of this limit has been questioned (Grandjean and Budtz-Jorgensen 2007). Still despite these evaluations cited above, the number of sizeable, prospective studies examining the association between mercury exposure and its neurotoxic effects in the general population is insufficient to accurately define the shape of the dose–response curve at low exposures. Although the full implications of these findings are not yet clear, they suggest that methylmercury can cause adverse effects in adults in the general population, and that methylmercury toxicity must be taken into account when evaluating the benefits of seafood (Wennberg et al. 2011).

Developmental neurotoxicity was first reported in 1952 (Engleson and Herner 1952), but despite accumulating evidence, the vulnerability of the developing nervous system was not taken into account in risk assessment internationally until relatively recently (Grandjean et al. 2010). Based on recent epidemiological studies focusing on the neurotoxic consequences of environmental methylmercury exposure in children, prenatal methylmercury exposures are more hazardous than postnatal. Additionally, when the effects of cofactors, such as maternal fish intake during pregnancy, are taken into account, the neurotoxicity of methylmercury can be explored at lower environmental concentrations. Nevertheless, more cohort studies are needed with extended follow-up to better ascertain the long-term effects, especially the negative consequences of early-life exposures during adolescence and adulthood. For example, a Faroe Islands cohort study is followed longitudinally and has so far revealed negative impacts of prenatal methylmercury exposure among teenagers (see Table 2.1) (Debes et al. 2006; Julvez et al. 2010; Murata et al. 2004a). Still, the absence of definitive scientific evidence is of course not a proper excuse for refraining from protecting vulnerable populations against this neurotoxicant.

An important hurdle facing researchers in this field is the lack of standardized neurobehavioral assessment protocols that comprise specific tests and scales sensitive to developmental toxicity independent of cross-cultural influences. Although no single test may be ideal, the difference in test batteries between studies means that meta-analyses cannot be carried out. A lack of comparability between a large

number of different tests makes it difficult to assess the validity of the outcomes and may bias the findings toward type II errors.

Another factor that has not been appropriately addressed is the possible gene–environment interaction caused by relevant heterogeneities. Methylmercury metabolism and toxicity may well differ between individuals due to genetic factors, but this issue has not so far been considered in the epidemiological studies reviewed. Such information is important and necessary in order to better understand the neurotoxic mechanisms and to identify the genetic variants that may increase the methylmercury vulnerability in exposed populations.

Confounding is potentially present in all observational studies, including those reviewed here. If a confounding variable is not controlled either in the study design or in the analysis phase, the true association between an exposure and a toxic effect outcome can be distorted. As stated earlier, most attention is usually paid to confounders that affect the outcomes in the same direction as the exposure under study. However, the control for negative confounding (opposite effect of the exposure) is perhaps just as essential in epidemiological studies of toxic exposures. In the case of methylmercury in fish and seafood, the negative confounding results from the effects of a related but beneficial parameter—nutrients—originating from the same source.

Even if this beneficial parameter is adjusted for, any imprecision of this confounder may cause underestimation of the effects of methylmercury toxicity. For example, dietary questionnaires have been used in studies to obtain information on the frequency of fish and seafood consumption, but crude dietary variables may poorly reflect the true confounder, i.e., essential nutrients from fish intake, and this imprecision causes an underestimation of the fish-adjusted mercury effect (Budtz-Jorgensen et al. 2007). For this reason, current safe limits for methylmercury exposure may be overly optimistic, as the data on methylmercury toxicity have not been adjusted for negative confounding. Future studies should assess both beneficial and adverse effects of fish and seafood intake at the same time using reliable exposure parameters to separate the opposite impacts on the outcomes including better nutrient data such as the long-chain omega-3 fatty acids.

Conclusions

The first observed cases of methylmercury poisoning occurred from incautious experimental practices almost 150 years ago whereas the first likely cases of developmental methylmercury poisoning were described in 1952 and subsequently reported from Minamata. Hence, the evidence that methylmercury is a developmental neurotoxicant has only evolved slowly within a time frame of about 50 years, despite shocking, prior documentation of debilitating congenital poisonings from Minamata, Japan, and other locations. Although the mothers of the poisoned infants seemingly escaped unscathed, the unique vulnerability of the developing human nervous system was not accepted by scientific committees until recently. Furthermore, scientific consensus on prenatal vulnerability was hampered by focusing on uncertainties in

the evidence, and international agreement on the need for protection against prenatal exposures was only reached in 2002.

A global assessment project for mercury was assembled in 2002 by the UN Environmental Programme based on the available evidence. In 2009, the member states arrived at an agreement on mercury pollution abatement. The EU and the US have already decided to ban mercury exports, and mercury in thermometers, scientific instruments, and other products presently is being phased out. However, all of these preventive measures occurred at a substantial delay following the discovery of conclusive and serious environmental health problems.

Acknowledgments This work was funded by the NIH, National Institute for Environmental Health Sciences (ES09797 and 013692). The contents of this chapter are solely the responsibility of the authors and do not necessarily represent the official views of the NIEHS, NIH, or any other funding agency.

References

- Amin-Zaki L, Majeed MA, Greenwood MR, et al. Methylmercury poisoning in the Iraqi suckling infant: a longitudinal study over five years. *J Appl Toxicol*. 1981;1:210–4.
- Auger N, Kofman O, Kosatsky T, et al. Low-level methylmercury exposure as a risk factor for neurologic abnormalities in adults. *Neurotoxicology*. 2005;26:149–57.
- Bakir F, Damluji SF, Amin-Zaki L, et al. Methylmercury poisoning in Iraq. *Science*. 1973;181:230–41.
- Bellinger DC. Interpreting epidemiologic studies of developmental neurotoxicity: conceptual and analytic issues. *Neurotoxicol Teratol*. 2009;31:267–74.
- Boucher O, Bastien CH, Saint-Amour D, et al. Prenatal exposure to methylmercury and PCBs affects distinct stages of information processing: an event-related potential study with Inuit children. *Neurotoxicology*. 2010;31:373–84.
- Budtz-Jorgensen E, Grandjean P, Weihe P. Separation of risks and benefits of seafood intake. *Environ Health Perspect*. 2007;115:323–7.
- Budtz-Jorgensen E, Debes F, Weihe P, et al. Structural equation models for meta-analysis in environmental risk assessment. *Environmetrics*. 2010;21:510–27.
- Cao Y, Chen A, Jones RL, et al. Does background postnatal methyl mercury exposure in toddlers affect cognition and behavior? *Neurotoxicology*. 2010;31:1–9.
- Carta P, Flore C, Alinovi R, et al. Sub-clinical neurobehavioral abnormalities associated with low level of mercury exposure through fish consumption. *Neurotoxicology*. 2003;24:617–23.
- Choi AL, Cordier S, Weihe P, et al. Negative confounding in the evaluation of toxicity: the case of methylmercury in fish and seafood. *Crit Rev Toxicol*. 2008a;38:877–93.
- Choi AL, Budtz-Jorgensen E, Jorgensen PJ, et al. Selenium as a potential protective factor against mercury developmental neurotoxicity. *Environ Res*. 2008b;107:45–52.
- Cordier S, Garel M, Mandereau L, et al. Neurodevelopmental investigations among methylmercury-exposed children in French Guiana. *Environ Res*. 2002;89:1–11.
- Crump KS, Kjellstrom T, Shipp AM, et al. Influence of prenatal mercury exposure upon scholastic and psychological test performance: benchmark analysis of a New Zealand cohort. *Risk Anal*. 1998;18:701–13.
- Davidson PW, Myers GJ, Cox C, et al. Longitudinal neurodevelopmental study of Seychellois children following in utero exposure to methylmercury from maternal fish ingestion: outcomes at 19 and 29 months. *Neurotoxicology*. 1995;16:677–88.

- Davidson PW, Myers GJ, Cox C, et al. Effects of prenatal and postnatal methylmercury exposure from fish consumption on neurodevelopment: outcomes at 66 months of age in the Seychelles child development study. *JAMA*. 1998;280:701–7.
- Davidson PW, Myers GJ, Cox C, et al. Methylmercury and neurodevelopment: longitudinal analysis of the Seychelles child development cohort. *Neurotoxicol Teratol*. 2006a;28:529–35.
- Davidson PW, Myers GJ, Weiss B, et al. Prenatal methyl mercury exposure from fish consumption and child development: a review of evidence and perspectives from the Seychelles child development study. *Neurotoxicology*. 2006b;27:1106–9.
- Davidson PW, Leste A, Benstrong E, et al. Fish consumption, mercury exposure, and their associations with scholastic achievement in the Seychelles child development study. *Neurotoxicology*. 2010;31:439–47.
- Debes F, Budtz-Jorgensen E, Weihe P, et al. Impact of prenatal methylmercury exposure on neurobehavioral function at age 14 years. *Neurotoxicol Teratol*. 2006;28:363–75.
- Despres C, Beuter A, Richer F, et al. Neuromotor functions in Inuit preschool children exposed to Pb, PCBs, and Hg. *Neurotoxicol Teratol*. 2005;27:245–57.
- Dolbec J, Mergler D, Sousa Passos CJ, et al. Methylmercury exposure affects motor performance of a riverine population of the Tapajos river, Brazilian Amazon. *Int Arch Occup Environ Health*. 2000;73:195–203.
- Edwards GN. Two cases of poisoning by mercuric methide. *Saint Bartholomew's Hospital Reports* 1 1865:141–50.
- Engleson G, Herner T. Alkyl mercury poisoning. *Acta Paediatr*. 1952;41:289–94.
- Grandjean P, Weihe P, White RF. Milestone development in infants exposed to methylmercury from human milk. *Neurotoxicology*. 1995;16:27–33.
- Grandjean P, Weihe P, White RF, et al. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. *Neurotoxicol Teratol*. 1997;19:417–28.
- Grandjean P, White RF, Nielsen A, et al. Methylmercury neurotoxicity in Amazonian children downstream from gold mining. *Environ Health Perspect*. 1999;107:587–91.
- Grandjean P, White RF, Sullivan K, et al. Impact of contrast sensitivity performance on visually presented neurobehavioral tests in mercury-exposed children. *Neurotoxicol Teratol*. 2001;23:141–6.
- Grandjean P, Landrigan PJ. Developmental neurotoxicity of industrial chemicals. *Lancet*. 2006;368:2167–78.
- Grandjean P, Budtz-Jorgensen E. Total imprecision of exposure biomarkers: implications for calculating exposure limits. *Am J Ind Med*. 2007;50:712–9.
- Grandjean P, Satoh H, Murata K, et al. Adverse effects of methylmercury: environmental health research implications. *Environ Health Perspect*. 2010;118:1137–45.
- Harada M. Congenital Minamata disease: intrauterine methylmercury poisoning. *Teratology*. 1978;18:285–8.
- Harada M. Minamata disease: methylmercury poisoning in Japan caused by environmental pollution. *Crit Rev Toxicol*. 1995;25:1–24.
- Harada M, Nakanishi J, Yasoda E, et al. Mercury pollution in the Tapajos River basin, Amazon: mercury level of head hair and health effects. *Environ Int*. 2001;27:285–90.
- Hightower JM, Moore D. Mercury levels in high-end consumers of fish. *Environ Health Perspect*. 2003;111:604–8.
- Hunter D, Bomford R, Russell DS. Poisoning by methyl mercury compounds. *Qurt J Med*. 1940;9:193–213.
- Hunter D, Russell DS. Focal cerebellar and cerebellar atrophy in a human subject due to organic mercury compounds. *J Neurol Neurosurg Psychiatry*. 1954;17:235–41.
- Innis SM, Palaty J, Vaghri Z, et al. Increased levels of mercury associated with high fish intakes among children from Vancouver, Canada. *J Pediatr*. 2006;148:759–63.
- Jedrychowski W, Perera F, Jankowski J, et al. Fish consumption in pregnancy, cord blood mercury level and cognitive and psychomotor development of infants followed over the first three years of life: Krakow epidemiologic study. *Environ Int*. 2007;33:1057–62.
- Julvez J, Debes F, Weihe P, et al. Sensitivity of continuous performance test (CPT) at age 14 years to developmental methylmercury exposure. *Neurotoxicol Teratol*. 2010;32:627–32.

- Kitamura S, Miyata C, Tomita M, et al. [Results of epidemiological investigation on unknown disease affected central nervous system, which occurred in the Minamata Area] (in Japanese). Kumamoto Igakkai Zasshi. 1957;31 Suppl 1:1–9.
- Kjellström T, Kennedy P, Wallis S, et al. Physical and mental development of children with prenatal exposure to mercury from fish. Stage I: preliminary tests at age 4. Solna, Sweden. National Swedish Environmental Protection Board. Report 1986; 3080.
- Kjellström T, Kennedy P, Wallis S, et al. Physical and mental development of children with prenatal exposure to mercury from fish. Stage II: interviews and psychological tests at Age 6. Solna, Sweden. National Swedish Environmental Protection Board. Report 1989; 3642.
- Lebel J, Mergler D, Branches F, et al. Neurotoxic effects of low-level methylmercury contamination in the Amazonian Basin. *Environ Res*. 1998;79:20–32.
- Lynch ML, Huang LS, Cox C, et al. Varying coefficient function models to explore interactions between maternal nutritional status and prenatal methylmercury toxicity in the Seychelles child development nutrition study. *Environ Res*. 2010;111:75–80.
- Marsh DO, Turner MD, Smith JC, et al. Fetal methylmercury study in a Peruvian fish-eating population. *Neurotoxicology*. 1995;16:717–26.
- McKeown-Eyssen GE, Ruedy J, Neims A. Methyl mercury exposure in northern Quebec. II. Neurologic findings in children. *Am J Epidemiol*. 1983;118:470–9.
- Murata K, Weihe P, Renzoni A, et al. Delayed evoked potentials in children exposed to methylmercury from seafood. *Neurotoxicol Teratol*. 1999a;21:343–8.
- Murata K, Weihe P, Araki S, et al. Evoked potentials in Faroese children prenatally exposed to methylmercury. *Neurotoxicol Teratol*. 1999b;21:471–2.
- Murata K, Weihe P, Budtz-Jorgensen E, et al. Delayed brainstem auditory evoked potential latencies in 14-year-old children exposed to methylmercury. *J Pediatr*. 2004a;144:177–83.
- Murata K, Sakamoto M, Nakai K, et al. Effects of methylmercury on neurodevelopment in Japanese children in relation to the madeiran study. *Int Arch Occup Environ Health*. 2004b;77:571–9.
- Myers GJ, Marsh DO, Davidson PW, et al. Main neurodevelopmental study of Seychellois children following in utero exposure to methylmercury from a maternal fish diet: outcome at six months. *Neurotoxicology*. 1995a;16:653–64.
- Myers GJ, Davidson PW, Cox C, et al. Neurodevelopmental outcomes of Seychellois children sixty-six months after in utero exposure to methylmercury from a maternal fish diet: pilot study. *Neurotoxicology*. 1995b;16:639–52.
- Myers GJ, Marsh DO, Cox C, et al. A pilot neurodevelopmental study of Seychellois children following in utero exposure to methylmercury from a maternal fish diet. *Neurotoxicology*. 1995c;16:629–38.
- Myers GJ, Davidson PW, Shamlaye CF, et al. Effects of prenatal methylmercury exposure from a high fish diet on developmental milestones in the Seychelles child development study. *Neurotoxicology*. 1997;18:819–29.
- Myers GJ, Davidson PW, Cox C, et al. Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study. *Lancet*. 2003;361:1686–92.
- National Research Council (U.S.). Committee on the Toxicological Effects of Methylmercury. Toxicological effects of methylmercury. Washington: National Academy Press; 2000.
- NIEHS. Workshop organized by Committee on Environmental and Natural Resources (CENR), Office of Science and Technology Policy (OSTP), The White House: Scientific issues relevant to assessment of health effects from exposure to methylmercury; 1998.
- Ninomiya T, Imamura K, Kuwahata M, et al. Reappraisal of somatosensory disorders in methylmercury poisoning. *Neurotoxicol Teratol*. 2005;27:643–53.
- Oken E, Wright RO, Kleinman KP, et al. Maternal fish consumption, hair mercury, and infant cognition in a U.S. Cohort. *Environ Health Perspect*. 2005;113:1376–80.
- Passos CJ, Mergler D. Human mercury exposure and adverse health effects in the Amazon: a review. *Cad Saude Publica*. 2008;24 Suppl 4:s503–20.
- Rissanen T, Voutilainen S, Nyyssönen K, et al. Fish oil-derived fatty acids, docosahexaenoic acid and docosapentaenoic acid, and the risk of acute coronary events: the Kuopio ischaemic heart disease risk factor study. *Circulation*. 2000;102:2677–9.
- Rothman KJ, Greenland S. Modern epidemiology. Philadelphia: Lippincott-Raven; 1998.

- Saint-Amour D, Roy MS, Bastien C, et al. Alterations of visual evoked potentials in preschool Inuit children exposed to methylmercury and polychlorinated biphenyls from a marine diet. *Neurotoxicology*. 2006;27:567–78.
- Schantz SL, Gardiner JC, Aguiar A, et al. Contaminant profiles in Southeast Asian immigrants consuming fish from polluted waters in northeastern Wisconsin. *Environ Res*. 2010;110:33–9.
- Shahristani H, Shihab K, Haddad I. Mercury in hair as an indicator of total body burden. *Bull World Health Organ*. 1976;53 (suppl.):105–112.
- Steuerwald U, Weihe P, Jorgensen PJ, et al. Maternal seafood diet, methylmercury exposure, and neonatal neurologic function. *J Pediatr*. 2000;136:599–605.
- Stewart PW, Reihman J, Lonky EI, et al. Cognitive development in preschool children prenatally exposed to PCBs and MeHg. *Neurotoxicol Teratol*. 2003;25:11–22.
- Stokes-Riner A, Thurston SW, Myers GJ, et al. A longitudinal analysis of prenatal exposure to methylmercury and fatty acids in the Seychelles. *Neurotoxicol Teratol*. 2011;33(2):325–8.
- Strain JJ, Davidson PW, Bonham MP, et al. Associations of maternal long-chain polyunsaturated fatty acids, methyl mercury, and infant development in the Seychelles child development nutrition study. *Neurotoxicology*. 2008;29:776–82.
- Surkan PJ, Wypij D, Trachtenberg F, et al. Neuropsychological function in school-age children with low mercury exposures. *Environ Res*. 2009;109:728–33.
- Suzuki K, Nakai K, Sugawara T, et al. Neurobehavioral effects of prenatal exposure to methylmercury and PCBs, and seafood intake: neonatal behavioral assessment scale results of Tohoku study of child development. *Environ Res*. 2010;110:699–704.
- Tatetsu S, Kiyota K, Harada M, et al. Neuropsychiatric study on Minamata disease-clinical and symptomatological study on Minamata disease (in Japanese). Medical school of Kumamoto university; 1972.
- Tavares LM, Camara VM, Malm O, et al. Performance on neurological development tests by riverine children with moderate mercury exposure in Amazonia, Brazil. *Cad Saude Publica*. 2005;21:1160–7.
- Tsubaki T. [Methylmercury poisoning along the Agano river—researches by Niigata University-] (in Japanese). *Rinsho Shinkeigaku*. 1968;8:511–20.
- Tsubaki T. [The follow up of Niigata Minamata disease] (in Japanese). *Kagaku*. 1972;42:526–31.
- Tsubaki T. [Clinical epidemiology about Niigata Minamata disease. In: Arima S, editor. In Minamata disease—researches during 20 years and problems at present 1979. pp. 291–300] (in Japanese). Seirinsha, Tokyo.
- Virtanen JK, Voutilainen S, Rissanen TH, et al. Mercury, fish oils, and risk of acute coronary events and cardiovascular disease, coronary heart disease, and all-cause mortality in men in eastern Finland. *Arterioscler Thromb Vasc Biol*. 2005;25:228–33.
- Von Oettingen WF. Poisoning; a guide to clinical diagnosis and treatment. New York: Hoeber; 1952.
- Weil M, Bressler J, Parsons P, et al. Blood mercury levels and neurobehavioral function. *JAMA*. 2005;293:1875–82.
- Wennberg M, Bergdahl IA, Hallmans G, et al. Fish consumption and myocardial infarction: a second prospective biomarker study from northern Sweden. *Am J Clin Nutr*. 2011;93(1):27–36.
- Wilson DB. Embryonic development of the head and neck: part 5, the brain and cranium. *Head Neck Surg*. 1980;2:312–20.
- World Health Organization. Environmental health criteria: 1. Mercury. Geneva: World Health Organization; 1976.
- World Health Organization. Environmental health criteria: 101. Methylmercury. Geneva: World Health Organization; 1990.
- Yokoo EM, Valente JG, Grattan L, et al. Low level methylmercury exposure affects neuropsychological function in adults. *Environ Health*. 2003;2:8.
- Yorifuji T, Tsuda T, Inoue S, et al. Long-term exposure to methylmercury and psychiatric symptoms in residents of Minamata. *Japan Environ Int*. 2011;37(5):907–13.
- Yorifuji T, Tsuda T, Takao S, et al. Long-term exposure to methylmercury and neurologic signs in Minamata and neighboring communities. *Epidemiology*. 2008;19:3–9.
- Yorifuji T, Tsuda T, Takao S, et al. Total hair mercury content in hair and neurological signs historical data from Minamata. *Epidemiology*. 2009;20:188–93.

Methylmercury and Neurotoxicity

Ceccatelli, S.; Aschner, M. (Eds.)

2012, XII, 376 p., Hardcover

ISBN: 978-1-4614-2382-9