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Twenty-Seven Years Studying the Human Neurotoxicity of Methylmercury Exposure[1]

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Research at the University of Rochester (U of R) has been focused on mercury for nearly half a century. Initially studies focused on dosimetry, especially the accuracy of measuring exposure, and experimental work with animal models. Clinical studies in human populations started when the U of R mercury group was asked to assist with dosimetry in the Iraq epidemic of 1971–1972. Initial clinical studies described the effects of methylmercury (MeHg) poisoning on adults and children. A dose–response curve for prenatal exposure was determined and it suggested that relatively low exposures might be harmful to the fetus. Since most human exposure to MeHg is dietary from fish consumption, these theoretical dangers had far-reaching implications. After Iraq, the Rochester team pursued exposure from fish consumption in both adults and children. Populations with high fish consumption were identified in Samoa and Peru for studying adults and in Peru and the Seychelles islands for studying children. The possible health threat to the fetus from maternal fish consumption quickly became the focus of research efforts. This paper reviews the Rochester experience in studying human exposure to MeHg from fish consumption.

Key Words: **Mercury; methyl mercury; clinical research; child development; Seychelles.**

INTRODUCTION

The study of mercury has been a priority at the University of Rochester (U of R) since the 1950s. Initially studies concentrated on measurement of exposure and the consequences of exposure to various forms of mercury on experimental animals (Magos *et al*., 1964; Clarkson and Rothstein, 1964; Clarkson *et al*., 1965; Clarkson and Magos, 1966, 1967; Clarkson and Greenwood, 1968). However, in 1972 following the Iraq poisoning research interest turned toward the human health effects of methylmercury (MeHg) exposure. Immediately after the poisoning was discovered there was great concern about the safety of commercial food since MeHg is tasteless and odorless and usually has a latency period of weeks before clinical effects are seen. The U of R team was asked by the Iraqi government to establish a laboratory and measure mercury in food to determine whether it was safe to consume. Fortunately, the commercial food was safe and the primary exposure was the consumption of MeHg-treated seed grain by large numbers of rural families. This presented a unique opportunity to examine the clinical outcomes and to relate symptoms and signs to accurate measures of exposure.

Initial studies in Iraq provided extensive experience in measuring exposure and documenting the effects of varying exposure levels at different ages (Clarkson *et al*., 1974, 1976, 1981a,b; Cox *et al*., 1989; Rustam and Hamdi, 1974; Rustam *et al*., 1975; Von Burg and Rustam, 1974a,b; Bakir *et al*., 1973, 1976; Magos *et al*., 1976; Greenwood *et al*., 1977, 1978; Greenwood, 1985; Amin-Zaki *et al*., 1974a,b,c, 1976, 1978, 1979, 1980, 1981; Elhassani *et al*., 1978; Marsh *et al*., 1977, 1980, 1981, 1987). In adults the earliest symptom reported was paresthesias and the earliest clinical finding was ataxia (Bakir *et al*., 1973). For prenatal exposure, a dose–response curve was found (Marsh *et al*., 1987; Cox *et al*., 1989, 1995). A series of studies examining the effects of human exposure subsequently followed in Canada (Wheatley *et al*., 1979; Kershaw *et al*., 1980; Phelps *et al*., 1980). As experience grew in measuring mercury in

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biological samples, the Environmental Health Sciences clinical laboratory became recognized for its expertise. A number of research opportunities related to mercury exposure arose from cooperation in measuring exposure (Davis *et al*., 1994; Grandjean *et al*., 1992; Gotelli *et al*., 1985; Englender *et al*., 1980; Fagan *et al*., 1977; Nierenberg *et al*., 1998).

However, the primary human exposure to MeHg is dietary from fish consumption. Consequently, research efforts turned to the study of individuals consuming large amounts of fish and whether low-level chronic exposure from this source could present a health risk. Could exposure at any age adversely affect the nervous system? The theoretical danger to the fetus from MeHg exposure following maternal fish consumption had the most far-reaching implications. This review will focus primarily on the clinical studies our team members have participated in which relate to human dietary exposure to MeHg from fish consumption.

Studies with Adults

Iraq. The Iraq poisoning epidemic occurred during the winter of 1971–1972 and presented a unique opportunity to study the effects of this neurotoxin. Iraqi physicians immediately recognized the cause of the poisoning since they had experience with MeHg poisoning from an outbreak in 1960 when nearly 1000 patients were affected (Al-Damluji, 1976). The Iraqi government promptly asked the U of R team to establish a laboratory to analyze food supplies for mercury contamination and to measure exposure in biological specimens. The Iraqi government promptly warned the population, collected the remaining treated grain, and prohibited the slaughter of animals (Al-Tikriti and Al-Mufti, 1976). The early recognition of MeHg as the cause and public action by the authorities limited the time of exposure to a few months. Even so, there were 6530 patients with poisoning admitted to hospital, 459 who died, and perhaps as many as 50,000 actually exposed (Bakir *et al*., 1973; Greenwood, 1985). Fortunately, commercial food sources were not contaminated. The primary exposure was MeHg-treated seed grain which had been disseminated for planting and which rural farmers used to bake bread.

Following the epidemic, both blood and hair levels of MeHg were measured. Blood levels fell quickly when exposure stopped and hair levels were more useful in recapitulating the exposure (Bakir *et al*., 1973). Hair was measured segmentally and the peak mercury exposure level was determined. This allowed an accurate determination of both the timing and the level of exposure in affected individuals. In collaboration with Iraqi colleagues the Rochester group carried out a series of clinical studies examining the effects of MeHg on adults (Bakir *et al*., 1973, 1976; Clarkson *et al*., 1974, 1976, 1981a, b; Greenwood *et al*., 1978; Magos *et al*., 1976; Rustam *et al*., 1975; Smith *et al*., 1976; Von Burg and Rustam, 1974a, b). These studies confirmed the devasting effects of this neurotoxin on adults and provided valuable information on the association between level of exposure and clinical effects. Paresthesias were found to be the first clinical symptom reported by patients (Bakir *et al*., 1973). The first clinical finding was ataxia. If the exposure was sufficiently high, dysarthria, deafness, and eventually death followed ataxia.

Samoa. U of R team members next sought an adult population that consumed large quantities of fish with high mercury levels to see whether clinical symptoms or signs could be detected (Marsh *et al*., 1974). They selected Samoa and examined two fish-eating populations there. The first study consisted of 88 men working on tuna fishing boats. These men were at sea for up to 47 weeks a year during which time their primary diet was the tuna they caught and rice. Their fish consumption was estimated at 10.4 oz daily. The second study consisted of 45 Samoans working in a tuna-packing factory. Their primary dietary protein was also fish, but in smaller amounts and with a more varied diet. Fish consumption was about 7 oz per day in males and 3.7 oz in females. The evaluations of both study groups consisted of a history and neurological examination along with biological samples to determine exposure. Hair mercury values ranged up to 24 ppm among shore workers (mean 8 ppm) and 48 ppm among the tuna fishermen (mean 17 ppm). No individual had any symptoms or signs suggestive of MeHg poisoning. In this population adults with MeHg exposure from consuming large quantities of fish reported no symptoms compatible with poisoning and showed no associated neurological abnormalities on examination.

Peru. The next adult population studied was from Northern Peru (Turner *et al*., 1974, 1980). One hundred ninety individuals from a coastal fishing community who consumed over 1 kg of fish weekly for many years were evaluated. They ranged in age from 1.5 to 82 years and had a mean blood MeHg level of 82 ppb (range of 11 to 275). Sixty-eight (35%) reported paresthesias, but there was no evidence of neurological impairment on examination. Therefore, 93 subjects from inland who consumed only small quantities of fish were examined. They had a mean

blood MeHg of 9.9 ppb (range 3.3 to 25.1) and 56 (60%) reported paresthesias. No association between paresthesias and MeHg exposure from regular long-term fish consumption could be established.

Studies with Children

Iraq. The opportunity to study prenatal and postnatal exposure to MeHg with accurate exposure data led to a number of studies on children (Amin-Zaki *et al*., 1974a,b,c, 1976, 1978, 1979, 1980, 1981; Elhassani *et al*., 1978; Cox *et al*., 1989, 1995; Marsh *et al*., 1977, 1980, 1981, 1987). Initial studies were observational ones of prenatal and postnatal exposure and the children's outcomes. In addition, studies of breast-feeding and treatment regimens were carried out (Greenwood *et al*., 1978; Elhassani *et al*., 1978). The concentration of MeHg in breast milk and its relation to maternal blood levels was determined and breast-feeding was found to slow the clearance of mercury (Amin-Zaki *et al*., 1974b, 1976, 1981).

One of the most important studies carried out was of prenatal exposure in mothers who were pregnant during the poisoning (Marsh *et al*., 1987; Cox, 1989, 1995). The prenatal exposure level was determined by measuring the mercury level in the maternal hair growing during pregnancy. Iraqi women had long hair and exposures could be determined over a period of years. The mothers were located and interviewed about their pregnancy and the children's development. Specifically the mothers were asked the age at which the child walked independently and first used two or more meaningful words. The children were then examined neurologically. Data were gathered on over 80 mother–infant pairs. A dose–response curve for the association between prenatal exposure and attainment of developmental milestones (walking unaided before or after 18 months of age and using two meaningful words before or after the age of 24 months) and neurological findings was determined. A dose–response curve for both developmental milestones and a score from the neurological examination suggested that prenatal exposure as low as 10 ppm peak mercury in maternal hair growing during pregnancy might be associated with adverse fetal consequences.

These findings raised concern about a possible public health issue as reviewed by Marsh (1994). It was previously known that most human exposure to MeHg was dietary and mainly from fish consumption. It was also known that individuals who consumed fish regularly often had hair mercury levels of 10 ppm or higher. If the dose–response curves from Iraq were applicable to prenatal exposure from fish consumption, as well as poisoning, then a significant public health problem might exist.

Although concerning in theory, it was unclear how applicable data from a poisoning episode were to exposure from dietary sources. In addition, the Iraq study had some limitations. Interviews of the mother were done through interpreters at a mean child age of 30 months. Birth dates were ascertained in relation to other events (i.e., seasons or holidays) since they are not important in the Arabic culture. The background rate of neurological abnormalities in the population was unknown. Covariates such as social and economic differences were not determined. There were substantial cultural differences between the families since they were widely scattered throughout Iraq. It seemed clear that studies in populations exposed to MeHg from consuming large amounts of fish were needed. Fortunately, such populations exist.

Peru. A study of prenatal exposure and its association with the child's development was first undertaken on the coast of Peru (Marsh *et al*., 1995b). A total of 131 mother–infant pairs from a fishing village were enrolled. The mothers regularly consumed fish and had a mean hair MeHg level of 7 ppm (range 0.9 to 28 ppm). The same protocol that was used in Iraq was employed. Mother's were interviewed to determine the developmental milestones and the children had a neurological examination. No association was found between the children's prenatal exposure to MeHg and their development or neurological findings. However, it was unclear how definitive these findings were. The study was cross sectional, the evaluations were limited, and it was not possible to follow the children longitudinally.

Seychelles. The U of R team next sought a population with prenatal MeHg exposure from consuming fish which could be studied intensively, longitudinally, and with a minimum of confounding factors. Matthews (1983) had described such a population from the Republic of Seychelles and this became the study site (Marsh *et al*., 1995a; Shamlaye *et al*., 1995). In the Republic of Seychelles most individuals consume fish daily and do not consume marine mammals. The islands are 1000 miles from the nearest continent and there is minimal local industry with no known local pollution. Basic and preventive health care is free, readily available, and of high quality. Over 90% of women have prenatal care and deliver in a single central hospital. Maternal consumption of alcohol and use of tobacco are very low. Perinatal mortality is very low (13.4/1000 in 1990) and children's immunization rates are high

(over 90%). There is no malaria or malnutrition. Education begins at age 3.5 years and is free, readily available, and of good quality. Over 90% of the population resides on the main island of Mahe and transportation around the island is excellent. In addition, the government, health authorities, and the people are cooperative, and the current conditions have been similar for many years.

In the early 1980s we started to monitor mercury exposure during pregnancy by measuring it in maternal hair samples taken at delivery. In 1987–1988 we enrolled a cross sectional pilot cohort on whom there was accurate prenatal exposure data (Cernichiari *et al*., 1995a; Myers *et al*., 1995a). Mother–child pairs were recalled and evaluated in their local health clinics. The assessment team consisted of a Seychellois nurse responsible for translating and a pediatric neurologist. All evaluators and personnel in Seychelles were blinded to the mother's mercury exposure. The evaluation consisted of a standardized questionnaire, a neurological examination, and administration of the Denver Developmental Screening Test–Revised. A total of 804 mother–child pairs were evaluated over a 1-year time period. After 15 exclusions for maternal or child medical conditions highly associated with developmental problems there were 789 children for analysis. No association between mercury exposure and any endpoint was seen. However, Kjellstrom and colleagues (1986) had proposed a nonstandard scoring procedure (questionable scores combined with abnormal scores) in an earlier study from New Zealand. Using the nonstandard procedure they found an association with mercury exposure, and when the Seychelles data were grouped in this manner an association was present (Myers *et al*., 1995a). As the children's prenatal MeHg exposure increased there was an increasing number of these nonstandard combined scores. The response rates were higher in males and decreased as the children got older. It appeared that an association between exposure and endpoints was present using more specific developmental testing than in Iraq or Peru. The use of nonstandard scoring to determine a relationship with MeHg exposure during the enrollment was concerning and plans for a more detailed main study continued.

Subsequently, a subset of 217 of the pilot cohort was tested at 66 months of age (Myers *et al*., 1995b). An association between development and prenatal MeHg exposure was present. However, when a small number of outliers and influential points were removed to normalize the data only one association remained. The associations were dependent on a few outliers and influential scores.

Eighty-eight pilot cohort children were evaluated at the age of 9 years with some of the test battery used for the main cohort study. These pilot data are now available and show associations between prenatal MeHg exposure and neurodevelopmental outcomes but in a beneficial direction (Davidson *et al*., 2000). For males, performance on the Boston Naming test increased 4 points for every 10 ppm of maternal hair MeHg. Also, for males timed scores on the Grooved Pegboard improved (i.e., decreased) 10 s for every 10 ppm of maternal hair MeHg, and scores on the Beery Buktenica Developmental Test of Visual Motor Integration improved (increased) 6 points for every 10 ppm of MeHg. The small sample size and the presence of some influential points in these analyses make us cautious in interpreting these data.

In 1989 enrollment of the main cohort began. Like the pilot study, exposure was measured in maternal hair samples growing during pregnancy and all examiners and Seychellois were blinded to the exposure level. A number of modifications were made to the protocol based on our experience with the pilot study and a review of the literature (Davidson *et al*., 1994). Evaluations of the children took place in age windows to reduce the problems of comparing developmental differences in children of different ages. The age windows were ± 2 weeks for evaluations at 6.5, 19, and 29 months, ± 3 months at 66 months, and ± 6 months at about 9 years of age. To accomplish this logistically, enrollment took place over a 12-month time period. The main study was restricted to the island of Mahe where 95% of the children reside. A Child Development Center was established where the children could be examined in an environment conducive to optimal performance. The questionnaire concerning history and covariates was expanded, as were the evaluations. Tests that had previously been reported to show associations with mercury exposure in humans or animals were added and the testing battery was expanded (Gunderson *et al*., 1988; Marsh *et al*., 1995a). The children's health records were obtained and examined for medical exclusions. Children with medical conditions highly associated with developmental problems (major congenital anomalies, perinatal seizures, epilepsy, significant head trauma, etc.) were excluded from analysis.

At 6.5 months we enrolled 779 mother–infant pairs (Myers *et al*., 1995c). Thirty-nine children met *a priori* exclusion criteria (15 with inadequate maternal hair to recapitulate exposure, 18 for medical exclusion criteria, and 6 twins). The final cohort for analysis at enrollment was 740. Testing has been carried out at regular intervals (6.5, 19, 29, 66, and

TABLE 1

Tests and Endpoints Evaluated in the Main SCDS Study through 66 Months and Those Examined at 108 Months

6 Months
- Neurological examination
  - Overall neurological score
  - Muscle tone
  - Deep tendon reflexes
- Fagan test of visual recognition memory
  - Memory score
  - Attention subscale
- Denver Developmental Screening Test

19 Months
- Developmental milestones (by maternal history)
  - Age child first walked
  - Age child first said two words
- Bayley Scales of Infant Development
  - Mental Developmental Index
  - Physical Developmental Index
  - Kohen–Raz (perceptual motor subscale)

29 Months
- Bayley Scales of Infant Development
  - Mental Developmental Index
  - Physical Developmental Index
  - Infant Behavior Record
- Activity
  - Attention
  - Cooperation
  - Happiness
  - Response to examiner

Response to mother

66 Months
- McCarthy Scales of Children's Abilities
  - General Cognitive Index
  - Verbal
  - Perceptual–performance
  - Memory
  - Quantitative
  - Motor
- Preschool Language Scale
  - Total language
- Woodcock–Johnson Achievement Test
  - Letter–word
  - Applied problems
- Bender–Gestalt
  - Errors
- Child Behavior Checklist
  - Overall
  - Internalization
  - Externalization
  - Attention
  - Anxiety
  - Withdrawal
  - Social problems
  - Learning problems
  - Conduct problems
  - Sexual problems

108 Months
- Wechsler Intellegence Scale for Children III
  - Full scale IQ
  - Verbal IQ
  - Performance IQ
  - Verbal comprehension
  - Perceptual organization
  - Processing speed
  - Freedom from distractibility
- Test of motor development (Bruinincks–Oseretsky)
  - Total score
- Berry–Buktenica Developmental Test of Visual Motor Integration
  - Developmental score
- Woodcock–Johnson Achievement Test
  - Letter–word
  - Applied problems
- Child Behavior Checklist
  - Overall
- Connors Teacher Rating Scale
  - Total score
- California Verbal Learning Test
  - Trials 1–5 total
  - List A, Short delay recall
  - List A, Long delay recall
- Wide Range Assessment of Memory & Learning
  - Design memory subtest
- Trial Making
  - Time to complete
  - Errors
- Finger Tapping
  - Average time-Preferred hand
  - Average time—Nonpreferred hand
- Grooved Pegboard
  - Average time—Preferred hand
  - Average time—Nonpreferred hand
  - Drops—Preferred hand
  - Drops–Nonpreferred hand
- Boston Naming Test
  - Total score
- Haptic discrimination test
  - Errors
- Connors Continuous Performance Task
  - Number of hits
  - Number of omissions
  - Number of commissions
  - Hit reaction time
  - Attentiveness (d')
  - Risk-taking (B)

96 months). The tests appear to be working well in this population (Davidson *et al*., 1995a), and attrition at evaluations of the cohort over the first 66 months was minimal (738 at 19 months, 736 at 29 months, and 711 at 66 months). All of the endpoints evaluated to date in Seychelles are listed in Table 1.

The results of primary and some secondary analyses through the 66-month evaluations have been reported (Myers *et al*., 1995c, d, 1997a, b; Davidson *et al*., 1995b, 1998, in press; Axtell *et al*., 1998). Developmental milestones were specifically examined since they were a key endpoint from the Iraq study (Marsh *et al*., 1987). In Seychelles there was no significant delay in milestone achievement (Myers *et al*., 1997a). A similar result has been reported from the Faroe Islands (Grandjean *et al*., 1995). A number of associations between both prenatal and postnatal indices of MeHg exposure and endpoints have been found in the Seychelles (Table 2). Birth weight was associated with prenatal exposure to MeHg. In the reduced model the gender interaction was statistically significant (0.05), and both slopes were positive. The slope (SE) for males was 0.015 (0.005) and for females 0.0008 (0.005), but only the slope for males was significant ($P = 0.0038$). At 29 months prenatal mercury exposure was associated with decreasing activity in males on the Infant Behavior Record from the Bayley Scales of Infant Development (Davidson *et al*., 1995b). As prenatal exposure increased the activity level decreased. The behavior rating scale is a subjective assessment and the significance of this finding is unclear. Prenatal exposure was associated with effect modification as described by Bellinger (2000) at the 19-month evaluation (Davidson *et al*., 1999). Children had higher scores on the BSID-MDI when their caregiver IQ fell in a higher category. This relationship was present at several levels of family income. At 66 months associations were present with prenatal and postnatal mercury exposure, but all were in a beneficial direction (Davidson *et al*., 1998). The total score from the Preschool Language Scale (PLS) was associated with both prenatal and postnatal exposure indices. Postnatal exposure was associated with improvements in the Applied Problems subtest from the Woodcock–Johnson Achievement Test and the error score from the Bender Gestalt Test, but the latter was present in males only.

The SCDS 9-year reevaluation of the Main Study cohort is now complete. It included a 4-h-long battery of neuropsychological tests given in two separate sessions. Many of the tests used were the same or similar to those in the Faroe Islands study (Grandjean *et al*., 1997). The data are currently being analyzed.

TABLE 2

Associations Found between Prenatal and Methylmercury Exposure and Endpoints in the Seychelles Child Development Study during the First 5.5 Years of Life

Cohort	Age	Test	Exposure	Males	Females	Reference
Main	Birth	Birth weight	Prenatal	B	NE	NIEHS Conference on MeHg 11/99 Available at www.niehs.nih.gov
	19 months	Enhanced BSID-MDI with increasing MeHg exposure in higher caregiver IQ groups at several levels of family income	Prenatal	B	B	Davidson *et al.*, 1999
	29 months	BSID-IBR—Activity[a]	Prenatal	?	NE	Davidson *et al.*, 1995b
	66 months	PLS—Total score	Prenatal	B[b]	B[b]	Davidson *et al.*, 1998
		PLS—Total score	Postnatal	B[b]	B[b]	Davidson *et al.*, 1998
		W–J Applied Problems	Postnatal	B[b]	B[b]	Davidson *et al.*, 1998
		Bender–Gestalt—Errors	Postnatal	B	NE	Davidson *et al.*, 1998
Pilot	96 months	Boston Naming Test	Prenatal	B	NE	Davidson *et al.*, 2000
		Beery–Buktenka (VMI)	Prenatal	B		Davidson *et al.*, 2000
		Grooved Pegboard	Prenatal			Davidson *et al.*, 2000
		Preferred hand		B	A	
		Nonpreferred hand		B	NE	

Note. A, adverse; B, beneficial; NE, no effect; BSID, Bayley Scales of Infant Development; MDI, Mental Developmental Index; IBR, Infant Behavior Record; W–J, Woodcock–Johnson Test of Achievement; PLS, Preschool Language Scale; MSCD, McCarthy Scales of Children's Development; GCI, MSCD general cognitive index, VMI, Visual motor integration (analogous to Bender).

[a]Activity during the testing session was rated by the tester. For males, activity decreased with increasing maternal MeHg. No association was seen for females. It is unclear whether this result was adverse or beneficial.

[b]Single slope. Gender × MeHg interaction was not significant.

In addition to clinical studies, we have sought pathological evidence that might suggest that MeHg exposure from fish consumption had adverse effects on the nervous system. Earlier work from the U of R indicated that MeHg exposure at measured brain tissue levels below 2 ppm might affect the central nervous system of animals (Rodier *et al*., 1984; Sager *et al*., 1984). Consequently, we examined neuropathological material from stillbirths and natural deaths in Seychelles (Lapham *et al*., 1995). No association between the mercury content of brain and histopathological changes was found. However, associations were found between the mercury content of various biological tissues (Cernichiari *et al*., 1995b). The concentration of mercury in six brain regions was highly correlated with hair mercury levels.

To date in the SCDS we have found no adverse associations between either prenatal or postnatal exposure from fish consumption and neurological, developmental, or neuropathological endpoints. The SCDS is continuing to follow the pilot and main cohorts as they mature and is testing the children with increasingly sensitive test measures.

DISCUSSION

The results of clinical studies carried out following the MeHg poisoning in Iraq confirmed the neurological deficits reported from Japan and provided data on the level of exposure associated with neurological and developmental findings. These data raised concern that exposure to MeHg from fish consumption might be associated with adverse effects. However, our subsequent studies in Samoa, Peru, and the Seychelles have consistently found no evidence to support this hypothesis. Our research has not identified any adverse associations between MeHg exposure from fish consumption and clinical symptoms or signs. However, our studies of both prenatal and postnatal measures of MeHg exposure from fish consumption in Seychellois children have been associated with beneficial effects.

These results differ from those found in a similar epidemiologic study being carried out in the Faroe Islands (Grandjean *et al*., 1997, 1998). The Faroe study reported adverse associations between prenatal MeHg exposure and tests of memory, attention, language, motor function, and visual spatial perception. There are many similarities between these two epidemiological studies. Both are double-blind studies examining large cohorts with prenatal dietary exposure to MeHg. However, there are also substantial differences including the data analysis. Table 3 outlines some of the important differences between these studies, and one or more of these may explain the differing conclusions.

Exposure to MeHg from fish consumption differs in a number of important ways from MeHg poisoning. With fish consumption the exposure is to very small amounts of MeHg over a long time period. The concentration of MeHg present in oceanic fish in the Seychelles averages about 0.3 ppm. In North America MeHg levels in fish are generally similar. However, ocean fish from polluted waters such as those at Minamata Bay in Japan had MeHg levels as high as 40 ppm, and freshwater fish from North America have been reported with concentrations as high as 10 ppm (Swedish Expert Group 1971; Shephard, 1976). The small amount of MeHg consumed with each exposure and spreading the exposure over a longer time period may alter the way the human body handles it. Clarkson (1995) has suggested that the liver may excrete or detoxify small amounts, but may be unable to handle larger amounts. Exposure to MeHg in conjunction with other components of fish such as selenium and amino acids may also

TABLE 3
Differences between the Seychelles and Faroe Island Epidemiologic Studies of Dietary Prenatal MeHg Exposure

Issue	Seychelles	Faroe Islands
Genetic/ethnic composition	African, Asian, and mixed	Scandinavian
Source of exposure to MeHg	Fish	Pilot whale and fish
Exposure to other toxins	None known	PCBs, possibly others
Measure of exposure	Maternal hair	Cord blood and maternal hair
Age at evaluation	6.5, 19, 29, 66, and 96 months	7 years
Exclusions	Medical problems highly associated with developmental delay	None
Covariates used in this study, but not in the other	7	4
Composition of test battery	Neurological Developmental Psychological	Neurological Neuropsychological Neurophysiological

influence its potential toxicity in other ways. Selenium may decrease any potentially toxic effects and amino acids may compete with MeHg for transport into the brain (Clarkson, 1995; WHO, 1990).

In addition, fish consumption may provide important nutrients and is an important source of calories and protein to many populations around the world, especially indigenous ones. Long-chain polyunsaturated fatty acids, mainly docosahexanoic and other omega 3 fatty acids, are high in fish and believed to be important in brain development (Innis, 1991, Uauy-Dagach and Valenzuela, 1996). Omega 3 fatty acids may simply improve brain performance enough that any adverse effects from this level of MeHg exposure are not apparent. Fish consumption has also been reported to have beneficial effects at later ages (Kromhout *et al*., 1985; Daviglus *et al*., 1997). We agree with Egeland and Middaugh (1997) that the benefits, alternatives, and possible risks of fish consumption should be weighed carefully before public health actions are taken that might reduce fish consumption.

SUMMARY

The clinical studies that our team has carried out in Samoa, Peru, and the Seychelles provide no evidence that consuming large quantities of fish is associated with adverse effects on adults or children. Our studies do show an association between test performance and MeHg exposure, but it is enhanced performance associated with both prenatal and postnatal exposure. Since MeHg is clearly neurotoxic there must be some factor in fish that covaries with exposure to account for improved performance. The absence of adverse effects is reassuring in terms of any significant risk to the child from prenatal or postnatal MeHg exposure from fish consumption. However, we are continuing to study the Seychelles cohorts with increasingly sensitive and sophisticated tests at older ages to identify associations that might appear as they mature. Restricting fish consumption without clear justification could potentially adversely affect children's development. This is especially true in societies where fish is the primary source of protein.

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REFERENCES

Al-Damluji, S. F. (1976). Organomercury poisoning in Iraq: History prior to the 1971–1972 outbreak. Conference on intoxication due to alkylmercury-treated seed, Baghdad, Iraq, 9–13 September, 1974. *Bull. WHO* **53** (Suppl.), 11–14.

Al-Tikriti, K., and Al-Mufti, A. W. (1976). An outbreak of organomercury poisoning among Iraqi farmers. Conference on intoxication due to alkylmercury-treated seed, Baghdad, Iraq, 9–13 September, 1974. *Bull. WHO* **53** (Suppl.), 15–21.

Amin-Zaki, L., Elhassani, S., Majeed, M. A., Clarkson, T. W., Doherty, R. A., and Greenwood, M. R. (1974a). Intra-uterine methylmercury poisoning in Iraq. *Pediatrics* **54,** 587–595.

Amin-Zaki, L., Elhassani, S., Majeed, M. A., Clarkson, T. W., Doherty, R. A., and Greenwood, M. R. (1974b). Studies of infants postnatally exposed to methylmercury. *J. Pediatr.* **85,** 81–84.

Amin-Zaki, L., Elhassani, S., Majeed, M. A., Clarkson, T. W., Doherty, R. A., and Greenwood, M. R. (1974c). Prenatal methylmercury poisoning in Iraq. *In* "Proceedings of the First International Mercury Conference," Vol. II, pp. 319–325. Fabrica National de Moneda U Timbre, Madrid, Spain.

Amin-Zaki, L., Elhassani, S., Majeed, M. A., Clarkson, T. W., Doherty, R. A., Greenwood, M. R., and Giovanoli-Jakubczak, T. (1976). Prenatal methylmercury poisoning in Iraq. *Am. J. Dis. Child.* **130,** 1070–1076.

Amin-Zaki, L., Majeed, M. A., Clarkson, T. W., and Greenwood, M. R. (1978). Methylmercury poisoning in Iraqi children: Clinical observations over two years. *Br. Med. J.* **1,** 613–616.

Amin-Zaki, L., Majeed, M. A., Elhassani, S. B., Clarkson, T. W., Greenwood, M. R., and Doherty, R. A. (1979). Prenatal methylmercury poisoning: Clinical observations over five years. *Am. J. Dis. Child.* **133,** 172–177.

Amin-Zaki, L., Elhassani, S. B., Majeed, M. A., Clarkson, T. W., Doherty, R. A., and Greenwood, M. R. (1980). Methylmercury poisoning in mothers and their suckling infants. *In* "Mechanisms of Toxicity and Hazard Evaluation" (B. Holmsted, R. Lauwerys, M. Mercier, and M. Roberfroid, Eds.), pp. 75–78. Elsevier/North-Holland Biomedical Press, Amsterdam.

Amin-Zaki, L., Majeed, M. A., Greenwood, M. R., Elhassani, S. B., Clarkson, T. W., and Doherty, R. A. (1981). Methylmercury poisoning in the Iraqi suckling infant: A longitudinal study over five years. *J. Appl. Toxicol.* **1,** 210–214.

Axtell, C. D., Myers, G. J., Davidson, P. W., Choi, A. L., Cernichiari, E., Sloane-Reeves, J., Shamlaye, C., Cox, C., and Clarkson, T. W. (1998). Semiparametric modeling of age at achieving developmental milestones after prenatal exposure to methylmercury in the Seychelles Child Development Study. *Environ. Health Perspect.* **106**(9), 559–564.

Bakir, F., Damluji, S. F., Amin-Zaki, L., Murtadha, M., Khalidi, A., Al-Rawi, N. Y., Tikriti, S., Dahir, H. I., Clarkson, T. W., Smith, J. C., and Doherty, R. A. (1973). Methylmercury poisoning in Iraq. *Science* **181,** 230–241.

Bakir, F., Al-Khalidi, A., Clarkson, T. W., and Greenwood, M. R. (1976). Clinical observations on treatment of alkylmercury poisoning in hospital patients. Conference on intoxication due to alkylmercury-treated seed, Baghdad, Iraq, 9–13 September 1974. WHO, Geneva. *Bull. WHO* **53** (Suppl.), 87–92.

Bellinger, D. (2000). Effect modification in epidemiologic studies of low-level neurotoxicant exposures and health outcomes. *Neurotoxicol. Teratol*. **22,** 133–140.

Cernichiari, E., Toribara, T. Y., Liang, L., Marsh, D. O., Berlin, M. W., Myers, G. J., Cox, C., Shamlaye, C. F., Choisy, O., Davidson, P., and Clarkson, T. W. (1995a). The biological monitoring of mercury in the Seychelles study. *Neurotoxicology* **16**(4), 613–628.

Cernichiari, E., Brewer, R., Myers, G. J., Marsh, D. O., Lapham, L. W., Cox, C., Shamlaye, C. F., Berlin, M., Davidson, P. W., and Clarkson, T. W. (1995b). Monitoring methylmercury during pregnancy: Maternal hair predicts fetal brain exposure. *Neurotoxicology* **16**(4), 705–710.

Clarkson, T. W., and Rothstein, A. (1964). The excretion of volatile mercury by rats injected with mercuric salts. *Health Phys.* **10,** 1115–1121.

Clarkson, T. W., Rothstein, A., and Sutherland, R. (1965). The mechanism of action of mercurial diuretics in rats: The metabolism of 203 Hg-labeled chlormerodrin. *Br. J. Pharmacol. Chemother.* **24,** 1–13.

Clarkson, T. W., and Magos, L. (1966). Studies on the binding of mercury in tissue homogenates. *Biochem. J.* **9,** 62–70.

Clarkson, T. W., and Magos, L. (1967). The effect of sodium maleate on the renal deposition and excretion of mercury. *Br. J. Pharmacol. Chemother.* **31,** 560–567.

Clarkson, T. W., and Greenwood, M. R. (1968). Simple and rapid determination of mercury in urine and tissues by isotope exchange. *Talanta* **115,** 54–555.

Clarkson, T. W., Smith, J. C., and Bakir, F. (1974). A preliminary report on a population that received a heavy exposure to methylmercury. *In* "Trace Substances in Environmental Health" (D. D. Hemphill, Ed.), pp. 127–135. Univ. of Missouri, Columbia.

Clarkson, T. W., Amin-Zaki, L., and Al-Tikriti, S. (1976). An outbreak of methylmercury poisoning due to consumption of contaminated grain. *Fed. Proc.* **35**(12), 2395–2399.

Clarkson, T. W., Magos, L., Cox, C., Greenwood, M. R., Amin-Zaki, L., Majeed, M. A., and Damluji, S. F. (1981a). Tests of efficacy of antidotes for removal of methylmercury in human poisonings during the Iraq outbreak. *J. Pharmacol. Exp. Ther.* **218**(10), 74–83.

Clarkson, T. W., Cox, C., Mash, D. O., Myers, G. J., Al-Tikriti, S., Amin-Zaki, L., and Dabbagh, A. R. (1981b). Dose–response relationships for adult and prenatal exposures to methylmercury. *In* "Measurement of Risk" (G. G. Berg and H. D. Maillie, Eds.), pp. 111–130. Plenum, New York.

Clarkson, T. W. (1995). Environmental contaminants in the food chain. *Am. J. Clin. Nutr.* **61** (Suppl.), 682S–686S.

Cox, C., Clarkson, T. W., Marsh, D. O., Amin-Zaki, L., Tikriti, S., and Myers, G. J. (1989). Dose–response analysis of infants prenatally exposed to methylmercury. An application of a single compartment model to single-strand hair analysis. *Environ. Res.* **31,** 640–649.

Cox, C., Marsh, D. O., Myers, G. J., and Clarkson, T. W. (1995). Analysis of data on delayed development from the 1971–1972 outbreak of methylmercury poisoning in Iraq: Assessment of influential points. *Neurotoxicology* **16**(4), 727–730.

Davidson, P. W., Myers, G. J., Cox, C., Shamlaye, C. F., Sloane-Reeves, J., Cernichiari, E., Marsh, D., Clarkson, T. W., and Tanner, M. A. (1994). Measuring neurodevelopmental outcomes of young children following prenatal dietary low dose methyl mercury exposures. *Environ. Sci.* **3**(1), 55–65.

Davidson, P. W., Myers, G. J., Cox, C., Shamlaye, C. F., Choisy, O., Sloane-Reeves, J., Cernichiari, E., Marsh, D. O., Berlin, M., Tanner, M. A., and Clarkson, T. W. (1995a). Neurodevelopmental test selection, administration and performance in the main Seychelles Child Development study. *Neurotoxicology* **16**(4), 665–676.

Davidson, P. W., Myers, G. J., Cox, C., Shamlaye, C. F., Marsh, D. O., Tanner, M. A., Berlin, M., Sloane-Reevesm, Cernichiari, E., Choisy, O., Choi, A., and Clarkson, T. W. (1995b). Longitudinal neurodevelopmental study of Seychellois children following *in utero* exposure to methylmercury from maternal fish ingestion: Outcomes at 19 and 29 months. *Neurotoxicology* **16,** 677–799.

Davidson, P. W., Myers, G. J., Cox, C., Axtell, C., Shamlaye, C., Sloane-Reeves, J., Cernichiari, E., Needham, L., Choi, A., Wang, Y., Berlin, M., and Clarkson, T. W. (1998). Effects of prenatal and postnatal methylmercury exposure from fish consumption on neurodevelopment. *J. Am. Med. Assoc.* **280**(8), 701–707.

Davidson, P. W., Myers, G. J., Shamlaye, C., Cox, C., Gao, P., Axtellm, C., Morris, D., Sloane-Reeves, J., Cernichiari, E., Choi, A., Palumbo, D., and Clarkson, T. W. (1999). Association between prenatal exposure to methylmercury and developmental outcomes in Seychellois children: Effect modification by social and environmental factors. *Neurotoxicology.* **20**(5), 833–842.

Davidson, P. W., Palumbo, D., Myers, G. J., Cox, C., Shamlaye, C. F., Sloan-Reeves, J., Cernichiari, E., Wilding, G. E., and Clarkson, T. W. (2000). Neurodevelopmental outcomes of seychellois children from the pilot cohort at 108 months following prenatal exposure to methylmercury from a maternal fish diet. *Environ. Sci.,* in press.

Daviglus, M. L., Stamler, J., Orencia, A. J., Dyer, A. R., Liu, K., Greenland, P., Walsh, M. K., Morris, D., and Shekelle, R. B. (1997). Fish consumption and the 30-year risk of fatal myocardial infarction. *N. Engl. J. Med.* **336,** 1046–1053.

Davis, L. E., Kornfeld, M., Mooney, H. S., Feidler, K. J., Haaland, K. Y., Orrison, W. W., Cernichiari, E., and Clarkson, T. W. (1994). Methylmercury poisoning: Long-term clinical, radiological, toxicological, and pathological studies of an affected family. *Ann. Neurol.* **35,** 680–688.

Egeland, G. M., and Middaugh, J. P. (1997). Balancing fish consumption benefits with mercury exposure. *Science* **278,** 1904–1905.

Elhassani, S., Amin-Zaki, L., Majeed, M. A., Clarkson, T. W., Doherty, R. A., Greenwood, M. R., and Kilpper, R. W. (1978). Exchange transfusion treatment of methylmercury-poisoned children. *J. Environ. Sci. Health* **13**(1), 63–80.

Englender, S. J., Atwood, R. G., Landrigan, P. J., Clarkson, T. W., Greenwood, M. R., and Smith, J. C. (1980). Organic mercury exposure from fungicide contaminated eggs. *Arch. Environ. Health* **35**(4), 224–228.

Fagan, D. G., Prichard, J. S., Clarkson, T. W., and Greenwood, M. R. (1977). Organ mercury levels in infants with omphaloceles treated with organic mercurial antiseptic. *Arch. Dis. Child.* **52,** 962–964.

Gotelli, C. A., Astolfi, E., Cox, C., Cernichiari, E., and Clarkson, T. W. (1985). Early biochemical effects of an organic mercury fungicide on infants: "Dose makes the poison." *Science* **22,** 638–640.

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

Grandjean, P., Weihe, P., and White, R. F. (1995). Milestone development in infants exposed to methylmercury from human milk. *Neurotoxicology* **16,** 27–34.

Grandjean, P., Weihe, P., White, R. F., Debes, F., Araki, S., Yokoyama, K., Murata, K., Sorensen, N., Dahl, R., and Jorgensen, P. J. (1997). Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. *Neurotoxicol. Teratol.* **19,** 417–428.

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

Greenwood, M. R., Dhahir, P., Clarkson, T. W., Farrant, J. P., Chartrand, A., and Khayat, A. (1977). Epidemiological experiences with the Magos reagents in the determination of different forms of mercury in biological samples by flameless atomic absorption. *J. Anal. Toxicol.* **1**(6), 265–269.

Greenwood, M. R., Clarkson, T. W., Doherty, R. A., Gates, A. H., Amin-Zaki, L., Elhassani, S., and Majeed, M. A. (1978). Blood clearance half-times in lactating and non-lactating members of a population exposed to methylmercury. *Environ. Res.* **16,** 48–54.

Greenwood, M. R. (1985). Methylmercury poisoning in Iraq. An epidemiological study of the 1971–1972 outbreak. *J. Appl. Toxicol.* **5**(3), 148–159.

Gunderson, V. M., Grant-Webster, K. S., Burbacher, T. M., and Mottet, N. K. (1988). Visual recognition memory deficits in methylmercury-exposed Macaca fasicularis infants. *Neurotoxicol. Teratol.* **10,** 373–379.

Innis, S. M. (1991). Essential fatty acids in growth and development. *Progress Lipid Res.* **30,** 39–103.

Kershaw, T. G., Clarkson, T. W., and Dhahir, P. H. (1980). The relationship between blood levels and dose of methylmercury in man. *Arch. Environ. Health* **35**(1), 28–36.

Kjellstrom, T., Kennedy, P., Wallis, S., and Mantell, C. (1986). Physical and mental development of children with prenatal exposure to mercury from fish. Stage 1. Preliminary tests at age 4. *Solna*, *National Swedish Environmental Board*. Report No. 3080, pp. 1–96.

Kromhout, D., Bosschieter, E. B., and Coulander, C. L. (1985). The inverse relation between fish consumption and 20-year mortality from coronary heart disease. *N. Engl. J. Med.* **312,** 1205–1209.

Lapham, L. W., Cernichiari, E., Cox, C., Myers, G. J., Baggs, R. B., Brewer, R., Shamlaye, C. F., Davidson, P. W., and Clarkson, T. W. (1995). An analysis of autopsy brain tissue from infants prenatally exposed to methylmercury. *Neurotoxicology* **16**(4), 689–704.

Magos, L., Tuffery, A. A., and Clarkson, T. W. (1964). Volitalization of mercury by bacteria. *Br. J. Ind. Med.* **21,** 294–298.

Magos, L., Bakir, F., Clarkson, T. W., Al-Jawad, A. M., and Al-Soffi, M. H. (1976). Tissue levels of mercury in autopsy specimens of liver and kidney. *Bull. World Health Org.* **53,** 93–96.

Marsh, D. O., Turner, M., Smith, J. C., Choi, W. J., and Clarkson, T. W. (1974). Methyl mercury in human populations eating large quantities of marine fish. II. American Samoa: Cannery workers and fishermen. *In* "Proc. First International Mercury Conf., May 1974, Barcelona," Vol. II, pp. 235–239. Fabrica National de Moneda y Timbre, Madrid, Spain.

Marsh, D. O., Myers, G. J., Clarkson, T. W., Amin-Zaki, L., and Tikriti, S. (1977). Fetal methylmercury poisoning: New data on clinical and toxicological aspects. *Trans. Am. Neurol. Assoc.* **102,** 1–3.

Marsh, D. O., Myers, G. J., Clarkson, T. W., Amin-Zaki, L., Tikriti, S., and Majeed, M. A. (1980). Fetal methylmercury poisoning: Clinical and toxicological data on 29 cases. *Ann. Neurol.* **7,** 348–353.

Marsh, D. O., Myers, G. J., Clarkson, T. W., Amin-Zaki, L., Tikriti, S., and Majeed, M. A. (1981). Dose–response relationship for human fetal exposure to methylmercury. *Clin. Toxicol.* **18,** 1311–1318.

Marsh, D. O., Clarkson, T. W., Cox, C., Myers, G. J., Amin-Zaki, L., and Al-Tikriti, S. (1987). Fetal methylmercury poisoning. *Arch. Neurol.* **44,** 1017–1022.

Marsh, D. O. (1994). Organic mercury: Clinical and neurotoxicological aspects. *In* "Handbook of Clinical Neurology, Interactions of the Nervous System" (F. A. deWolff, Ed.), Part 1, Vol. 20 (64), pp. 413–429. Elsevier, Amsterdam.

Marsh, D. O., Clarkson, T. W., Myers, G. J., Davidson, P. W., Cox, C., Cernichiari, E., Tanner, M. A., Lednar, W., Shamlaye, C. F., Choisy, O., Hoareau, C., and Berlin, M. (1995a). The Seychelles study of fetal methylmercury exposure and child development: Introduction. *Neurotoxicology* **16**(4), 583–596.

Marsh, D. O., Turner, M. D., Smith, J. C., Allen, P., and Richadale, N. (1995b). Fetal methylmercury study in a Peruvian fish-eating population. *Neurotoxicology* **16,** 717–726.

Matthews, A. D. (1983). Mercury content of commercially important fish of the Seychelles, and hair mercury levels of a selected part of the population. *Environ. Res.* **30,** 305–312.

Myers, G. J., Marsh, D. O., Cox, C., Davidson, P. W., Shamlaye, C. F., Tanner, M. A., Choi, A., Cernichiari, E., Choisy, O., and Clarkson, T. W. (1995a). A pilot neurodevelopment study of Seychellois children following *in utero* exposure to methylmercury from a maternal fish diet. *Neurotoxicology* **16**(4), 629–638.

Myers, G. J., Davidson, P. W., Cox, C., Shamlaye, C. F., Tanner, M. A., Choisy, O., Sloane-Reeves, J., Marsh, D. O., Cernichiari, E., Choi, A., Berlin, M., and Clarkson, T. W. (1995b). Neurodevelopmental outcomes of Seychellois children sixty-six months after *in utero* exposure to methylmercury from a maternal fish diet: Pilot study. *Neurotoxicology* **16**(4), 639–652.

Myers, G. J., Marsh, D. O., Davidson, P. W., Cox, C., Shamlaye, C. F., Tanner, M. A., Choi, A., Cernichiari, E., Choisy, O., and Clarkson, T. W. (1995c). Main neurodevelopmental study of Seychellois children following *in utero* exposure to methylmercury from a maternal fish diet: Outcome at six months. *Neurotoxicology* **16**(4), 653–664.

Myers, G. J., Davidson, P. W., Cox, C., Shamlaye, C. F., Tanner, M. A., Marsh, D. O., Cernichiari, E., Lapham, L. W., Berlin, M., and Clarkson, T. W. (1995d). Summary of the Seychelles Child Development Study on the relationship of fetal methylmercury exposure to neurodevelopment. *Neurotoxicology* **16**(4), 711–716.

Myers, G. J., Davidson, P. W., Shamlaye, C. F., Axtell, C. D., Cernichiari, E., Choisy, O., Choi, A., Cox, C., and Clarkson, T. W. (1997a). Effects of prenatal methylmercury exposure from a high fish diet on developmental milestones in the Seychelles Child Development Study. *Neurotoxicology* **18,** 819–830.

Myers, G. J., Davidson, P. W., Cox, C., Shamlaye, C. F., Choisy, O., Cernichiari, E., Choi, A., Sloane-Reeves, J., Axtell, C., Gao, P., and Clarkson, T. W. (1997b). The Seychelles Child Development Study: Results and new directions through twenty-nine months. *Water Air Soil Pollut.* **97,** 53–61.

Nierenberg, D. W., Nordgren, R. E., Chang, M. B., Siegler, R. W., Blayney, M. B., Hochberg, F., Toribara, T. Y., Cernichiari, E., and Clarkson, T. W. (1998). Delayed cerebellar disease and death after accidental to dimethylmercury. *N. Engl. J. Med.* **338,** 1672–1676.

Phelps, R. W., Clarkson, T. W., Kershaw, T. G., and Wheatley, B. (1980). Interrelationships of blood and hair mercury concentrations in a North American population exposed to methylmercury. *Arch. Environ. Health* **35,** 161–168.

Rodier, P. M., Aschner, M., and Sager, P. R. (1984). Mitotic arrest in the developing CNS after prenatal exposure to methylmercury. *Neurobehav. Toxicol. Teratol.* **6,** 379–385.

Rustam, H., and Hamdi, T. (1974). Methyl mercury poisoning in Iraq. A neurologial study. *Brain* **97**(3), 500–510.

Rustam, H., Von Burg, R., Amin-Zaki, L., and Elhassani, S. (1975). Evidence for a neuromuscular disorder in methylmercury poisoning: Clinical and electrophysiological findings in moderate to severe cases. *Arch. Environ. Health* **30,** 190–195.

Sager, P. R., Aschner, M., and Rodier, P. M. (1984). Persistent, differential alterations in developing cerebellar cortex of male and female mice after methylmercury exposure. *Dev. Brain Res.* **12,** 1–11.

Shamlaye, C. F., Marsh, D. O., Myers, G. J., Cox, C., Davidson, P. W., Choisy, O., Cernichiari, E., Choi, A., Tanner, M., and Clarkson, T. W. (1995). The Seychelles Child Development Study on neurodevelopmental outcomes in children following *in utero* exposure to methylmercury from a maternal fish diet: Background and demographics. *Neurotoxicology* **16**(4), 597–612.

Shephard, D. A. E. (1976). Methyl mercury poisoning in Canada. *Can. Med. Assoc. J.* **114,** 110–114.

Smith, J. C., Farris, F. F., and Von Burg, R. (1976). Chemical type of mercury in patients in the outbreak of organomercury poisoning in Iraq. *Bull. WHO* **53,** 61–64.

Swedish Expert Group. (1971). Methylmercury in fish. A toxicological–epidemiological evaluation of risks. *Nord. Hyg. Tidskr.* **4**(Suppl.), 19–364.

Turner, M. D., Marsh, D. O., Rubio, C. E., Chiriboga, J., Chiriboga, C., Smith, J. C., and Clarkson, T. W. (1974). Methylmercury in populations eating large quantities of marine fish. I. Northern Peru. *In* "Proc. First International Mercury Conf., May 1974, Barcelona," Vol. II, pp. 229–234. Fabrica National de Moneda y Timbre, Madrid, Spain.

Turner, M. D., Marsh, D. O., Smith, J. C., Clarkson, T. W., Inglis, J. B., Rubino, E. C., Chiriboga, J., and Chiriboga, C. C. (1980). Methylmercury in populations eating large quantities of marine fish. *Arch. Environ. Health* **35,** 367–378.

Uauy-Dagach, R., and Valenzuela, A. (1996). Marine oils: The health benefits of n-3 fatty acids. *Nut. Rev.* **54**(110), S102–S108.

Von Burg, R., and Rustam, H. (1974a). Conduction velocities in methylmercury poisoned patients. *Bull. Environ. Contam. Toxicol.* **12**(1), 81–85.

Von Burg, R., and Rustam, H. (1974b). Electrophysiological investigations of methylmercury intoxication in humans. Evaluation of peripheral nerve by conduction velocity and electromyography. *Electroencephalogr. Clin. Neurophysiol.* **37**(4), 381–392.

Wheatley, B., Barbeau, A., Clarkson, T. W., and Lapham, L. (1979). Methylmercury poisoning in Canadian Indians—The elusive diagnosis. *Can J. Neurol. Sci.* **6**(4), 417–422.

World Health Organization. (1990). Environmental Health Criteria 101 Methylmercury. Geneva, Switzerland, pp. 1–144.