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Neurobehavioral dysfunction
as possible sentinel
of methylmercury exposure

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Methylmercury neurotoxicity

Abstract

The main concern regarding methylmercury neurotoxicity relates to adverse effects on the brain during development. Many environmental chemicals may act as developmental neurotoxicants, but solid documentation from epidemiological studies exists only on methylmercury, lead, and polychlorinated biphenyls (PCBs). Neurobehavioral tests may reveal subtle dysfunctions, but the tests chosen must be valid and appropriate for the setting. In a prospective study in the Faroe Islands, the main neuropsychological functions affected by prenatal methylmercury exposure were attention, language and memory. Deficits in visuospatial function were mainly related to postnatal exposures. These associations were stable after adjustment for confounders and exclusion of the children with the highest exposures to methylmercury and PCBs. Tests with good psychometric properties were more likely to show an association with mercury exposure. Greater sensitivity was also seen with tests administered by specialized academic staff rather than a trained technician. Despite highly significant effects on nervous system function, the deficits were subtle, and mercury exposure explained only a small part of the variation. Available evidence suggests that neurotoxicity may have severe implications on public health, but current methods are not amenable to application as sentinels of adverse health effects in environmental health surveillance.

Key words: Assessment, risk Child, preschool Environmental pollution Food contamination Neuropsychological tests Prenatal exposure delayed effects

Environmentally-induced neurotoxicity is an important public-health concern, as amply illustrated by the adverse effects of developmental lead exposure (Needleman, 1990). Many other substances are neurotoxic to humans (Kimbrough et al., 1989), but the overall impact of these exposures is unknown. An important question in research, diagnosis and health surveillance is to which degree the neurotoxic effects of environmental pollutants are specific and whether pathognomonic features exist.

With regard to methylmercury, the critical adverse effect is neurotoxicity, and pregnant women and small children constitute the most vulnerable group (USEPA, 1997). To ascertain the health impact of environmental methylmercury exposures, the question is therefore whether its adverse health effects can be recognized by specific diagnostic techniques. In considering this issue, one must first examine the types of effects caused by neurotoxicants in general, the characteristics of developmental neurotoxicity, and the sensitivity of tests used to determine neurobehavioral deficits. Based on this information, the specificity of the profile of methylmercury-induced neurotoxicity and its usefulness as sentinel, i.e., effect biomarker, will then be addressed.

Clinical appearance of human neurotoxicity

Of the organ systems adversely affected by environmental chemicals, the nervous system may be the most sensitive. This conclusion seems plausible, as a major role of the nervous system is to react to stimuli from the environment. Evidence to support this notion comes from a review of human intoxications caused by industrial chemicals (Kimbrough et al., 1989). When disregarding carcinogens, allergens and irritants, 220 substances have caused clinical signs of poisoning as

documented in published scientific papers. Although this number must necessarily be a vast underestimation of the true number of toxic chemicals in the environment, the relative distribution of organ system effects is illustrative. Thus, according to the evidence reviewed, a total of 149 chemicals (68%) have been verified to cause some type of neurotoxicity (Grandjean, Sandoe, and Kimbrough, 1991).

A large group of these substances is known to cause nonspecific central nervous system (CNS) inhibition with narcosis and coma. Another group of neurotoxicants may cause cholinergic symptoms. Among the persistent neurotoxicants, lead, methylmercury and polychlorinated biphenyls (PCBs) are known to cause developmental neurotoxicity. Although many other neurotoxicants can probably cause adverse effects in infants and children as well as adults, the main evidence available in this field relates to these three substances. Although not necessarily representative of all developmental neurotoxicants, a discussion of developmental neurotoxicity must therefore include comparisons of the evidence related to lead, methylmercury, and PCBs.

Because of the vulnerability of the nervous system, a large proportion of pollutants must be expected to possess neurotoxic properties. However, the nervous system, like other organs, does not necessarily express a sufficient number of different clinical profiles that would allow specific diagnosis of the causative exposures. Further, it must be recognized that the evidence at hand probably represents just a mere reflection of the true extent of environmentally-induced neurotoxicity.

A published case of human poisoning only reveals the outcome of one particular combination of variables that may influence the adverse effects. Cases examined may not have

received the same neurotoxicant exposure and would then represent different points on the dose-effect relationship curve. The time and duration of exposure as well as the time of examination may affect the clinical appearance. In addition, individual susceptibility may involve preexisting disease, enzyme deficiencies, or other intrinsic factors, which can play an important role in the variability of clinical manifestations. Also, patterns of intellectual skills and weaknesses differ among different individuals, and some people are inherently better, e.g., at verbally mediated tasks while others excel at visual-motor activities. Such differences are important because, at least at low dosages, exposure to neurotoxicants may affect the 'fragile skills' disproportionately to or earlier than robust abilities. Thus, caution should be exerted when extrapolating from individual case reports to the full range of exposure situations that could potentially produce clinical manifestations. Likewise, while epidemiological studies attempt to reveal overall tendencies in exposed populations, the heterogeneity of individual performance on neurobehavioral outcomes is likely to weaken the exposure associations. For these reasons, the available scientific evidence probably underestimates the true extent and the full picture of environmentally-induced neurotoxicity.

Characteristics of developmental neurotoxicity

Because of immaturity and ongoing development, the developing nervous system is much more vulnerable to injury from toxic agents than is the adult brain (Dobbing, 1968; Court et al., 1996). The development of the CNS involves a number of processes, which occur within a rigidly controlled time frame, and these processes must take place according to a complicated schedule and in a certain sequence. For this reason, windows of susceptibility to toxic interference can

occur that do not exist in the mature brain. If a developmental process in the brain is halted or inhibited, there is little chance for repair, and a small change may have substantial consequences if the time schedule is defused. As brain development continues well after birth, the increased vulnerability continues to some degree until the CNS is completely formed.

Although many processes in brain development have been reasonably well characterized, much remains to be understood about the adverse effects that may occur as a result of neurotoxicant exposures. Thus, environmental exposures can potentially affect neuron migration, axon growth, synapse formation and pruning, glia development and other processes, but the mechanisms of individual neurotoxicants are still poorly understood (Court et al., 1996). The growth of glia cells and myelination of axons continue for several years, and, at 6 years of age, the brain has already reached 80% of its final weight, although at this age the body of the child corresponds to only about 30% of the adult weight.

Studies in experimental teratology show that exposures to toxicants during early gestation is likely to cause miscarriage or malformations, while later exposures are more likely to cause functional damage (Court et al., 1996). With regard to neurotoxicity, the timing of exposure must therefore be considered in relation to the windows of susceptibility. However, this notion is of less relevance to persistent pollutants, as their prolonged retention in the body would cause a protracted internal exposure, thereby leading to long-term toxicity that may be difficult to relate to specific developmental processes.

The neuropathological literature on Minamata disease provides specific information on neuroanatomical correlates of methylmercury exposure in fetal life and early childhood that was sufficient to cause death. Prenatal exposure produces the most widespread brain damage,

childhood exposure produces widespread, though less extensive damage, and relatively focal neurological damage is found among exposed adults. Autopsy findings in children with exposure *in utero* included the following most significant findings (Choi, 1989): cortical (visual, auditory, and post- and pre-central) lesions, granular changes in the cerebellum, hypoplastic changes in the cytoarchitecture of the brain, neuronal malfunctioning, and remarkable reduction in brain size. Lesser findings included central granular atrophy and focal cortical lesions. In mild cases, the lesions tended to localize in the occipital lobe and postcentral gyrus. In other words, widespread brain damage was seen affecting even the cellular organization of the brain.

Sensitivity of neurobehavioral tests

This extensive damage associated with severe prenatal neurotoxicant exposure may be associated with deficits in many types of sensory, intellectual, behavioral and motor functioning. Such effects on CNS development would tend to be lasting, although shaped later on by maturation and compensation processes (Dietrich and Bellinger, 1994). On the other hand, effects incurred prenatally may not become apparent until the nervous system has matured sufficiently to express the dysfunctions. Simple milestone data and early developmental tests may therefore be too crude to reveal the full extent of neurobehavioral damage. In addition, poor correlation with neurobehavioral scores at older ages suggests that such tests have limited predictive validity with regard to subsequent cognitive development.

For these reasons, neurobehavioral tests must be selected that are appropriate for the developmental stage chosen for the examination. Because a detailed neurobehavioral examination may not be sufficiently informative until a child has reached school age, account

must be taken also of other factors that may affect neurological development during the interval between initiation of the toxic exposure and the diagnostic testing.

Prospective studies of children with prenatal exposure to neurotoxicants have reported decreased scores on omnibus tests, including developmental scales and intelligence scales (Gladden et al., 1988; Jacobson, Jacobson, and Humphrey, 1990; Kjellström, Kennedy, and Wallis, 1989; Needleman, 1990). These tests clearly possess some degree of sensitivity to widespread functional and neuroanatomical damage. As a variety of functions, abilities and behaviors may be affected, tests which are more specific in their measurement of cognitive processing abilities have some important advantages. They give investigators a glimpse into the specific cognitive deficits which may underlie or explain behavioral impairments and problems in living observed in exposed populations. They also provide insight into the possible underlying neuropathology existing in low-dose exposures for which neuropathological data will not be available.

The findings of delayed and persistent effects of fetal and early childhood exposure support the choice of early school age for testing. By age 6-7 years, the children have developed sufficiently to perform a wide variety of neurobehavioral tests, and they are capable of cooperating for most functional tasks. The sensitivity to neurotoxicant-induced deficits may therefore be the greatest at this developmental stage.

The criteria for tests selected as appropriate for this age must include a high diagnostic sensitivity, as demonstrated in prior developmental studies of neurotoxicant exposures, and high statistical sensitivity, with a wide range of scores possible without floor or ceiling effects, and acceptable test-retest reliability (White et al., 1994).

The diagnostic sensitivity of a given test will depend on the circumstances, including age, sex, culture, and socioeconomic setting. While the above criteria for test selection may be used for guidance in test selection, the sensitivity cannot be determined *a priori*. Thus, because of the limited experience from studies of methylmercury-exposed children, the specificity of cognitive functions measured and the diagnostic sensitivity must be judged from similar studies of children exposed to other neurotoxicants.

Likewise, the statistical sensitivity will depend on several factors, including the age of the children, and whether they have started school. For example, floor effects will be more likely with tests that are particularly difficult for the youngest children. Tests that provide a better separation between slight differences in performance would be more sensitive to subtle deficits in a population study.

In the Faroese birth cohort of 1,022 children, the prenatal methylmercury exposure level was determined from the mercury concentration in the cord blood. More than 90% of these children were examined at age 7 years (Grandjean et al., 1997). Use of physical examination tests did not reveal any clear-cut mercury-related abnormalities. However, mercury-related neuropsychological deficits were particularly pronounced in the domains of language, attention, and memory, and to a lesser extent in visuospatial and motor functions. The tests used had been translated into the native language and piloted to be appropriate for the Faroese setting, and the associations seemed not to be due to possible confounders, including maternal intelligence, parental education, paternal employment, daycare, and other socioeconomic factors. The associations also remained after exclusion of highly-exposed children with the highest exposures to mercury or PCBs (Grandjean et al., 1997; Budtz-Jørgensen et al., 1999).

When interpreting these results, the psychometric properties must be taken into account. The reaction time measure on the computer-assisted Continuous Performance Test showed a highly significant association with the prenatal mercury exposure. A total of 312 different reaction times were recorded in these children. Another measure of attention, the Digit Spans subtest of the Wechsler Intelligence Scale for Children-Revised (WISC-R) showed only nine different scores in this study. For comparison, a related neuropsychiatric test involved catching a ball with a diameter of 15 cm thrown from a distance of 3 m, where the result was scored as automatic, questionable or poor. Only eight children (1%) failed to catch the ball, so this clinical task may be too easy to reveal slight neurotoxic damages at this age. The different degrees of association with neurotoxicant exposure (Table 1) must therefore be considered in the light of the degree of separation of slight differences in performance. While all associations with mercury exposure levels were in the direction expected, the lowest p-value was obtained for the computer-assisted test.

The sensitivity may also be influenced by the circumstances of test administration. Thus, neuropsychological tests carried out with an interpreter in a school gymnasium on the island of Madeira showed no definite association with measures of methylmercury exposure in 7-year-old children, while significant correlations were obtained with evoked potential latencies recorded under optimal conditions (Murata et al., 1999). In the Faroese study, the Similarities subtest of the WISC-R was first administered by a clinical neuropsychologist. Because of time constraints the test was then transferred to a trained technician. The overall results showed no significant association with mercury exposure (Grandjean et al., 1997). However, the results obtained by the neuropsychologist were significantly associated with mercury exposure, while no such tendency

was seen when the test was carried out by the technician (Table 2). After adjustment for covariates, the children scored an average of one point less with the technician ($p = 0.004$). Apart from the Similarities test, all paper-and-pencil tests in this study were administered by the neuropsychologist only.

Specificity of methylmercury-related neurobehavioral dysfunctions

Congenital methylmercury poisoning appears like a spastic paresis syndrome, but the full clinical picture of Minamata disease includes paresthesias, constriction of visual fields, disordered handwriting, unsteady gait, intention tremor, impairment of hearing and speech, positive Romberg sign, mental deficiency, excessive sweating and hypersalivation (Harada, 1995). While constriction of visual fields may be almost pathognomonic for methylmercury poisoning, it is the combination of signs and symptoms that constitutes a specific pattern that allows an etiologic diagnosis. However, Minamata children with mental retardation thought to be of uncertain origin showed prenatal methylmercury exposures higher than in healthy controls but less than those seen in children recognized with congenital poisoning (Akagi et al., 1998).

Methylmercury poisoning is not a clinical entity that either appears in full scale or not at all. At lower exposure levels, less severe symptoms occur, and the clinical picture then becomes increasingly non-specific and difficult to distinguish from variations within normal range. Neuropsychological tests may be highly useful in diagnosing early brain damage and in revealing associations of subtle dysfunctions with an exposure. For example, IQ testing appears to offer some sensitivity to methylmercury toxicity at age 6 years (Kjellström, Kennedy, and

Wallis, 1989), although other omnibus tests used at younger ages have revealed none or only equivocal associations (Davidson et al., 1998). Since the neuroanatomical basis is known, specific tests that reflect cognitive processing abilities would have important advantages and might be more sensitive (White et al., 1994).

Most of the early studies on developmental lead neurotoxicity described the adverse effects in terms of IQ results (Needleman, 1990). However the neurotoxic effects depend on the lead exposure level and the stage of CNS development at the time of insult. The heterogeneity of outcomes of exposures at different stages of development in different population groups has resulted in inconsistencies in the outcomes identified in cross-sectional and retrospective studies. For example, the deficits of children who were younger than two years when poisoned were primarily in language function, whereas the deficits of the poisoned between the age of two and three years involved primarily visuospatial skills (Shaheen, 1984). However, as documented by prospective studies (Bellinger, Stiles, and Needleman 1992; Dietrich, Berger, and Succop, 1993), lead seems to affect several other specific brain functions, in particular attention and motor coordination.

Prenatal methylmercury exposure is mainly associated with dysfunctions in domains other than visuospatial skills (Grandjean et al., 1997). However, postnatal exposure shows a significant association with deficits on visuospatial function (Grandjean et al. 1999) (Table 3). This finding is in accordance with the profile of adverse effects in a family with severe methylmercury exposure (Davis et al., 1994). Thus the apparent predominance of visuospatial dysfunction in most lead-exposed children (Shaheen, 1984; Hansen et al., 1989) may be an effect of the timing of exposure rather than a reflection of a lead-specific damage.

In addition to the timing of developmental exposure, the possible occurrence of concomitant exposures to other neurotoxicants must be taken into regard. For example, the Faroese children were also exposed to persistent organochlorine substances. However, adjustment for the cord-PCB concentration affected only a few of the outcome variables showing a significant association with mercury (Grandjean et al., 1997). Also, in a second Faroese cohort, neonatal neurological function was significantly affected by the mercury concentration in cord blood, but not by PCB concentrations in maternal serum and in milk (Steuerwald et al., 2000).

There is little doubt that PCB exposure may cause neurotoxic effects (Gladen et al., 1988; Jacobson et al., 1990). However, the neurobehavioral variables may have been affected by prevalent exposures to methylmercury (Humphrey and Budd, 1996), and the degree of confounding is unknown. In addition, it is possible that other organochlorine pollutants may have affected the PCB-associated dysfunctions (Jacobson and Jacobson, 1997). On the other hand, seafood and freshwater fish contain essential nutrients, and some adverse effects on fetal brain development could also potentially be counteracted by a healthier maternal diet. These complex interactions are still poorly understood.

Prospects for sentinel profiles of neurotoxicity

There are important reasons to pursue environmental health surveillance in regard to neurotoxic effects. In the Faroese study, each doubling in prenatal mercury exposure corresponded to a decrease in performance of 5-10% of the standard deviation (Table 3), which would correspond to about 1 IQ point or a delay of one-to-two months in mental development (Grandjean et al., 1997). Because rapid development occurs at the age of school entry, such delays may be

important. Also, even small shifts in a measure of central tendency may be associated with large changes in the tails of the distribution. Although it is not yet known to what extent such delays are permanent, the experience with lead neurotoxicity suggests that the effects are likely to remain and may even become more apparent with time. Thus, a study of subjects who had suffered excess lead exposure as children clearly revealed that, 50 years later, they were less educated and less successful in life than a control group (White et al., 1993).

For surveillance purposes in environmental health, the ideal parameter to be recorded would be sufficiently specific to provide insight as to the identity of the pollutant that caused the event or change (Rutstein et al., 1983). Such sentinel environmental events are useful, e.g., for mapping mesothelioma cases as an indicator of asbestos exposure. However, specific diseases or events are only likely to exist for a small number of environmental hazards. In particular, neurotoxicity is not likely to be revealed by available health statistics on hospital discharge diagnoses or causes of death. Neurobehavioral tests are likely to reveal subtle neurobehavioral effects only in large epidemiological studies, and the correlation coefficients in Table 1 suggest that the neurotoxicant exposure explains only a few percent of the total variance of the test. Thus, current neurobehavioral tests do not lend themselves to being applied as sentinel indicators.

The absence of a true indicator of the societal impact of environmental neurotoxicants may have implications on the efforts spent on prevention of such exposures. Although true sentinels may not be identified, future research should address the long-term implications of neurotoxic effects caused by persistent pollutants.

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References

- Akagi, H., Grandjean, P., Takizawa, Y., and Weihe, P. 1998. Methylmercury dose estimation from umbilical cord concentrations in patients with Minamata disease. *Environ. Res.* **77**, 98-103.
- Bellinger, D.C., Stiles, K.M., and Needleman, H.L. 1992. Low-level lead exposure, intelligence and academic achievement: a long-term follow-up study. *Pediatr.* **316**, 1037-43.
- Budtz-Jørgensen, E., Keiding, N., Grandjean, P., White, R.F., and Weihe, P. 1999. Methylmercury neurotoxicity independent of PCB exposure (letter). *Environ. Health Perspect.* **107**, A236-7.
- Choi, B.H. 1989. The effects of methylmercury on the developing brain. *Progr. Neurobiol.* **32**, 447-470.
- Court, J., Cuomo, V., Eriksson, P., Perry, E., Pickles, A., Ray, D., Rodier, P., Stanton, M., Taylor, E., and Varga.Khadem, F. 1996. *Perinatal Developmental Neurotoxicity*. Report R4. Institute for Environment and Health, Leicester.
- 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. *JAMA* **280**, 701-707.
- Davis, L.E., Kornfeld, M., Mooney, H.S., Fiedler, 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.
- Dietrich, K.N., and Bellinger, D. The assessment of neurobehavioral development in studies of

the effects of prenatal exposure to toxicants. In: *Prenatal Exposure to Toxicants: Developmental Consequences*, pp. 57-85. (Needleman, H.L., and Bellinger D., Eds.). Johns Hopkins University Press, Baltimore.

Dietrich, K.N., Berger, O.G., and Succop, P.A. 1993. Lead exposure and the motor developmental status of urban 6 year-old children in the Cincinnati prospective study. *Pediatr.* **91**, 301-307.

Dobbing, J. 1968. Vulnerable periods in developing brain. In: *Applied Neurochemistry*, pp. 287-316. (Davison, A.N., and Dobbing, J., Eds.). Davis, Philadelphia.

Gladen, B.C., Rogan, W.J., Hardy, P., Thullen, J., Tingelstad, J., and Tully, M. 1988. Development after exposure to polychlorinated biphenyls and dichlorophenyl dichloroethene transplacentally and through human milk. *J. Pediatr.* **113**, 991-995.

Grandjean, P., Sandoe, S.H., and Kimbrough, R.D. 1991. Nonspecificity of clinical signs and symptoms caused by environmental chemicals. *Hum. Exp. Toxicol.* **10**, 167-173.

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

Grandjean, P., Budtz-Jørgensen, E., White, R.F., Jørgensen, P.J., Weihe, P., Debes, F., and Keiding, N. 1999. Methylmercury exposure biomarkers as indicators of neurotoxicity in 7-year-old children. *Am. J. Epidemiol.* **150**, 301-305.

Hansen, O.N., Trillingsgaard, A., Beese, I., Lyngbye, T., and Grandjean, P. 1989. A neuropsychological study of children with elevated dentine lead level: Assessment of the effect of lead in different socioeconomic groups. *Neurotoxicol. Teratol.* **11**, 205-213.

Harada, M. 1995. Minamata disease: methylmercury poisoning in Japan caused by environmental pollution. *Crit. Rev. Toxicol.* **25**, 1-24.

Humphrey, H.E.B., and Budd, M.L. 1996. Mercury exposure in the Michigan cohorts. *Toxicol. Ind. Health* **12**, 499-505

Jacobson, J.L., and Jacobson, S.W. 1997. Evidence for PCBs as neurodevelopmental toxicants in humans. *Neurotoxicol.* **18**, 415-424.

Jacobson, J.L., Jacobson, S.W., and Humphrey, H.E.B. 1990. Effects of in utero exposure to polychlorinated biphenyls and related contaminants on cognitive functioning in young children. *J. Pediatr.* **116**, 38-45.

Kimbrough, R.D., Mahaffey, K.R., Grandjean, P., Sandoe, S.H., and Rutstein, D.R. 1989. *Clinical effects of environmental chemicals, a guide to etiologic diagnosis*. Hemisphere, New York.

Kjellström, T., Kennedy, P., and Wallis, S. 1989. *Physical and Mental Development of Children with Prenatal Exposure to Mercury from Fish*. Stage 2, interviews and psychological tests at age 6. (Report 3642) National Swedish Environmental Protection Board, Stockholm.

Murata, K., Weihe, P., Renzoni, A., Debes, F., Vasconcelos, R., Zino, F., Araki, S., Jørgensen, P.J., White, R.F., and Grandjean, P. 1999. Delayed evoked potentials in Madeiran children exposed to methylmercury from seafood. *Neurotoxicol Teratol* **21**, 343-348.

Needleman, H.L. 1990. The future challenge of lead toxicity. *Environ. Health Perspect.* **89**, 85-89.

Rutstein, D.D., Mullan, R.J., Frazier, T.M., Halperin, W.E., Melius, J.M., and Sestito, J.P. 1983. Sentinel Health Events (occupational): a basis for physician recognition and public health

surveillance. *Am. J. Public Health* **73**, 1054-1062.

Shaheen, S. 1984. Neuromaturation and behavior development: The case of childhood lead poisoning. *Developm. Psychol.* **20**, 542-550.

Steuerwald, U., Weihe, P., Jørgensen, P.J., Bjerve, K., Brock, J., Heinzow, B., Budtz-Jørgensen, E., and Grandjean, P. 2000. Maternal seafood diet, methylmercury exposure, and neonatal neurological function. *J Pediatr* **136**, 599-605.

USEPA (U.S. Environmental Protection Agency). 1997. *Mercury Study Report to Congress*. Washington, DC.

White, R.F., Debes, F., Dahl, R., and Grandjean, P. 1994. Development and field testing of a neuropsychological test battery to assess the effects of methylmercury exposure in the Faroe Islands. *Proceedings of the International Symposium on Assessment of Environmental Pollution and Health Effects of Methylmercury*, pp. 127-140. University of Kumamoto, Kumamoto, Japan.

White, R.F., Diamond, R., Proctor, S.P., Morey, C., and Hu, H. 1993. Residual cognitive deficits 50 years after lead poisoning during childhood. *Br. J. Ind. Med.* **50**, 613-622.

WHO (World Health Organization). 1988. *Principles of Studies on Diseases of Suspected Chemical Etiology and their Prevention*. Environmental Health Criteria 72. Geneva.

Table 1. Partial correlation coefficients for three outcome parameters and the logarithmic transformation of the mercury concentration in cord blood as adjusted for potential confounders (Grandjean et al., 1997). Results are computed for 417 children examined during the first year of the study and for whom all variables were available.

Test	Partial r	p value	Number of different responses
Catching ball	0.02	0.74	3
Digit Span forward	-0.12	0.02	9
CPT reaction time*	0.18	<0.001	232

*Continuous Performance Test, Neurobehavioral Evaluation System.

Table 2. Regression coefficients (betas) for the logarithmic transformation of the mercury concentration in cord blood as predictor of the WISC-R Similarities score in 860 7-year-old Faroese children as adjusted for potential confounders (Grandjean et al., 1997). Results are compared between those obtained by a clinical neuropsychologist and by a trained hospital technician.

Examiner	Number	Beta	p value
Neuropsychologist	282	-1.53	0.043
Technician	578	0.24	0.59
Both*	860	-0.05	0.90

*adjusted for examiner

Table 3. Change (expressed as % of SD) in neuropsychological test performance at age 7 years associated with a doubling of the mercury concentration of five exposure biomarkers in 917 Faroese children after adjustment for confounder (with p values given in parentheses) (Grandjean et al., 1999) .

Test	Maternal Hair	Cord blood	Hair at 1yr	Hair at 7yr	Blood at 7yr
NES Continuous Performance Test					
Reaction time	8.99 (0.035)	15.93 (<0.001)	12.29 (0.045)	5.08 (0.159)	6.54 (0.122)
Boston Naming Test					
With cues	-7.47 (0.009)	-10.47 (<0.001)	3.47 (0.403)	-2.40 (0.299)	-4.60 (0.107)
Bender Visual Motor Gestalt Test					
Delayed recall	-1.26 (0.679)	-4.64 (0.104)	-0.11 (0.979)	-5.93 (0.016)	-7.59 (0.013)

*Neurobehavioral Evaluation System.