Mercury Exposure and Child Development Outcomes

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ABSTRACT. Mercury is ubiquitous in the global environment, ensuring universal exposure. Some forms of mercury are especially neurotoxic, including clinical signs at high doses. However, typical human exposures occur at low to moderate doses. Only limited data about neurotoxicity at low doses are available, and scientists differ in their interpretation. Dose–response data on neurodevelopment are particularly limited. Despite or perhaps because of the lack of sufficient or consistent scientific data, public concern about a link between mercury exposure and developmental disabilities has been rising. After reviewing the data, the US Environmental Protection Agency proposed a reference dose (an estimate of a daily dose that is likely to be without a risk of adverse effects over a lifetime) for methyl mercury that is substantially lower than previous guidelines from the World Health Organization, the US Agency for Toxic Substances and Disease Registry, and the US Food and Drug Administration. Some questions have been raised about the Environmental Protection Agency’s guidelines, but the issue remains unresolved. Meanwhile, consumer groups have raised questions about the potential link between mercury exposure and autism spectrum disorders as well as other adverse neurodevelopmental outcomes. This hypothesis has prompted some parents to seek regulatory, legal, or medical remedies in the absence of firm evidence. This article reviews what is known about mercury neurotoxicity and neurodevelopmental risk. Our intent is to focus the debate about mercury on 1) additional research that should be sought and 2) defining the principal issues that public policy makers face. Pediatrics 2004;113:1023–1029; mercury, developmental neurotoxicity, child neurocognitive development.

ABBREVIATIONS. MeHg, monomethyl mercury; EPA, Environmental Protection Agency; CNS, central nervous system; SCDS, Seychelles Child Development Study; PCB, polychlorinated biphenyl; NRC, National Research Council.

Mercury is naturally present in the environment. It is part of the composition of the earth’s crust and may be found in air, water, soil, aquatic sediments, and living plants and animals. It occurs in several chemical forms, including elemental mercury (pure mercury) and both inorganic and organic mercury compounds. Elemental mercury is sometimes referred to as metallic mercury or mercury vapor. Elemental mercury vaporizes at room temperature.

Of the approximately 3400 metric tons per year of elemental mercury released into the global environment, 95% resides in terrestrial soils, 3% in ocean surface waters, and the remaining 2% in the atmosphere. Approximately 70% of the mercury in the environment comes from anthropogenic sources, primarily emissions from coal-fired electric power generation facilities and waste dumps, although natural sources such as volcanos and mines also deposit it in the environment. Some mercury is released by cremation of human or animal remains. Mercury is used in a variety of industrial applications and manufacturing processes and in medical devices such as sphygmomanometers and thermometers. It constitutes 50% of dental amalgams, and ethylmercury was used as a vaccine preservative. Increases in power plant emissions and industrial uses during the past 100 years have been accompanied by a 3-fold increase in environmentally available mercury. In these forms, mercury remains in the environment indefinitely.

SOURCES OF HUMAN ENVIRONMENTAL EXPOSURE TO MERCURY

Organic Mercury

The principal source of human exposure to organic mercury is fish consumption. This form of mercury is monomethyl mercury (MeHg). Sea mammals and shellfish also carry variable concentrations of MeHg in their tissues. The predominant source of MeHg in the aquatic environment is atmospheric mercury deposited on the surfaces of bodies of water that is then biomethylated by microorganisms and subsequently biomagnified as it ascends the food chain. Most fish that live in US waters have <0.5 ppm, but some older, larger carnivorous fish at the top of the food chain can contain >1 ppm. Although the dominant health concerns arise from gestational exposure, infants and children may be exposed postnatally to MeHg from breast milk should their mothers consume foods that contain high levels or if they consume fish or foodstuffs that contain fish products.

For many years, vaccines such as pertussis, diptheria, tetanus, Haemophilus influenza type b, and hepatitis B were preserved with small amounts of thimerosal, a preparation composed of 49% ethylmercury. When infants were immunized with these vaccines, they were exposed to small doses of this organic mercury compound (12.5–25.0 µg/dose). The exposure varied with the weight of the infant, so smaller infants who received multiple vaccines at 1 visit...
could have been exposed to a dose of ethyl mercury that on that day was near or above the US Environmental Protection Agency’s (EPA’s) current permissible daily dose, or reference dose (derived by dividing the no observed effect level [the dose at which no effects have been observed] by an uncertainty factor)\(^1\) of 0.1 \(\mu g/kg/d\), but not near or above the reference doses accepted by other US federal agencies. The difference resulted when the various agencies adopted different uncertainty factors. The American Academy of Pediatrics and the US Public Health Service in a joint statement issued in 1999 concluded that there was insufficient scientific evidence that developmental neurotoxicity could result from such exposures, but it also recommended that pharmaceutical companies use alternative preservatives.\(^4\) Since then, thimerosal has been removed from most vaccines distributed in the United States.

**Inorganic Mercury**

Children are exposed to inorganic mercury compounds, elemental mercury or mercury vapor less commonly. Inhalation of vapor usually occurs during industrial processes using elemental mercury such as extraction of gold from ore. However, in some ethnic groups, mercury compounds are used for cosmetics in formulations that release vapor.\(^5\) Recently, Hispanic women have been reported to use a beauty cream that contains calomel (mercurous chloride) that can also produce inorganic mercury intoxication\(^6\) in exposed women with symptoms similar to those of metallic mercury intoxication.

Certain sects use elemental mercury in religious ceremonies. The EPA issued a report on the practice because it presents a serious health risk.\(^7\) As the report indicates, certain Latino and Afro-Caribbean traditions, such as Sanataria, Voodoo, and Espiritismo, wear mercury amulets, sprinkle it on the floor, or even add it to a candle or an oil lamp. Perhaps because of its physical form, a liquid metal, it is invested with magical properties. It is believed to attract luck, love, or wealth. It is used to speed the action of spells. It is sometimes used as a medication, especially for gastrointestinal disorders. Because, for such religious purposes, it is purchased through religious supply stores known as botanicas, which may obtain the mercury illicitly, little is known of the extent of use and use patterns.

The most common route for human exposure to inorganic mercury takes place via dental amalgams. Mercury vapor escapes during the preparation and placement of amalgam restorations, and some of the vapor may be inhaled (see reference\(^8\) for review). Drasch et al\(^9\) reported that mercury levels in autopsy tissues from fetuses and infants were correlated with the number of dental amalgams in the mother, but their sample was small. A recent study by Vahter et al\(^10\) examined the different species of mercury in the blood of pregnant women. They found high correlations between inorganic mercury levels in blood and urine during early pregnancy, a significant correlation between cord and maternal blood, and decreased mercury levels during lactation, presumably the result of excretion in milk.

Some pregnant women experience an increase in dental problems such as caries and gingivitis and become candidates for dental restorations. According to Winn et al,\(^11\) 95% of pregnant women have at least 1 carious lesion. Furthermore, the proportion of decayed or missing filled surfaces increases during the reproductive years, from 12% between the ages of 18 and 24 years, to 27% from ages 25 to 34 years, to 41% from ages 35 to 44 years. Some pregnant women also experience an increase in dental problems such as caries and gingivitis during lactation, presumably the result of excretion in milk.

### FACTORS THAT INFLUENCE EXPOSURE

**Timing**

The fetal brain is especially susceptible to damage from exposure to organic mercury. The data are less clear concerning prenatal exposure to inorganic mercury. There is some animal evidence that effects of low exposures to MeHg early in development may not appear until later in life.\(^15\) Such delayed neurotoxicity appearing years after exposure has yet to be documented in humans and remains an open question. Some data on MeHg to be reviewed later indicate that the consequences of prenatal exposure to low doses can be detected in children several years later.

**Type of Dose**

Some evidence indicates that the distribution of dose over time may play a role in determining effects of exposure.\(^16\) A single, brief, peak exposure, such as occurred in poisoning episodes\(^17,18\) may deliver an acute dose to the brain that theoretically might be high enough to produce central nervous system (CNS) damage. Chronic dosing such as might result
from consuming a diet high in ocean fish, given the appropriate pharmacokinetics, might also accumulate a high enough tissue burden over time to cause damage. Unfortunately, insufficient data are available to quantify these theoretical hypotheses.

**NEUROTOXICITY OF MERCURY**

Human exposure to toxic levels of mercury vapor in adults causes the classic triad of erethism (bizarre behavior, eg, excessive shyness or aggression), tremor, and gingivitis. The cardinal neurologic sign of toxic vapor exposure is tremor that may be accompanied by a variety of neuropsychological effects ranging from emotional lability at high exposure levels to subtle performance deficits at lower levels. Children are seldom exposed to high levels of vapor, which occur mainly in occupational settings, but under such circumstances, they may exhibit a syndrome known as acrodynia (painful limbs) or pink disease. During the first half of the 20th century, children were often treated with teething powder that contained inorganic mercury in the form of calomel, and acrodynia was common. Clinically, it consisted of irritability, photophobia, erythema of the hands and feet, hypertension, and failure to thrive. Death sometimes occurred. There is speculation but no clear evidence that exposure to the small amounts of mercury vapor from dental amalgams may be harmful. This is presently being actively investigated.

Exposure to MeHg in high doses has profound effects on the CNS and can be rapidly fatal. In adults, symptom onset starts with sensory disturbance followed by visual field constriction, ataxia, cognitive decline, and death. Neuropathology indicates that the occipital cortex and cerebellum are most affected. Prenatal exposure, which was first reported from Japan and later Iraq, resulted in diffuse CNS damage with disruption of cellular migration. However, neuropathologic studies of prenatal MeHg exposure at low dosages from fish consumption have not identified such damage.24

**DEVELOPMENTAL EXPOSURE EFFECTS**

**Methylmercury**

During the 1950s, outbreaks of MeHg poisoning occurred in several places in Japan. The best known of these took place in Minamata and Niigata. More than 21,000 individuals filed claims with the Japanese government as actually having the disease. In Minamata alone, nearly 600 people died. These outbreaks were caused by industrial discharges of mercury into coastal waters or rivers. Fish that were contaminated by these discharges were subsequently caught and consumed by local residents. Poisoned individuals experienced neurologic impairment, including paresthesias, and symptoms resembling Hunter-Russell syndrome, consisting of visual field constriction, ataxia, impaired hearing, and speech impairment.

A later outbreak in Iraq resulted from the consumption of bread made from seed grain coated with a MeHg fungicide. This outbreak affected 6,530 individuals, 439 of whom died. The levels of MeHg documented in the fish in Japan and in the seed grain in Iraq were far higher than those occurring from natural dietary exposure.

In Minamata, Japan, pregnant women who consumed the contaminated fish manifested mild or no symptoms but gave birth to infants with severe developmental disabilities, including cerebral palsy, mental retardation, and seizures. This outcome, called congenital Minamata disease, first indicated that the fetal brain may be highly sensitive to MeHg exposure. After the outbreaks in Minamata and Niigata, 22 cases of congenital Minamata disease were documented. Their level of prenatal exposure to MeHg was never ascertained, and no information is available on dose–response relationships in these children.

The outbreak of MeHg poisoning in Iraq was studied by investigators from the University of Rochester (see reference 27 for a summary). A total of 83 women who were pregnant during the outbreak were identified and participated in a limited developmental assessment of their offspring. Prenatal exposure levels ranged between 1 and 600 ppm as measured in maternal hair growing during pregnancy, an excellent biomarker of exposure. In contrast, MeHg levels seen in fish eaters who consumed multiple fish meals per week in the Seychelles did not exceed 36 ppm in hair. The Iraqi children were examined for neurologic symptoms at an average age of 30 months, and the mothers were interviewed at that time to determine developmental milestones. The results suggested a dose–response curve associated with delayed milestones that seemed to indicate an adverse effect at exposures as low as 10 to 20 ppm in maternal hair. For many years thereafter, these findings were used as a basis for determining the permissible daily intake for MeHg exposure. However, the study was not well controlled, the children’s birth dates were determined in relation to calendar events and not independently verifiable, little was known about cultural differences among cohort families, and the background rate of neurodevelopmental and neurologic deficits in Iraq was unknown. Most important, the source of exposure in Iraq was not fish consumption, and the number of children with neurologic findings was small, limiting the generalizability of the results.

After the publication of the Iraq data, several other small-scale studies of prenatal effects of dietary exposure to MeHg were conducted in other locales, including Peru, Canada, and New Zealand, and, more recently, the Philippines, Brazil, and French Guiana. These studies all were conducted on relatively small samples, and some suffered from methodologic limitations. Moreover, the reported exposure levels varied, although they all can be considered relatively low. Although some of these studies showed adverse effects, the results varied from study to study and no consistent pattern of findings has emerged. Of note are the French Guiana findings of subtle neurobehavioral effects at a mean exposure level of subtle neurobehavioral effects at a mean exposure level.
of approximately 12 ppm in maternal hair, somewhat higher than the other studies.

In the mid-1980s, 2 large well-designed and well-executed cohort studies were initiated, one in the Republic of Seychelles called the Seychelles Child Development Study (SCDS)\textsuperscript{19,21,26} and the other in the Faeroe Islands.\textsuperscript{20} Both locales are well suited to epidemiologic studies, affording many natural controls over confounders, and both populations consume large quantities of seafood. Both studies determined prenatal MeHg exposure and ascertained neurodevelopmental outcomes after delivery. Exposure levels were similar (mean: 4.0 ppm in Faeroes and 6.0 in Seychelles). The SCDS examined their main cohort ($n = 779$) 5 times after birth (6.5, 19, 29, 66, and 107 months). The Faeroese cohort was examined at 7 years and again at 14 years.

The findings from the 2 studies were different. In the SCDS, of a total of 46 primary endpoints measured across 5 ages, only 1 endpoint showed a possible adverse association with prenatal MeHg exposure. In boys the time to complete the grooved pegboard for the nonpreferred hand at 107 months of age increased with exposure. Two additional endpoints (language function at 66 months and the attention-deficit/hyperactivity disorder index from the Teacher Rating Scale at 107 months) showed enhancements with increasing prenatal MeHg exposure at low levels. The Faeroes study reported adverse associations between prenatal MeHg exposure and tests of memory, attention, language, and visual spatial perception measured at 7 years of age. In some cases, these divergent results occurred on identical test measures. The results from the Faeroese examinations at 14 years of age are not yet available. It is interesting that another finding from their examination of the children at 7 years was an adverse association between prenatal MeHg exposure and cardiovascular measures, including heart rate and blood pressure.\textsuperscript{37}

The SCDS and the Faeroes study differ in several important ways. In the SCDS, exposure resulted entirely from nearly daily fish consumption. In the Faeroes, exposure was attributable mainly to pilot whale meals consumed episodically while fish consumption is lower than in the Seychelles population. Pilot whales have much higher levels of mercury than typical ocean fish and also contain other contaminants, such as Polychlorinated biphenyls (PCBs). No PCB exposure was detected in the SCDS. Recently, the Faeroes investigators\textsuperscript{36} reported that MeHg neurotoxicity might be potentiated by PCBs, although they believe that the data continue to show direct adverse effects of MeHg even after correction for PCBs. It is possible that the delivery of a high intermittent dose of MeHg may affect CNS development differently than daily low-dose exposure, although this hypothesis has yet to be tested.

The Faeroes study used umbilical cord blood and maternal hair as the primary biomarkers of exposure, whereas the SCDS used only maternal hair. Hair samples permit recapitulation of the entire pregnancy period, whereas cord blood ascertainment exposure only during the last trimester near the time of delivery. Earlier exposures would not be reflected in cord blood. The Faeroes researchers reported that, using hair samples, associations with developmental outcomes were still present but weaker.

The Faeroes team recently reported results from a new cohort of 182 infants whose development at 2 weeks postpartum was assessed with the Neurologic Optimality Score.\textsuperscript{39} Adverse effects were found to be associated with prenatal mercury exposure. A recent review of this study suggested that the results were difficult to interpret because the Neurologic Optimality Score is not highly predictive of later development.\textsuperscript{40} The Steuerwald data\textsuperscript{39} seem to contradict the earlier finding of Grandjean et al\textsuperscript{41} of an association between prenatal exposure and accelerated developmental milestones at 1 year of age.

Expert groups have reviewed the Faeroes and Seychelles studies on several occasions. Both the Agency for Toxic Substances and Disease Registry\textsuperscript{42} and the National Institute of Environmental Health Sciences\textsuperscript{43} reviewed the scientific merit of the studies and concluded that both were methodologically sound and reached scientifically valid conclusions for their respective populations. They concluded that the different results may reflect the differential influences of biological factors not yet identified. The National Research Council (NRC) was charged to “evaluate the body of evidence that led to EPA’s current RfD [reference dose] for MeHg...and determine if the critical study, endpoint of toxicity, and uncertainty factors used by EPA in the derivation of the RfD for MeHg are scientifically appropriate”\textsuperscript{44} (p. 2). The NRC review included the New Zealand data,\textsuperscript{31,32} which previous reviews had discounted because of its small sample size and confounding. The NRC report concluded that sufficient evidence was available to concur with the EPA’s recommendation to lower the reference dose from 0.5 to 0.1 $\mu$/kg/day. They based their decision on the McCarthy Perceptual-Performance Scale from the New Zealand study and the Boston Naming Test from the Faeroes study. They considered the latter “the most sensitive, reliable endpoint”\textsuperscript{44} (p. 299). The data from the SCDS were discounted because no significant adverse effects were reported. Subsequently, the Faeroes group reported that the PCBs present in whale meat and blubber might be confounding the mercury exposure.\textsuperscript{38} They stated, “The cord PCB concentration was associated with deficits on the Boston Naming Test,” and, “the association between cord PCB and cord-blood mercury ($r = 0.42$) suggested possible confounding.”

**Ethylmercury**

Bernard et al\textsuperscript{45} and others have hypothesized that postnatal exposure to thimerosal may be associated with autism spectrum disorders and learning or speech disorders. However, no direct test of this association has yet been reported (see reference\textsuperscript{46} for review). Exposure to ethyl mercury is thought to cause the same pattern of developmental effects as MeHg, but there are only a few reported cases of ethyl mercury poisoning.\textsuperscript{47} There is evidence that the half-life of ethyl mercury is somewhat shorter than
that of MeHg. Most important, the evidence regarding the cause of autism spectrum disorders points only to genetic mutations caused by certain in utero exposures. There is no evidence of an association between autism and postnatal exposure to any neurotoxicant. The US Institute of Medicine has reviewed this issue and concluded that, although it is biologically plausible, there is presently insufficient evidence to support or refute the hypothesis that ethyl mercury in vaccines and autism spectrum disorder prevalence are associated. The report called for additional public health and biomedical research to explicate further this possible association.

**Inorganic Mercury**

Remarkably little is known about the developmental neurotoxicity of elemental mercury or inorganic mercury compounds. Despite its ubiquitous presence in our environment and its lengthy history in toxicology, it remains a reservoir of unanswered but important health risk questions. The most serious lack is information about the consequences of exposure during early child development. No human studies as yet document any adverse effects of prenatal or early postnatal exposure to elemental mercury or mercury vapor. Three studies are presently under way, but it may be some time before they are concluded. Many studies have confirmed adverse effects for adults in the workplace and almost all of the contemporary reports of pink disease in the medical literature point to mercury vapor as the exposure source. Even so, the World Health Organization noted that, even for adults, information is insufficient to propose a no observable adverse effect level.

Laboratory animal studies of developmental neurotoxicity consist mainly of reports from a single laboratory. Khayat and Dencker observed that exposing pregnant mice acutely to mercury vapor led to substantial deposition of mercury in fetal tissue. Danielsson et al detected effects such as adult hyperactivity and learning deficits in the offspring of pregnant rats that were exposed to metallic mercury at a level of 1800 μg/m³. Despite many flaws in the experimental design, the results of Fredriksson et al in neonatal rats serve as the basis for a calculated minimal risk level of 0.02 μg/m³ for acute inhalation exposure. People with many amalgam restorations show elevated urinary levels of mercury and higher concentrations in brain, but the health implications are unclear. Although dentists now handle mercury in various forms, its volatility can lead to toxic signs. Accidental spills can deposit mercury vapor on the sites of toxicology, it remains a reservoir of unanswered but important health risk questions. The most serious lack is information about the consequences of exposure during early child development. No human studies as yet document any adverse effects of prenatal or early postnatal exposure to elemental mercury or mercury vapor. Three studies are presently under way, but it may be some time before they are concluded. Many studies have confirmed adverse effects for adults in the workplace and almost all of the contemporary reports of pink disease in the medical literature point to mercury vapor as the exposure source. Even so, the World Health Organization noted that, even for adults, information is insufficient to propose a no observable adverse effect level.

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**Public Policy Issues**

There is no doubt that both organic and inorganic mercury vapor are dose-dependent neurotoxicants. Faced with data that point to the increased bioavailability of mercury in the environment, scientists need to inform governments worldwide of the level of exposure that can cause adverse health effects, and governments need to develop public health policies that minimize human exposure. Despite disagree-
ment in the scientific literature about the lowest dose at which human health effects may result, some governments have promulgated policies and laws that severely limit or eliminate the use of mercury preservatives in vaccines, inorganic mercury in dental amalgams, or human consumption of fish during pregnancy.

Regulatory bodies in the United States, such as the Food and Drug Administration, the EPA, and the Agency for Toxic Substances and Disease Registry, have interpreted the scientific literature in different ways. Such inconsistent interpretations that are not always based on science can lead to confusion for the public. Unfortunately, the gap between science and policy concerning low-dosage exposure to mercury may not be narrowed for some time. Under such circumstances, we must rely on the scientific evidence, incomplete as it may be, that most directly relates to exposures being regulated.

The National Academy of Sciences review of the relevant human epidemiologic evidence on MeHg, which we reviewed earlier, recommended that the EPA adopt as its reference dose the risk analysis of data from the Faeroese and New Zealand studies. However, there is substantial uncertainty associated with this estimate, and the exposure from consumption of pilot whale differs from exposure sources in the United States. The NRC review committee estimated that on the basis of current fish consumption patterns among pregnant women of childbearing age in the United States, “over 60,000 children are born each year at risk for adverse neurodevelopmental effects due to in utero exposure to MeHg” (p. 327). Unfortunately, the basis for that estimate is not provided in the report or supported by existing literature.

In warning the public about the risks of mercury exposure from consuming fish, we face the alternative risk of frightening consumers into refraining from fish consumption when fish is a primary source of nutrition among many groups. Dietary changes that affect essential protein and nutrient intake during pregnancy could prove to be more dangerous to the fetus than the poorly defined risk associated with exposure to MeHg in the fish. Similarly, parents in some parts of the United Kingdom have decided to forego having their children immunized for exposure to mercury from the vaccines. Such practices, if they occurred on a large enough scale, could compromise disease control, leading to a greater risk to child health than mercury might present.

Public policies related to regulation of exposure to mercury thus are very complex and are not easily addressed. In a recent comprehensive review of mercury neurotoxicity, Clarkson concluded, “As we . . . reflect on the extensive research [on mercury] conducted in our lifetime, we must reluctantly agree with the title of a BBC documentary broadcast over 25 years ago that this metal still remains ‘an element of mystery.’ As we decide on such regulatory questions, we must strive to limit the gap between science and policy if we are to choose answers wisely” (p. 21).

REFERENCES


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The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/113/Supplement_3/1023