Neurotoxicity of Lead, Methylmercury, and PCBs in Relation to the Great Lakes

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There is ample evidence identifying lead, methylmercury, and polychlorinated biphenyls (PCBs) as neurotoxic agents. A large body of data on the neurotoxicity of lead, based on both epidemiologic studies in children and animal models of developmental exposure, reveals that body burdens of lead typical of people in industrialized environments produce behavioral impairment. Methylmercury was identified as a neurotoxicant in both adults and the developing organism based on episodes of human poisoning; these effects have been replicated and extended in animals. High-dose PCB exposure was recognized as a developmental toxicant as a result of several episodes of contamination of cooking oil. The threshold for PCB neurotoxicity in humans is less clear, although research in animals suggests that relatively low-level exposure produces behavioral impairment and other toxic effects. Tissue levels in fish below which human health would not be adversely affected were estimated for methylmercury and PCBs based on calculated reference doses (RfDs) and estimated fish intake. Present levels in fish tissue in the Great Lakes exceed these levels for both neurotoxicants. Great Lakes fish and water do not pose a particular hazard for increased lead intake. However, the fact that the present human body burden is in a range at which functional deficits are probably suggests that efforts should be made to eliminate point sources of lead contamination in the Great Lakes basin. — Environ Health Perspect 103(Suppl 9):71–87 (1995)

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Introduction

There are a number of contaminants in the Great Lakes that are neurotoxic or potentially so. There is a large database from the animal literature and human epidemiologic studies on two of these, lead and methylmercury. The database is less complete for a third class of contaminants, polychlorinated biphenyls (PCBs). While it is reasonably certain that PCBs are neurotoxic, there are fewer human studies upon which to determine a no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL) than for lead or methylmercury. For most other Great Lakes contaminants, data regarding neurotoxicity are lacking, or levels to which the population is exposed are not considered cause for concern. For example, there is reason to be concerned about substances such as toxaphene, hexachlorobenzene (HCB), and hexachlorocyclohexanes (HCHs) based on their chemical structure, but neurotoxicity data are almost nonexistent. Other agents known to be neurotoxic, such as organotin compounds and various pesticides, are found in the Great Lakes basin at levels that are orders of magnitude lower than those that have even been tested in animals or at which neurotoxicity has occurred in humans. Therefore, discussion of neurotoxicity is restricted to lead, methylmercury, and PCBs.

Lead has been known to be neurotoxic since ancient times. As a result of human activity, the present body burden of lead is 2 to 3 orders of magnitude above background levels. In the last 15 years, it has become clear that exposure to lead in utero or during childhood at body burdens that are presently typical of humans in industrialized countries results in deficits in intelligence quotient (IQ) and in other behavioral problems. Approximately 20 epidemiologic studies, both prospective and retrospective, provide extremely strong and consistent evidence. A large body of animal data indicates that lead produces behavioral impairment and is also consistent with respect to the types of impairment observed in children. It is also becoming increasingly clear that there is no apparent threshold for these effects at present day body burdens. Moreover, the generation of women exposed to the most lead since ancient times is presently at reproductive age and will provide a significant source of in utero lead exposure via bone stores. The most significant sources of lead exposure are food (indirectly from environmental fallout) and water via lead or lead-soldered plumbing.

The Great Lakes basin does not present a particular hazard with regard to lead exposure; however, given that there is no threshold for behavioral impairment produced by lead in the developing organism, every effort should be made to eliminate any industrial sources of lead from the Great Lakes basin.

Methylmercury was recognized as a neurotoxic agent following outbreaks of human poisoning through contaminated fish in Japan in the 1950s and 1960s. Later episodes of human poisoning in Iraq due to ingestion of grain treated with an organomercury fungicide provided an excellent database for neurotoxic effects, including detailed estimates of thresholds for various end points. It is clear that the fetus is much more sensitive than the adult. The most sensitive end points identified to date are developmental delays in children exposed in utero. A reasonably good animal database exists that replicates the types of neurotoxicity observed in humans. Consumption of contaminated fish represents the most important source...
of exposure to methylmercury. Reference doses (RfDs) based on developmental neurotoxicity in humans in the Iraqi episode are in the range of 0.06 to 0.07 μg/kg/day. Similar estimates based on the available animal data, particularly from monkeys, suggest an RfD of 0.05 μg/kg/day. The levels of methylmercury observed in Great Lakes fish represent a potential hazard to offspring of women who consume large quantities of fish. Further studies, including ongoing prospective epidemiologic studies, should serve to refine levels at which toxicity is known to occur.

It is certain that high doses of PCBs produce reproductive toxicity in humans. Two well-designed prospective epidemiologic studies in humans provide evidence for behavioral deficits associated with low-level in utero exposure to PCBs. In one study, exposure was via contaminated Great Lakes fish and, in the other study, there was no identified source of exposure. A possible limitation of these studies, particularly the former, is failure to assess and control for other potential neurotoxicants such as methylmercury that are potentially correlated with PCB level. However, there is a significant body of data from monkeys in which behavioral deficits were observed as a result of developmental exposure to PCBs. Developmental and neurotoxic effects have also been confirmed in other animal models. The most significant source of PCB exposure in the general population is contaminated fish. RfDs promulgated by a number of state and Federal agencies in the United States are 0.05 μg/kg/day or lower, based on data from both animal and human developmental studies. Women who are frequent consumers of Great Lakes fish would exceed this number by a significant amount.

**Lead**

Lead has been recognized as a poison from ancient times to the present (1,2). Recently, attention has focused on the subtle effects of environmental exposure at levels presently considered normal in our industrialized age (3–8). The recognition that lead produces intellectual impairment in children, as well as other health effects, has resulted in the progressive tightening of the regulation of the uses of lead in the United States and other countries, including the phaseout of lead from gasoline (9), a decrease in the amount of lead allowable in drinking water, and abatement of lead from buildings contaminated with lead paint.

Although lead is a common element in the earth’s crust, its ubiquitous presence in bioavailable forms in the environment is due largely to the activities of humans (10,11). The industrial revolution and the addition of lead to gasoline in the 1920s have resulted in dramatic increases in environmental lead levels (12,13). Present environmental levels are estimated to be several orders of magnitude above preindustrial levels (Table 1 (14)). The burden of lead in human bones is presently 500-fold greater than in prehistoric times, and the present-day diet of Americans contains 100 times more lead than prehistoric diets (14).

In the 1940s it was recognized by astute physicians that children who had been treated for lead poisoning suffered permanent neurologic damage including poor school performance, impulsive behavior, short attention span, restlessess, and occasional neurologic signs (15). High-level lead exposure in children at that time was caused by lead-based paint. These observations were later replicated by other investigators (16–18). Early in the 1970s, deficits in IQ, fine motor performance, and behavioral disorders such as distractibility and constant need for attention were observed in children who had never exhibited overt signs of lead intoxication (19,20). Concern arose in the United States and elsewhere that the many tons of lead being introduced into the environment every year by the use of leaded gasoline, as well as other industrial processes, were producing significant health effects, particularly in children. A new understanding of the insidious effects of lead on the intellectual capacity of a large number of children arose in 1979 with the landmark study of Needleman et al. (21). These investigators reported decreased IQ and increased incidence of distractibility and inattention in middle-class children with no exposure to lead from paint.

Largely as a result of the Needleman et al. study (21), there has been intense research into the health effects of lead and on the sources of exposure to the general population over the last 15 years. The issue has generated a great deal of political as well as scientific controversy. The result of this intense scrutiny is that probably more is known about the health effects of lead than about any other noncarcinogenic environmental contaminant. The result in the United States has been a rapid decrease over the last two decades by the Centers for Disease Control and Prevention (CDC) in the blood level considered to be safe for children to a present level of 10 μg/dl (22).

**Epidemiologic Studies**

There have been several recent reviews on the neurobehavioral effects of low-level lead exposure in children, including metaanalyses (23–25) and a discussion on methodological issues critical to interpretation of the literature (26). These studies have consistently concluded that an increased body burden of lead in children is associated with a decrease in IQ. Schwartz (23) found that the association between lead exposure and children’s IQ remained strong even with the inclusion or exclusion of the strongest individual studies; moreover, he concluded that there was no evidence of a threshold down to blood lead concentrations as low as 1 μg/dl. This paper is not a definitive review of the epidemiologic literature but rather an overview of the types of effects that have been observed and the body burden at which they occur.

**Cross-sectional Studies**

There have been a number of cross-sectional (retrospective) studies since 1979 concerning the effects of lead on intellectual and behavioral functions in children. The general trend has been to study children with increasingly lower body burdens of lead and to focus on middle-class rather than disadvantaged children. These studies

| Medium | Estimated natural lead concentrations | Typical present-day lead concentrations | Approximate ratio, present-day/natural |
|--------|--------------------------------------|----------------------------------------|---------------------------------------|
| Air    | 0.01–0.1 ng/m^3                      | 0.1–100 ng/m^3                         | 10–1,000                              |
|        | 0.1–1.0 ng/m^3                       | 0.1–10 μg/m^3                          | 100–10,000                            |
| Soil   | Rural/remote                         | 5–25 μg/g                              | 1–2                                   |
|        | Inhabited                            | 5–25 μg/g                              | 10–5,000                              | 2–200                                |
| Water  | Fresh                                | 0.005–0.1 μg/g                         | 1                                     |
|        | Ocean                                | 0.001 μg/g                             | 10                                    |
|        | Foods                                | 0.0001–0.1 μg/g                        | 100                                   |

From the National Academy of Sciences, Committee on Lead in the Human Environment (14).
have been extensively reviewed (5,7,27). Such studies have usually included some measure of intelligence (IQ), school functioning, teachers' rating of classroom behavior, or specific measures of attentional mechanisms. Fulton et al. (28) reported a linear relationship between intellectual functioning and log blood lead concentration for blood lead values between about 5 and 25 μg/dl (mean about 10 μg/dl) in children living in Edinburgh, Scotland, with no indication of a threshold for lead effect (Figure 1). Results were significant after adjusting for potential confounders. In a study in Denmark, children with average blood lead levels of 5.7 μg/dl were impaired in comparison to children with blood lead levels of 3.7 μg/dl (29). A number of other studies published since 1980 have also reported an association between increased lead burden and poorer cognitive performance (30-41). Needleman et al. (42) reported dose-dependent disordered classroom behavior as measured by a teacher's rating scale, which was subsequently replicated by others (33,39,43). High-lead children also exhibited more deviant performance on tests of conduct problems, inattentive-passive, and hyperactivity scales (39,43). A study of middle-class children in New Zealand also reported high correlations between log blood lead (mean=11 μg/dl) and measures of inattention and hyperactivity after adjusting for confounding variables (44). Such early attentional deficits and their associate behaviors place children at risk for academic failure and behavior problems (45). It is therefore not surprising that early increased lead levels resulted in increased grade retention or need for special education. In a follow-up of the children from the Needleman et al. 1979 study (42), tooth lead levels in 5- and 6-year-olds predicted an increase in grade retention and a 2-fold increase in the need for academic aid in teenagers (46), as well as an increased incidence of dropping out of high school and having deficits on various performance measures (47). Barrett (48) reported a dose-related increase in unsatisfactory school performance as a function of increased free erythrocyte protoporphyrin (FEP) levels (a measure of lead exposure).

Lead is associated with increased reaction time and increased errors on various performance and vigilance tasks (32,37,40,41,49). Using the National Health and Nutrition Examination Survey II (NHANES II) database, Schwartz and colleagues (50) found an association between lead and increased hearing threshold in children with blood levels between 5 and 45 μg/dl, with no threshold for effect; they also found slowed nerve conduction velocity at blood lead levels above 20 to 30 μg/dl (51). Blood lead levels of 15 μg/dl and below are also associated with changes in electroencephalogram (EEG) pattern and auditory evoked potentials (52,53).

Prospective Studies

There are a number of prospective studies examining the developmental effects of environmental lead exposure in which a large body of data has been collected over a number of years. The mothers were recruited before the birth of their infants, and the infants followed in a longitudinal manner. This design is stronger than a cross-sectional design, and these studies have provided convincing data regarding developmental deficits produced by low-level lead exposure (23,24,27,54-56).

In a study by Bellinger and colleagues (52), performance on the Bayley Mental Development Index (MDI) at 6, 12, and 24 months of age was associated with cord but not postnatal blood lead levels. The difference between the high (mean=14.6 μg/dl) and low (mean=1.8 μg/dl) blood lead groups was 4 to 7 points. Assessment of these children at 57 months of age (58) revealed that performance on the General Cognitive Index of the McCarthy Scales was associated with blood lead levels at 24 but not 57 months of age, after adjusting for possible confounders. Blood lead values averaged 6.8 μg/dl at 24 months and 6.4 μg/dl at 57 months. These children were evaluated for school dysfunction at 8 years of age (59); umbilical cord blood level >10 μg/dl was associated with problems in both sexes, although the pattern differed between boys and girls. When these children were retested at 10 years of age, a 10-μg/dl increase in blood lead at 24 months was associated with a 5.8-point decline on full-scale IQ on the Wechsler Intelligence Scales for Children—Revised (WISC-R) and an 8.9-point decline on the Kaufman Test of Educational Achievement (Figure 2) (60). Recent blood lead levels were associated with perseverative behavior on the Wisconsin Card Sorting Test, a test of abstract thinking, sustained attention, and ability to change response strategy according to environmental requirements (61).

In a study by Dietrich and colleagues (62,63), it was found that each log unit increment in blood lead (mean at birth = 4.5 μg/dl) was associated with a covariate-adjusted reduction of 5.7 points on the MDI at 6 months of age; the reduction was 8.0 points if the effect on gestational age and birth weight were included. At 1 year after birth, prenatal blood lead levels were negatively correlated with MDI, Bayley Psychomotor Development Index (PDI), and Bayley Infant Behavioral Record (IBR). The IBR revealed higher activity levels and more negative social–emotional response. These effects appeared to have attenuated in this group of disadvantaged children by 4 years of age (64), although prenatal and postnatal blood lead levels were negatively associated with auditory processing ability in these children at 5 years of age (65). When these children were reassessed at 6.5 years of age, lifetime blood lead concentration in excess of 20 μg/dl was associated with a 7-point decrease in performance IQ on the WISC-R compared to children with blood lead levels less than 10 μg/dl (Figure 3) (66).

In a third prospective study in Port Pirie, South Australia (67-69), a decrease of 2 points in the MDI scale for every 10-μg/dl increase in blood lead levels was observed at 24 months of age. Performance was found to be more related to postnatal than prenatal blood lead levels; however, no assessment

Figure 1. British Ability Scales Combined (BASC) Score (mean and 95% confidence interval) as a function of log blood lead levels in 6- to 9-year-old children in Edinburgh, Scotland. Adjusted for covariates. From Fulton et al. (28).

Figure 2. Mean (±SE) adjusted WISC-R Full-Scale IQ scores and the Kaufman Test of Educational Achievement—Brief form (K-TEA) in 10-year-old children classified by blood lead levels at 24 months of age. From Bellinger et al. (60).
was performed before 2 years of age. It is possible that early testing would have revealed significant prenatal exposure effects. In a follow-up assessment (70), previous blood lead levels were found to be inversely correlated with performance on the McCarthy Scales of Children’s Abilities at 4 years of age. Subjects with blood lead levels of 30 μg/dl had a general cognitive score 7.2 points lower than children with blood lead levels of 10 μg/dl; there was no evidence of a threshold for effect. These deficits persisted to 7 years of age, with a 4 to 5 point drop in IQ for blood levels between 10 and 30 μg/dl (71).

Recent studies provide evidence that low-level lead exposure also causes reproductive problems per se. Maternal blood lead levels are associated with increased incidence of preterm delivery (68) and decreased gestational age (62,72), although this has not been a consistent finding (73,74). Increased blood lead has also been found to be associated with increased spontaneous abortion (68). Higher lead burden may also be associated with minor but not major physical abnormalities (75), although this is not a universal finding (68,76). Maternal blood lead level is also associated with abnormal reflexes, poor muscle tone, and neurologic soft signs such as jitteriness, hypersensitivity, and abnormal cry in the infant (76,77). It must be stressed that the maternal and infant blood levels in these studies were in the range considered normal or average for people in industrialized societies (in the range of 2–15 μg/dl in most cases). It is well established that premature or small-for-date infants are at greater risk for a variety of behavioral and other health problems. Such children have more trouble in school and require special help more often than other children (78,79). The effects of lead on intellectual functioning may at least in part be a consequence of its effects on reproductive outcome. In fact, controlling for effects such as gestational age in evaluation of behavioral effects may underestimate the effects of lead.

Long-term Consequences of Environmental Lead Exposure

The positive results obtained in the prospective studies deserve attention in a different vein. The implication of the findings is that the lead body burden of women, reflected by maternal and cord blood lead levels, is important to at least the early well-being of children. The women and their offspring described in these studies had blood lead levels that are typical in our present environment—the result of simply living in a present-day industrialized society. One important unanswered (and unaddressed) question is the contribution of total maternal body burden, rather than blood level, to the risk to the infant. Bone, containing over 90% of lead stores, is the most significant compartment for lead storage in the body, and it is established that lead increases in bone throughout the lifespan of humans (80). Since a large portion of women are now delaying childbearing until relatively late, it may be that they are exposing their fetuses to an increased burden of lead as a result of mobilization from bone. The calcium turnover from bone is increased during pregnancy and lactation, and there is some evidence that bone lead may be mobilized as well as a result of pregnancy and lactation long after exposure has ceased (81). The amount of lead in milk in humans is correlated with people having lived in a high-traffic area for at least 5 years regardless of whether this occurred during childhood or adulthood (82). Since women who were born in the 1950s and 1960s will have in general a significantly higher total body burden of lead than previous generations due largely to indirect exposure resulting from leaded gasoline, this represents a potentially important problem for years to come, despite the fact that the concentration of lead in the general environment is presently decreasing.

Animal Data

The animal data on the behavioral effects of developmental lead exposure are remarkably consistent with the human data, both in terms of the types of behavioral deficits observed and the blood levels at which they occur. It has been established for some time that developmental lead exposure produces behavioral impairment in animals (83). Initial studies using simple learning tasks in rats exposed prenatally plus postnatally usually produced positive results on simple discrimination problems (84–86). Difficult problems were more sensitive to disruption by developmental lead exposure in rats (87) and sheep (88).

An extensive body of data has been collected over the last decade and a half on the behavioral effects of lead in animal models [for reviews, see Rice (89–91), Davis et al. (92)]. Reproducible robust deficits in learning and short-term memory have been demonstrated on a variety of behavioral tasks as a result of developmental lead exposure in two different species of monkeys in two laboratories, one at the University of Wisconsin and the other at the Health Protection Branch in Canada. Research performed at the University of Rochester in which rats were dosed beginning postweaning has also demonstrated impairment of learning ability. In the monkey, behavioral deficits have been observed consistently on a number of tasks in four cohorts of monkeys dosed with lead from birth onward; the lowest exposed cohort had blood lead levels during infancy of 15 μg/dl and steady-state blood lead levels of 11 μg/dl. Deficits were observed from the juvenile period, when testing began, through adulthood. Permanent deficits have also been observed in a number of cohorts dosed early in life (prenatally or postnatally until approximately 1 year of age) and tested at various ages—as long as 6 to 8 years after cessation of lead exposure. In no study in either the rat or the monkey was a no-effect dose identified. The present section provides an overview of the types of deficits observed in animal models in relation to congruence with the epidemiologic data.

The types of behavioral tasks used to assess lead-induced impairment included intermittent schedules of reinforcement, spatial and nonspatial discrimination reversal with and without irrelevant stimuli, spatial delayed alternation, spatial and nonspatial delayed matching to sample, repeated acquisition, and sequential and concurrent visual discrimination (90,91). Functions assessed by these tasks include learning, memory, and attentional processes. Impairment on a number of these tasks has been observed in different groups and species of animals in different laboratories. Detailed assessment of performance such as
analysis of error pattern revealed perseveration, increased distractibility, inability to inhibit inappropriate responding, and difficulty in changing response strategy as behavioral deficits underlying the poorer performance of lead-treated animals (89,91). These findings are similar to those reported in children in terms of behavioral functions impaired by lead; short attention span, increased distractibility, and impulsivity have been identified by teacher’s and parent’s ratings scales as being consequences of increased body burdens of lead, while impairment on vigilance tasks and increased simple reaction time suggests impairment in attentional processes.

A specific example of an analogous impairment between lead-exposed monkeys and children is the discrimination reversal paradigm in monkeys and the Wisconsin Card Sort Test in children. In the nonspatial version of the discrimination reversal task, the monkey was presented with two stimuli that varied in one or more ways (i.e., form, shape, color, position) (93). The monkey was required to respond to a specified stimulus (e.g., always choose the red rather than the green, irrespective of position or shape) in order to be rewarded with a preferred food or juice. When the monkey learned the task to a predetermined criterion, the rule was changed (reversed) so that the previously incorrect stimulus became the correct one (e.g., green rather than red). A number of such reversals were instituted; normal monkeys learn each successive reversal more quickly, displaying a learning curve. Monkeys were tested on a series of three tasks with the relevant stimulus dimension changed between tasks; for example, “attend to the color and ignore the shape” was changed to “attend to the shape and ignore the color.” In addition, the last two tasks included irrelevant stimuli of the former relevant stimulus class. For example, a task requiring the monkey to attend to shapes such as a cross and a square was followed by a task requiring attention to color but with the cross and square superimposed on the colors in a balanced design. The inclusion of irrelevant cues provided the opportunity to assess distractibility (or perseveration). This task makes similar demands to the Wisconsin Card Sort Test in that both require the subject to extract general rules, to change response strategy in response to the consequences of their own behavior (i.e., whether a response or set of responses is correct or incorrect), and to ignore a formerly relevant stimulus dimension. Both lead-exposed monkeys (93) and children (61) are impaired in their ability to adjust to the requirements, perseverating in response strategies that are no longer effective. Effects were observed in monkeys with blood lead levels of 11 µg/dl as well as in a number of cohorts with higher blood lead levels.

In a study on possible sensitive periods for deleterious effects produced by lead, monkeys were exposed to lead either continuously from birth, only during infancy, or beginning after infancy. Lead levels were about 30 to 35 µg/dl when monkeys were exposed to lead and given access to infant formula and 19 to 22 µg/dl when dosed with lead after withdrawal of infant formula (94). These monkeys were tested as juveniles on the same nonspatial discrimination reversal tasks described above (93). Both the group dosed continuously from birth and the group dosed beginning after infancy were impaired over the course of the reversals in a way similar to that observed in the study discussed above, including increased distractibility by irrelevant cues. The higher exposure levels in this study were reflected in impairment on all three tasks whereas in the previous study, lead treated monkeys were impaired on only the first two tasks. The group exposed only during infancy was unimpaired on these tasks.

Performance on a series of spatial discrimination reversal tasks, analogous to the nonspatial discrimination reversal tasks already described, was assessed in this same group of monkeys (95). Contrary to the results of the nonspatial discrimination reversal task in which the group dosed only during infancy was unimpaired, all three dose groups were impaired to an equal degree. These data suggest that spatial and nonspatial tasks may be affected differentially depending on the developmental period of lead exposure. Such results have important implications for interpretation of the epidemiologic literature; in particular, differential effects on various cognitive domains may be expected within and across studies, depending on the pattern of blood lead levels and the potential for sensitive periods for various effects. For example, impairment on the Wisconsin Sort Test described above was linked to concurrent blood lead levels in the children when tested at 10 years of age, whereas results on standard intelligence tests best correlated with 2-year-old blood lead levels. It may be naive to expect that the pattern of effects would or should be the same across epidemiologic studies.

The modern body of data regarding the behavioral toxicity produced by developmental lead exposure in animals, which consists of several dozen research publications, is consistent not only in documenting reproducible effects on a variety of behavioral tasks but also in identifying underlying behavioral processes responsible for the behavioral impairment revealed by assessment of global measures of performance. Moreover, it may be inferred from epidemiologic studies that these same behavioral processes are impaired in children as a result of increased lead exposure (91). This congruence between the behavioral deficits identified in animal models and children, as well as the similarity of blood lead levels at which these effects are observed, provide strong support for the assertion that the deficits in cognitive function observed in the epidemiologic studies are a direct consequence of lead exposure.

**Contribution from Great Lakes Sources**

The greatest source of lead for most children is food and drinking water, although direct inhalation also contributes to body burden. Much of the lead in food is the result of the historical fallout from leaded gasoline, and lead in water may result from lead or lead-soldered plumbing or environmental contamination. In addition, exposure through flaking and peeling lead-based paint is a significant contributor to the lead burden of many children, particularly in the United States. The intake and body burden of lead in present-day humans is 2 to 3 orders of magnitude above preindustrial levels, and there is no apparent threshold for many of the behavioral deficits observed in children. Fish from the Great Lakes do not provide an elevated intake of lead compared to other foods. The Canadian Health Department guideline for lead in drinking water is 10 µg/l. In an analysis of water from seven cities bordering the Great Lakes, only water that was collected from the distribution system, rather than raw water samples, exceeded this guideline (96). Data for 1990 to 1992 from the Canadian drinking water surveillance program suggest that, in general, the Canadian guideline was not exceeded by water from treated sewage that was returned to the Great Lakes. Plumbing contributes a much greater amount of lead to drinking water than a Great Lakes source, and the Great Lakes basin does not provide any particular hazard that is not present in the general environment. However, the fact that
the present human body burden is in a range at which functional deficits are probable suggests that all reasonable efforts should be made to minimize point sources of lead contamination in the Great Lakes basin.

**Methylmercury**

Although the toxicity of mercury compounds has been recognized for centuries, the outbreak of methylmercury poisoning in the late 1950s in Minamata, Japan, focused attention on the potential devastation of neurotoxic agents in the environment (97–100). The source of the exposure was a chlordalkali plant that dumped methylmercury directly into surface water, which was then accumulated by marine biota, passed up the food chain to fish, and eventually ingested by the human population of the area. Thousands of people were exposed and hundreds of people became clinically ill during the years before and shortly after the hazard was recognized. A subsequent outbreak of organomercury poisoning occurred in Iraq in 1971 to 1972 when grain treated with an organomercury fungicide was ground for bread rather than stored for spring planting; thousands of people became clinically ill and hundreds died as a result of exposure. As a consequence of these tragic episodes, the toxicity produced by organomercury compounds in humans is well characterized. Effects include mental disturbances, paresthesias, visual deficits, disturbances of gait, tremor, and weakness. The fetus or nursing infant is more sensitive to the effects of methylmercury than the adult, and signs include cerebral palsy and mental retardation. The neurotoxic effects produced in humans have been well replicated in animal models. Methylmercury exposure in monkeys produces the same types of visual and somatosensory deficits observed in humans. Rodents have been used to explore the motor deficits produced by methylmercury. Developmental exposure results in greater impairment than adult exposure, and the overt neurotoxic effects observed in infant monkeys are similar to those observed in infant humans.

**Effects in Humans**

The effects of methylmercury toxicity in humans are well documented and have been extensively reviewed (97–100). In adults in Japan, the most common complaints were of sensory and motor disturbances including vision, hearing, and somatosensory dysfunction, unsteadiness of gait and disequilibrium, muscle weakness, and dysarthria (101). Data from human mother–infant pairs suggest that infants are born with higher blood mercury levels than their mothers have (102–104). It is not clear whether infants eliminate mercury more slowly than their mothers (102,103) or whether children eliminate mercury more slowly than adults after methylmercury exposure. Neonatal and in utero exposures to methylmercury often result in more severe signs of intoxication in the offspring than in the mother (105–109); signs of intoxication include cerebral palsy, mental retardation, and delayed walking and speech (105–110). In a study in New Zealand of children exposed to methylmercury in utero, relatively low maternal hair mercury levels were associated with increased deficits in motor, language, psychological, scholastic, and behavioral tests at 4 (111) and 6 (112) years of age.

Deficits in visual function are a hallmark of methylmercury intoxication in humans (113–115). In adult methylmercury poisoning, the most conspicuous finding is constriction in visual fields; however, other visual deficits have also been reported in adults, including deficits in spatial (116,117) and temporal (118,119) visual function. Developmental exposure at high levels may result in oculomotor manifestations and blindness (103,120–123), whereas less severe poisoning may result in changes in acuity (116) and constriction of visual fields (106,107). The pattern of damage produced by methylmercury in the human visual system has been well delineated, with primary visual cortex being a major site of damage. In adult poisoning, the most severe damage is in calcarine fissure (105,124,125), which corresponds to the peripheral visual fields. In postnatal or in utero exposure, however, damage is more diffuse with neuronal loss in all areas of visual cortex (105,126–128), as well as in many other brain areas. Retina and optic nerve are presumed not to be involved (118).

Hearing deficits have been frequently observed. Frequency of hearing deficits in adults as a result of methylmercury poisoning ranges from 42 (115) to 85% (101,110). Assessment of pure tone detection thresholds, tested in the range of speech frequencies, revealed hearing impairment in half the ears tested (129). Severe hearing impairment, deafness, and delayed speech development have resulted from in utero exposure to methylmercury (103,122,130).

Paresthesias are also frequently reported in adults as a result of methylmercury exposure (131). In fact, it appears that the most sensitive effect of methylmercury exposure in adults is paresthesias (Figure 4), with a threshold of 25 to 40 mg total mercury uptake. The World Health Organization (WHO) has relied largely on the Iraqi data in generating dose–response relationships for toxicity associated with methylmercury (98–100). It was estimated that long-term daily mercury intake of 3 to 7 μg/kg body weight (bw) associated with blood mercury levels of 200 μg/l and hair concentrations of about 50 μg mercury per gram would be associated with a 5% incidence of early effects in adults. Effects in the fetus occur at maternal body burdens considerably lower than effects in the adult. For example, the threshold in maternal hair associated with delayed walking in the infants of exposed mothers may be one-fifth of that necessary to produce the earliest effects in adults (Figure 5) (100).

**Animal Studies**

Many of the effects of methylmercury observed in humans have been replicated and extended in animal models (132,133). In some respects the rodent does not represent an optimum model for effects in humans. The rodent brain does not have the pattern of deep sulci of the human (and monkey) brain, which are preferentially damaged by methylmercury (125). Therefore, the pattern of central nervous system damage is different between primates and rodents (128). This difference is reflected in differences in the pattern of neurologic, sensory, and behavioral effects observed in rodents and primates, including humans. Early studies in rodents...
DEMONSTRATED MOTOR DEFICITS AS A RESULT OF PRENATAL EXPOSURE, ALTHOUGH THE PATTERN OF CEREBRAL PALSY AND SEVERE SENSORY IMPAIRMENT CHARACTERISTIC OF HIGH DOSE IN UTERO EXPOSURE IN HUMANS WAS NOT OBSERVED. IN CONTRAST, EXPOSURE OF ADULT (134) OR NEONATAL (135) MONKEYS TO METHYLMERCURY REPLICATED THE PATTERN OF SENSORY AND MOTOR IMPAIRMENT PRODUCED IN HUMANS. THE TOXICOINKINETICS OF METHYLMERCUry ARE ALSO QUITE DIFFERENT BETWEEN PRIMATES AND RODENTS. FOR EXAMPLE, THE RATIO OF MERCURY BETWEEN BRAIN AND BLOOD FOLLOWING METHYLMERCUry EXPOSURE IS 2 TO 5 FOR MONKEYS FOLLOWING MODERATE-LEVEL CHRONIC EXPOSURE (136-139), WHICH IS SIMILAR TO THE ESTIMATES FOR HUMANS (140). THIS IS IN MARKED CONTRAST TO THE ESTIMATED BRAIN-BLOOD RATIOS OF THE RAT (0.06), ALTHOUGH THE ESTIMATE FOR THE MOUSE IS 1.2 (140).

ONE OF THE HALLMARKS OF METHYLMERCUry NEUROTOXICITY IN THE ADULT HUMAN IS DEFICITS IN VISUAL FUNCTION AS A RESULT OF NEUROPATHOLOGIC DAMAGE TO CALCANEAL FISSURE. ATTENTION HAS FOCUSED ON CONSTRUCTION OF VISUAL FIELDS, ALTHOUGH OTHER DEFICITS SUCH AS IMPAIRED SPATIAL VISUAL FUNCTION HAVE ALSO BEEN OBSERVED (117). CONSTRUCTION OF VISUAL FIELDS HAS BEEN REPLICATED IN THE ADULT MACAQUE MONKEY (141), WHICH EXHIBITS A PATTERN OF DAMAGE IDENTICAL TO THAT IN THE HUMAN. OTHER FUNCTIONAL DEFICITS IN VISUAL FUNCTION HAVE ALSO BEEN DOCUMENTED IN ADULT MONKEYS EXPOSED TO METHYLMERCUry. DEFICITS IN LOW-LUMINANCE FORM VISION WERE DETECTED ON A VISUAL DISCRIMINATION TASK; THESE EFFECTS PRECEDED MORE GLOBAL VISUAL DEFICITS (134).

DECREMENTS IN DETECTION OF A FLICKERING STIMULUS AT LOW LUMINANCE HAVE BEEN OBSERVED IN MONKEYS THAT ALSO DEMONSTRATED CONSTRUCTION OF VISUAL FIELDS (141), WHICH REPLICATES EFFECTS OBSERVED IN HUMANS (119). DECREASED FlickER SENSITIVITY HAS ALSO BEEN OBSERVED IN SQUIRREL MONKEYS EXPOSED TO METHYLMERCUry (142). MONKEYS IN THESE STUDIES HAD BLOOD MERCURY LEVELS OF 2.0 TO 3.0 PARTS PER MILLION (PPM). IN ADULT MONKEYS EXPOSED TO METHYLMERCUry, EXTENSIVE AND CONSISTENT NEUROPATHOLOGIC CHANGES SIMILAR TO THOSE IN ADULT HUMANS ARE OBSERVED IN VISUAL CORTEX (142-146). CHANGES IN THE OPTIC NERVE WERE NOT OBSERVED.

SINCE IT WAS CLEAR FROM THE EPISODES OF HUMAN MERCURY POISONING THAT THE DEVELOPING ORGANISM IS MORE SENSITIVE TO THE EFFECTS OF METHYLMERCUry INTOXICATION THAN THE ADULT, STUDIES AT THE CANADIAN HEALTH PROTECTION BRANCH HAVE ASSESSED SENSORY SYSTEM FUNCTION IN MONKEYS EXPOSED DEVELOPMENTALLY TO METHYLMERCUry. ONE GROUP OF FIVE MONKEYS WAS EXPOSED FROM BIRTH TO 7 YEARS OF AGE WITH 50 µG/KG/DAY OF MERCURY AS METHYLmercuric CHLORIDE. BLOOD TOTAL MERCURY LEVELS WERE 0.6 TO 0.9 PPM. A SECOND GROUP WAS EXPOSED IN UTERO PLUS POSTNATALLY TO 4 YEARS OF AGE; MATERNAL DOSES WERE 10, 25, OR 50 µG/KG/DAY, AND BLOOD MERCURY LEVELS WERE IN EQUILIBRIUM BEFORE BREEDING. MATERNAL BLOOD MERCURY LEVELS WERE 0.3 TO 1.4 PPM. FIVE INFANTS WERE BORN IN THE HIGHEST DOSE GROUPS, TWO AT THE INTERMEDIATE DOSE, AND ONLY ONE AT THE LOWEST DOSE. VISUAL DEFICITS WERE OBSERVED IN BOTH GROUPS OF MONKEYS AND IN ALL DOSE GROUPS (I.E., 50, 25, OR 10 µG/KG/DAY MATERNAL EXPOSURE) (147,148); TREATED MONKEYS EXHIBITED IMPAIRED HIGH-FREQUENCY SPATIAL AND LOW-FREQUENCY TEMPORAL VISION WITH NO CONSTRUCTION OF VISUAL FIELDS.

RELATIVELY LITTLE RESEARCH HAS BEEN PERFORMED IN ANIMALS ON THE EFFECTS OF METHYLMERCUry ON THE AUDITORY SYSTEM, AND MOST EXPERIMENTS WERE PERFORMED IN ADULT ANIMALS AFTER ACUTE HIGH-LEVEL EXPOSURE. DAMAGE HAS BEEN OBSERVED IN THE HAIR CELLS OF THE ORGAN OF CORTI (149-151). MEASUREMENT OF BRAIN STEM AUDITORY- EVOKED POTENTIALS REVEALED DEFICITS ACROSS ALL AUDITORY FREQUENCIES IN MICE (152). HOWEVER, LOW-DOSE CHRONIC EXPOSURE MAY PRODUCE A DIFFERENT PATTERN OF DAMAGE COMPARED TO HIGH-DOSE ACUTE EXPOSURE, AS HAS BEEN OBSERVED FOR OTHER METALS SUCH AS LEAD. THE MONKEYS EXPOSED ONLY POSTNATALLY EXHIBITED IMPAIRMENT OF HIGH-FREQUENCY HEARING 7 YEARS AFTER CESATION OF METHYLMERCUry EXPOSURE (153).

INDICATIONS OF DELAYED NEUROTOXICITY IN MONKEYS AS A RESULT OF DEVELOPMENTAL METHYLMERCUry EXPOSURE HAS ALSO BEEN REPORTED (154). THIRTEEN-YEAR-OLD MONKEYS DOSED POSTNATALLY TO 7 YEARS OF AGE (DISCUSSED ABOVE) WERE OBSERVED TO BE CLUMSY AND TO TAKE LONGER TO RETRIEVE RAISINS 6 YEARS AFTER CESATION OF METHYLMERCUry EXPOSURE. INDEPENDENT CLINICAL ASSESSMENT BY TWO VETERINARIANS ALSO REVEALED A HIGHER INCIDENCE OF FAILURE TO RESPOND TO A LIGHT TOUCH OR PIN PRICK TO THE HANDS, FEET, OR TAIL IN METHYLMERCUry-EXPOSED MONKEYS. IN ADDITION, OBSERVATION OF THESE MONKEYS IN THE LARGE CAGES IN WHICH THEY HAD EXERCISED AND SOCIALIZED SINCE INFANCY REVEALED CLUMSINESS IN SOME TREATED INDIVIDUALS, A TENDENCY FOR THE HIND FEET TO SLIP DOWN THE BARS WHEN CLIMBING, AND A PREFERENCE FOR CLIMBING FROM AREA TO AREA RATHER THAN JUMPING. THESE MONKEYS HAD UNDERGONE ROUTINE CLINICAL ASSESSMENT OF SENSORY AND MOTOR FUNCTION FROM INFANCY TO ABOUT 4 YEARS OF AGE, WITH NO SIGNS OF TOXICITY NOTED. THE OBSERVATION OF OVERT TOXICITY AT AGE 13, 6 YEARS AFTER CESATION OF DOING, THEREFORE REPRESENTS DELAYED NEUROTOXICITY AS A CONSEQUENCE OF METHYLMERCUry EXPOSURE. THESE OBSERVATIONS WERE PURSUED OBJECTIVELY BY MEASURING VIBRATION SENSITIVITY IN THE FINGER TIPS IN THESE MONKEYS (155). METHYLMERCUry-TREATED MONKEYS EXHIBITED HIGHER SENSORY THRESHOLDS, WHICH INDICATED A REDUCED ABILITY TO DETECT VIBRATION. THESE RESULTS ARE CONSISTENT WITH THE REPORTS OF PARESTHESIAS IN METHYLMERCUry-EXPOSED HUMANS.

EFFECTS OF DEVELOPMENTAL METHYLMERCUry EXPOSURE ON INTELLIGENT FUNCTION HAVE ALSO
been pursued in animal models. In a study on the effects in utero exposure to methylmercury in the monkey, females received 50, 70, or 90 μg/kg/day of methylmercury. The offspring from the lowest dose group were tested on an object permanence task beginning at 2 weeks of age (156). This task tested the infants' ability to realize that an object placed out of sight was still present. Methylmercury-exposed infants took longer to learn this task than control monkeys, as well as being retarded in the development of the skill of simply reaching for an object in view. These same infants were tested on a series of visual recognition tasks beginning at about 1 month of age (157,158). In this task, the preference of the infant for a new stimulus, assessed by the time spent looking at a novel versus familiar picture, is interpreted as being indicative of memory processes. This test is used with human infants and is thought to be highly predictive of later performance on intelligence tests during childhood. Methylmercury-exposed infant monkeys were impaired on this task. Blood levels of the mothers in the lowest dose group were 1.1 ppm, with infant levels of 1.0 ppm at birth. This group of monkeys exhibited facilitated performance on a test of spatial learning and memory as adults (159). Monkeys exposed to methylmercury from birth to 7 years, or in utero to 4 years of age, exhibited no impairment in their ability to learn the complex tasks required for testing of sensory system function.

In a collaborative study involving six laboratories in the United States, the effects of 2.0 or 6.0 mg/kg of methylmercury in rats administered on gestational days 6 to 9 were studied on negative geotaxis, olfactory orientation, auditory startle habituation, activity, activity following a pharmacologic challenge, and a visual discrimination task (160). Facilitation of auditory startle at the high dose of methylmercury was reliably observed across laboratories with inconsistent or minimal effects on activity, pharmacologic challenge, and the discrimination task, in the presence of overt signs such as decreased weight gain and delayed developmental landmarks. Additional research with a different battery of tests using a subset of the rats from the U.S. collaborative study revealed delayed righting and swimming ontogeny and decreased activity (161). Impairment was also observed on performance in a complex water maze, a task heavily dependent upon intact motor function. Most effects were observed only at the high dose.

In a collaborative study in Europe, rat dams were exposed to methylmercury in drinking water during pregnancy and lactation. Delayed sexual maturity and impaired righting and swimming ability were observed in the offspring (162). Assessment of complex learning measured by visual discrimination reversal and spatial delayed alternation performance revealed increased response latencies and an increased incidence of failure to respond during a trial with no effect on accuracy of performance (163,164). In addition, the pattern of locomotor behavior in a complex activity monitor differed between control and methylmercury-treated offspring, with treated rats exhibiting less behavioral diversity. In a follow-up study involving five European laboratories, dams were exposed to methylmercury in doses of 0.0025 to 5.0 mg/kg/day on days 6 to 9 of gestation (165). This study in general confirmed results of the previous study with respect to the lack of effect on accuracy of performance in the visual discrimination and delayed alternation tasks. Methylmercury-treated offspring exhibited delayed vaginal opening, impaired swimming behavior, decreased locomotor activity, increased amplitude in auditory startle, and decreased activity on a variety of end points in the learning tasks. Most effects were observed only at the highest dose, but impaired swimming ability, increased auditory startle, and failure to respond on a spatial alternation task were observed at 0.5 mg/kg. Delayed vaginal opening was observed at 0.025 mg/kg, the lowest dose at which an effect was observed.

In another study in which methylmercury was used to validate a test battery, dams were exposed on days 6 to 15 with 1.2, or 6 mg/kg of methylmercury (166). No effects were observed on T-maze alternation, locomotor activity, amplitude or habituation of auditory startle, observational assessment, or olfactory discrimination at the lowest two doses. (The highest dose was lethal.)

The effects of methylmercury on intermitent schedules of reinforcement have also been studied. Monkeys exposed in utero plus postnatally, discussed above, displayed a pattern of response on a fixed interval schedule that suggested a decreased ability to discriminate time (167). Rats prenatally exposed to methylmercury were found to exhibit retarded acquisition of a lever-press response, with more responses during extinction than control rats (168); this suggests impairment of inhibitory mechanisms in methylmercury-treated rats. In a pair of studies specifically designed to be sensitive to the known effects of methylmercury neurotoxicity in the rodent, rat dams were gavaged with methylmercury on days 6 to 9 of gestation at doses between 0.005 and 0.50 mg/kg (169,170). Offspring were impaired in their ability to perform on a DRH schedule of reinforcement in which a number of responses on a lever were required in a specified (short) period of time. Methylmercury-treated offspring performed normally when required to press a lever twice within 1 sec to be reinforced [differential reinforcement of high rate (DRH) 2/1] but not when the response requirement was incrementally increased to DRH 4/2 and then DRH 8/4. Both male and female rats were reliably affected at a dose of 0.01 mg/kg, the lowest dose at which effects have been observed in rodents. The robust effects observed on this paradigm may be the result of motor impairment, although cognitive deficits or decreased motivation also may have contributed to the poorer performance of the treated rats. Squirrel monkeys exposed during the last half of gestation to variable doses of methylmercury were found to be impaired on an intermittent schedule of complex learning at 5 to 6 years of age (171). Monkeys were free to respond on two levers, which were programmed to deliver reinforcement at different densities (i.e., one lever was richer than the other). The behavior of control monkeys was sensitive to the difference in reinforcement densities between the two levers while that of the methylmercury-treated monkeys was not.

It is clear that the most salient effect of methylmercury exposure in animals is impairment of motor and sensory function. In the rodent, motor deficits were reliably observed as a result of developmental exposure. Prenatal exposure in the monkey replicates the cerebral palsy observed in humans exposed to high doses. At lower doses, developmental exposure produced deficits in all sensory systems examined—visual, auditory, and somatosensory (vibration). The effects on cognitive function are less clear. In rodents, results were largely negative or showed a weak high-dose effect. In the monkey, deficits were observed during infancy as a result of in utero exposure; effects during adulthood, as a result of even relatively long-term developmental exposure, failed to reveal deficits on most tasks, although intermittent schedules may be sensitive to methylmercury-induced alterations in behavior. In general, the results from the
animal literature are in good agreement with effects in humans in which sensory and motor deficits are also the most prominent features of toxicity under low or moderate exposure conditions.

**Contribution from Great Lakes Sources**

The main exposure route to methylmercury in the general population is through consumption of contaminated fish. There are sufficient data on the neurotoxic effects of methylmercury from episodes of human poisoning, particularly data from the Iraqi episode, to reasonably estimate the intake associated with specific adverse effects (100). For adults, an intake of 50 μg per person per day would result in a 0.3% incidence of paresthesias; an intake of 3 to 7 μg/kg of mercury per day would result in a 5% incidence of effects in the adult population. The current U.S. Environmental Protection Agency (U.S. EPA) RfD is 0.3 μg/kg/day based on paresthesia in adults. However, the developing fetus is affected at a threshold one-fifth of that at which effects occur in the mother, or 0.6 to 1.4 μg/kg of mercury per day to the mother. [In fact, there may not be a threshold (100).] Assumption of a safety factor of 10 for intraspecies variability would result in an allowable intake of 0.06 to 0.14 μg/kg of mercury per day. In the monkey, neurotoxicity was reliably detected as a result of in utero or postnatal exposure to 50 μg/kg/day. (Neurotoxicity was also apparent at 10 or 25 μg/kg/day, but the total sample consisted of only three monkeys.) Assuming a safety factor of 1000 for extrapolation between species, individual variability and the fact that 50 μg/kg/day is a LOAEL rather than a NOAEL would result in an allowable intake in humans of 0.05 μg/kg/day, which is consistent with the estimates from the human data. The most sensitive study in rats in which a LOAEL of 0.01 mg/kg and a NOAEL of 0.005 mg/kg were identified would also yield an RfD of 0.05 μg/kg/day. In an extensive review of the human data, Stern (172) suggested an RfD of 0.07 μg/kg/day of mercury per day to protect against developmental toxicity. The U.S. EPA Office of Water derived an RfD of 0.06 μg/kg/day in a draft document. Both of these calculations are based on the Iraqi studies demonstrating neurologic signs or delayed walking in infants born to mothers consuming methylmercury. Gilbert and Grant-Webster (173) suggested an RfD of 0.025 to 0.06 μg/kg/day based on both the epidemiologic and animal data.

The estimates of fish intake that have been used to estimate risk to various populations vary widely. For example, the U.S. EPA (174) estimated the 50th percentile intake for recreational anglers to be 30 g/day, with the 90th percentile at 140 g/day. Bolger et al. (175) estimated intakes at 13 g/day and 26 to 40 g/day for the 50 and 90th percentiles, respectively, for fish caught by recreational anglers, based on the assumption that one fishing trip results in the consumption of 8 oz of fish. Current Canadian guidelines assume an intake of 20 g of fish per day for the general population and 40 g/day for frequent fish eaters. The Market Research Corporation of America's 1982 to 1987 14 Day Menu Census 1V study (176) reported a mean intake of 32 g/day and a 90th percentile of 64 g/day for the fish-eating portion of the population. Stern (172) performed a Monte Carlo analysis based on these latter intake estimates and levels of mercury in fish intended for human consumption published by the National Marine Fisheries Service. In that analysis, 52% of the fish had total mercury levels ≤0.05 μg/g and 5% of the catch had mercury levels ≤0.25 μg/g. Stern concluded that a substantial proportion of women (23%) would exceed a maximum allowable intake based on an RfD of 0.07 μg/kg/day, and 0.5% of women would exceed the 7 μg/kg/day intake demonstrated to cause in utero developmental effects.

Assuming an RfD of 0.07 μg/kg/day, methylmercury consumption should not exceed about 4 μg/day for a 62-kg woman. An intake of 20 g of fish per day, the Canadian estimate for the general population, would yield maximum allowable levels in fish of 0.30 μg/g. An intake of 64 g/day, the 90th percentile based on the Market Research Corporation data and used by Stern in his analysis, would yield a maximum allowable level of mercury in fish of 0.06 μg/g. Mercury levels in Great Lakes fish routinely exceed even the higher of these numbers. For example, in a survey of walleye in northern Wisconsin Lakes in 1990 to 1991, 45% had levels greater than 0.5 μg/g (177). Data from 1991 from the Canadian Department of Fisheries and Oceans for commercial fish intended for human consumption taken from the four Great Lakes bordering Canada revealed levels averaging 0.14 to 0.32 μg/g depending on location and fish species (including piscivorous and nonpiscivorous fish) (unpublished data). The average for the entire sample of over 400 fish was 0.23 μg/g. There are significant gaps in the data required for a definitive analysis of the proportion of women of childbearing age who may be considered at risk as a result of consumption of Great Lakes fish. Among these are the distribution of the amount of Great Lakes fish consumed, particularly for individuals or groups consuming large amounts of fish; the pattern of species of fish consumed by individuals; the geographical source of the fish; and other sources of methylmercury exposure such as tuna or shark. Nonetheless, the data presently available suggest that consumption of Great Lakes fish represents a potential hazard to offspring of women consuming large quantities of fish.

### Polychlorinated Biphenyls

Polychlorinated biphenyls are a family of chemicals containing 209 different isomers (congeners). Their major use was as a dielectric in transformers and capacitors, although they had other industrial uses as well. They were in widespread use from the 1930s until the 1970s; they are presently a worldwide pollution problem because they are resistant to either chemical or biologic degradation and they (like methylmercury) accumulate in the food chain. It is clear from both the animal literature and human epidemiologic studies that the developing organism is more sensitive to behavioral deficits produced by PCBs than the adult. At least two prospective studies have been published that assess the relationship between PCB exposure and adverse effects in infants, which have been critically reviewed (178,179). There is also a recent review of the animal literature with respect to developmental toxicity associated with PCBs (179). Several studies have been performed in monkeys at the University of Wisconsin on the reproductive effects and later behavioral consequences in the offspring of exposure to PCB mixtures. Studies in rodents have also revealed behavioral impairment as a result of developmental exposure to PCBs. The following sections provide a brief review of the literature, with emphasis on body burdens at which effects were observed.

### Human Epidemiologic Studies

In 1968 a tragic epidemic in Japan occurred as a result of contamination of rice oil with PCBs and small amounts of other contaminants (180). Infants born to mothers who consumed the contaminated oil had dark pigmentation of the skin, low birth weight, early eruption of the teeth, and swollen gums and eyelids. In another incident in
Japan, affected children had hypotonic reflexes, were dull and apathetic, and had low IQs (181). Children born after a similar incident in Taiwan were followed for at least 6 years (182). These children exhibited delayed developmental milestones and deficits on the Bayley, WISC, and Rutter scales. These effects were observed at exposure levels that produced overt signs including gum hypertrophy, deformed or pigmented nails, acne, hyperpigmentation, and hair loss. In addition, these children were also exposed concurrently to more toxic polychlorinated dibenzo- furans.

An extensive prospective study involved Michigan children born to women who consumed fish from Lake Michigan (183-190). Reduction in birth weight, head circumference and gestational age were associated with consumption of contaminated fish. Fish consumption in the mothers was also associated with lower scores on the Brazelton Neonatal Behavioral assessment in the infants. Decreased visual recognition memory in this same set of infants at 7 months of age was associated with both maternal fish consumption and cord serum PCB levels (186). Visual recognition memory has been shown to be highly predictive of performance on later tests of intelligence (191-194). There was no association with postnatal exposure through nursing, and there was no association between polybrominated biphenyl (PBB) levels and outcome in these infant studies. This cohort was tested again at 4 years of age; cord PCB levels were associated with decreased weight (188) and poorer short-term memory (Figure 6) (189). These measures were not associated with concurrent blood levels of PCBs, PBBs, lead, or dichlorodiphenyl-trichloroethane (DDT). (A number of other possible contaminants were not detected in blood.) Hyperactivity was associated with concurrent blood PCB levels (188).

A cohort of breast-fed infants was followed prospectively for 60 months in a North Carolina study (195-197). Mothers had no known excessive exposure to PCBs. Higher in utero PCB exposure as assessed by maternal milk fat PCBs was associated with hypotonicity and hyporeflexia on the Brazelton Neonatal Behavioral Assessment; there was no association with birth weight or head circumference (198). Higher transplacental but not postnatal PCB exposure was associated with lower Bayley Scale scores at 6 and 12 months of age (195). There was no association between either prenatal or concurrent PCB levels and a negative outcome on the McCarthy Scale of Children's Ability at 3 to 5 years of age. Dichlorodiphenyl-dichloroethane (DDDE) levels were also measured in this study and were largely unrelated to outcome variables.

The most sensitive indicator of neurotoxicity was a deficit in visual recognition memory in infants in the Michigan study. Tilson et al. (179) estimated the NOAEL, by visual inspection of the data, to be 1.0 ppm PCB in the fat of breast milk. They assumed a 60-kg woman with 25% fat to derive a daily intake of 0.027 μg/kg/day; this would result in a 1.0-ppm level in milk fat, which they assumed to be equivalent to the level in body fat. The human RFD derived was therefore 2.7 × 10^-3 μg/kg/day.

**Figure 6.** Adjusted McCarthy Verbal scale scores (A) and McCarthy Memory scale scores (B) at 4 years of age as a function of maternal blood PCB levels. Group sample-size numbers are in parentheses. From Jacobson et al. (189).

**Animal Studies**

Many of the same or similar effects observed in the human epidemiologic studies have been observed in animal studies, particularly in monkey studies performed at the University of Wisconsin. Two series of experiments were performed: one with Aroclor 1248 and the other with Aroclor 1016; both experiments were developmental studies. In general, offspring were exposed in utero and through breast milk until 4 months of age. Reproductive outcome was assessed and the offspring underwent extensive behavioral testing into adulthood.

In the Aroclor 1016 study, adult females were exposed to 0, 0.25, or 1.0 ppm PCBs in the diet (199,200), which corresponded to approximately 0.007 and 0.028 mg/kg body weight (bw) per day for the low- and high-dose groups, respectively. Birth weight of the infants was significantly reduced in the high- but not the low-dose group (201), with no difference in head circumference or crown-to-rump length. Overt signs in the form of hyperpigmentation were present in both groups of infants. Behavioral assessment was first performed when offspring were 14 months old (199,200); high-dose monkeys were impaired on a spatial discrimination reversal task. This same group of monkeys was tested on a spatial delayed alternation task (a spatial learning and short-term memory task) at 4 to 6 years of age (200,202). Neither group was different from controls, although the high-dose group was impaired relative to the low-dose group. This was due to a slightly improved performance of the low-dose and slightly impaired performance of the high-dose group relative to controls. These data yield a NOAEL of 0.7 × 10^-2 mg/kg/day based on learning and memory impairment and infant birth weight, and consideration of fetotoxicity and chloracne results in a LOAEL of 0.7 × 10^-2 mg/kg/day with no NOAEL.

In the Aroclor 1248 studies, females were exposed to 0, 0.5, or 1.0 ppm PCBs in the diet 3 days per week beginning before breeding and continuing until offspring were weaned at 4 months of age. Additional groups of females were exposed to 2.5 ppm either concurrent with breeding, or in which exposure ceased 1.0, 1.5, or 3.0 years before breeding; these females produced a number of sets of offspring. Concurrent exposure to 2.5 ppm resulted in reduced birth weight (203) and deficits in discrimination-reversal learning (204). These monkeys were hyperactive when young (204) and hypoaactive at 44 months of age (205). Monkeys exposed concurrently to 0.5 ppm were hyperactive at 12 months of age (206). The group born to mothers 1.0 year after cessation of exposure to 2.5 ppm showed facilitated performance on a shape discrimination-reversal task (199), which the authors interpreted as a deficit in the treated group's ability to learn the irrelevance of the shape cue on a previous
The performance of the 1.0 ppm group was not impaired on this task. Monkeys born to mothers 1.5 or 3.0 years after cessation of exposure to 2.5 ppm PCBs were impaired on a spatial alternation task at 4 to 6 years of age (200).

The concentrations in the feed of 0.5, 1.0, and 2.5 ppm represent approximate intakes of 0.008, 0.016, and 0.089 mg/kg/day, respectively. (Mothers exposed to 2.5 ppm ingested about 290 mg [0.63 mg/week] of PCBs over 86 to 89 weeks; mothers exposed to 1.0 ppm ingested 7.5 mg/kg over 16 months.) It is difficult to establish RfDs from these data since infants born as long as 3.0 years after maternal exposure to 2.5 ppm exhibited impaired learning; the exposure levels of this cohort are unknown. However, the most sensitive effect in a concurrently exposed group was hyperactivity observed in the 0.5-ppm group at 1 year of age. The RfD derived from this end point would be $8 \times 10^{-9}$ mg/kg/day.

There is a relatively large body of data on the effects of developmental toxicity of PCBs in the rodent, which focuses on neurotoxicity (179) or developmental end points (207). Tilson et al. (179) concluded that the most consistently observed effect across species was hyperactivity, although cognitive deficits were also observed in rodents as well as in monkeys. It is clear that the rodent is less sensitive than the monkey or human; Tilson et al. (179) derive RfDs from the rodent data two orders of magnitude higher than those based on monkey data.

The human and animal data are in good agreement with respect to the types of deficits observed. The monkey, like the human, develops chloracne and hyperpigmentation as a result of developmental PCB exposure. Changes in neuromotor function were consistently observed in both rodent and monkey studies. In both the Michigan and North Carolina studies, the Brazelton assessment revealed abnormally weak reflexes and deficient fine motor control. Both human and animal studies revealed cognitive deficits. In particular, the memory deficits observed on the visual recognition task in the Michigan study are consistent with the impairment of memory and attention observed in monkeys. The human studies are problematic in that exposure through fish also potentially resulted in exposure to other neurotoxic agents correlated with PCB levels in contaminated fish. While some of these potential confounders were assayed in the Michigan studies, the failure to determine methylmercury levels is a potentially serious weakness. However, the congruence between the monkey and human data suggests that the deficits observed in the human studies result at least in part from PCB exposure.

**Contribution from Great Lakes Sources**

The U.S. EPA has derived an RfD for Aroclor 1016 of 0.07 µg/kg bw per day from the monkey data (208) based on a NOAEL for reduction in birth weight of 7.0 µg/kg bw per day (0.25 ppm in feed) (197–200) and an uncertainty factor of 100. Tilson et al. (179) have calculated a LOAEL from the 1248 monkey studies of 14 µg/kg bw per day based on behavioral data; there was not a NOAEL. The recommended RfD derived from these data was 0.014 µg/kg bw per day. Based on the calculations in the above section, the RfD based on the observed hyperpigmentation in the Aroclor 1016 monkey study would be 0.007 µg/kg per day, and for the 1248 study, it would be 0.008 µg/kg/day.

Tilson et al. (179) derived a NOAEL for humans of 0.027 µg/kg/day based on impaired visual recognition memory in infants in the Michigan study. However, some of the assumptions upon which this calculation was based have been criticized (e.g., Great Lakes Sport Fish Advisory Task Force (GLSFAF) (209)), particularly the assumption that there is no metabolism or excretion of PCBs. Estimates of half-lives in humans (not necessarily women) range from 1.8 years to 9.9 years (210–212), depending on which commercial mixture or congener is considered. Estimates for congener 153, the most common congener found in Lake Michigan anglers (209), is 5.4 to 9.9 years (213). Assuming a half-life of 1 year yields a NOAEL based on visual recognition memory of 0.475 µg/kg/day, while assumption of a 10-year half-life results in a NOAEL of 0.0475 µg/kg/day (209). Therefore, these various estimates would yield an RfD between 0.0027 and 0.0475 µg/kg/day depending on assumptions concerning degree of metabolism.

The Agency for Toxic Substances and Disease Registry (214) derived a minimum risk level (similar to an RfD) of 0.005 µg/kg/day based on immune effects in monkeys. The Tennessee Valley Authority developed an RfD of 0.05 µg/kg/day, and the Ohio River Valley Sanitation Commission (215) derived an RfD of 0.1 µg/kg/day for low chlorinated PCBs such as Aroclor 1016 or 1242 and an RfD of 0.01 µg/kg/day for more highly chlorinated PCBs such as Aroclor 1254. The National Wildlife Federation (216) derived an RfD of 0.01 µg/kg/day based on the behavioral data from the monkey; the GLSFAF (209) derived an RfD of 0.05 µg/kg/day based on the behavioral data from the Michigan epidemiologic study. The Joint FAO (Food and Agriculture Organization)/WHO Expert Committee on Food Additives (217) did not establish a value for tolerable intake in humans; they concluded that 0.04 mg/kg/day was a no-effect dose based on the monkey studies.

Assuming an RfD of 0.01 µg/kg/day, a 90th percentile intake of 64 g/day of fish would yield an allowable level in fish of approximately 0.01 µg/g, and an RfD of 0.05 µg/kg/day would yield a value of approximately 0.05 µg/g. The Lake Ontario Toxics Management Plan (218) reported levels in coho salmon from the Credit River in 1988 of 1 µg/g; levels in lake trout in the same year were >3 µg/g. De Vault (219) reported PCB levels in lake trout in Lake Superior to be <0.5 µg/g, while levels in Lake Michigan were >2.5 µg/g; they reported that levels over the last few years appear to have stabilized after decreasing for more than a decade. According to a document from the State of the Great Lakes conference (220), PCB levels in walleye in Lake Erie increased between 1989 and 1992 to levels of over 2 µg/g. The GLSFAF (209) reported that the average PCB levels in coho salmon in Lake Michigan are currently 0.8 µg/g. Data from the Canadian Department of Fisheries and Oceans for 1991, based on approximately 450 samples of Great Lakes fish including piscivorous and nonpiscivorous fish, revealed an average PCB level of 1.38 µg/g. Similar levels were found in a recent independent analysis of commercial Great Lakes fish (221). It is apparent that PCB levels at many sites are considerably higher than recommended levels based on the RfDs derived by a number of agencies and, in fact, are well into the range that may be expected to produce developmental neurotoxicity.
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