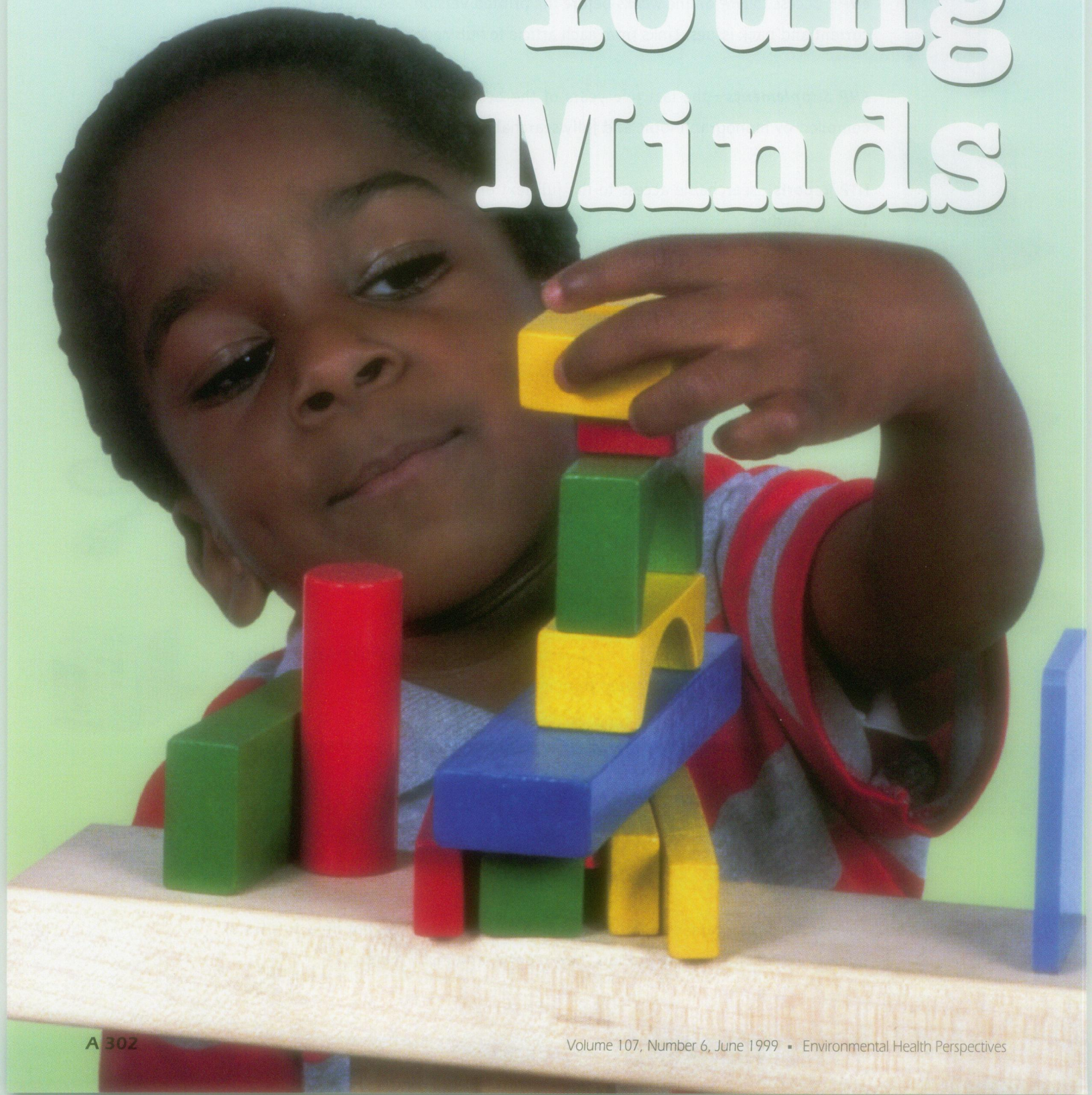
Poisoning Young Minds



Behavioral and developmental problems in children are among the most pervasive sociological issues in the United States today. Learning disabilities, intellectual retardation, dyslexia, attention deficit/hyperactivity disorder (ADHD), autism, and propensity to violence are eventually diagnosed in 3% of all children born in the United States, says Philip J. Landrigan, a pediatrician who chairs the Department of Community and Preventative Medicine at the Mount Sinai Medical Center in New York. Evidence is mounting that, in some cases at least, these disorders may be linked to exposure to chemicals in the environment.

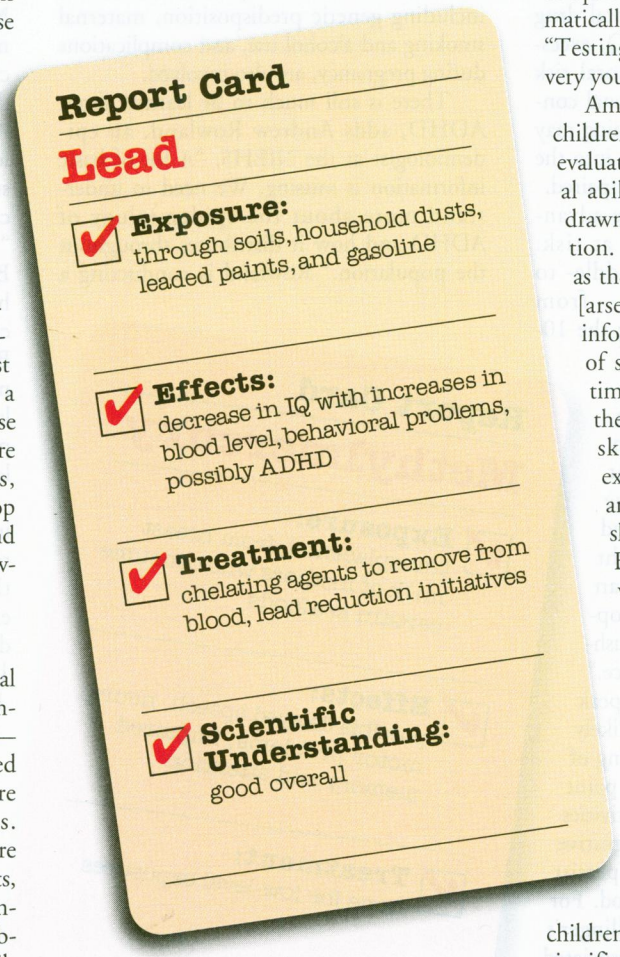
With the focus in toxicology shifting toward the study of low-level effects, researchers are finding that neurobehavioral end points in exposed children and animals can be observed at doses far below those that cause more obvious signs of toxicity. Chemically induced problems with coordination, perception, and cognitive ability in children can be hard to identify, and teasing their sources out of a host of genetic and sociocultural influences is a difficult task. But as data to support these end points continue to accumulate, pressure is mounting to improve test methods, explore causation mechanisms, and develop appropriate strategies for risk assessment and policy making regarding the effects of low-level chemical exposures in children.

Testing Behavior

Neurobehavioral effects from environmental chemicals in children have been most convincingly documented for three chemicals—lead, methylmercury, and polychlorinated biphenyls (PCBs)—although pesticides are also suspected of causing such effects. Solvents and polyaromatic hydrocarbons are also associated with neurobehavioral effects, but as these exposures are usually encountered in occupational settings or upon deliberate inhalation, the risk to very young children is smaller.

One reason for the lack of data on neurobehavioral effects is that documenting subtle behavioral changes in children is enormously complex. The nature of behavior itself is highly variable and dynamic. Bernard Weiss, a professor in the Department of Environmental Medicine at the University of Rochester School of Medicine and Dentistry in New York, describes behavior as a complicated expression of central nervous system function that doesn't necessarily bear a transparent relationship to the underlying structures and chemical processes. Expressions of behavior can be difficult to pinpoint and are highly dependent on age and developmental status at the time of testing. For these reasons, neurobehavioral studies are usually conducted by teams of toxicologists and developmental psychologists who have to navigate a tangled web of contributing factors such as parental IQ, drug and alcohol use of the mother during pregnancy, nutrition, and concurrent chemical exposures.

To identify neurobehavioral problems in exposed infants, researchers often rely on developmental psychology test batteries to evaluate a wide range of sensory–motor skills. One example is the Bayley Scales of Infant Development (BSID). Depending upon the age of the child, one of two forms of the test is used. The BSID I covers the age range of 1–30 months, whereas the BSID II covers the age range of 30–42 months. Both forms of the test evaluate cognitive skills such as memory, language, habituation, and problem solving, in addition to psychomotor development skills such as balance, locomotion, and fine motor coordination. According to David Bellinger, an associate professor of neurology at the Harvard Medical School, the BSID allows researchers to infer whether a child's development is progressing at a normal pace and form. Because this test assesses a broad range of skills, he adds, it is especially helpful to researchers who are unsure of how a chemical's effects are likely to be expressed. However, sensory–motor tests such as the BSID are likely to be less sensitive than tests targeted at specific brain functions that might be particularly vulnerable to a given exposure. These more specific skill tests are usually given to older children. "The range of options for testing children increases dramatically as they get older," says Bellinger. "Testing options for use with infants and very young children are few in number."



Among the tests used to assess older children are the traditional IQ tests, which evaluate different dimensions of intellectual ability, from which inferences can be drawn about central nervous system function. IQ tests are described by Bellinger as the "jewel of the psychologist's testing [arsenal]" because they provide a little information about each of a broad range of skills in a relatively short period of time. However, IQ tests are limited in their ability to identify which specific skills are impaired in a chemically exposed child. For this reason, they are sometimes supplemented by more skill-specific evaluations (such as the Bender Visual Motor Gestalt Test, which assesses visual and spatial skills) in order to obtain additional information about the nature of a chemical's effects.

Lead: A Continuing Problem

The best characterized of all the neurobehavioral toxicants is lead, which is widely considered to be the single most significant environmental health threat to U.S. children today. Low-level lead exposures can significantly impair cognitive and motor function in children, particularly if the exposures occur before the age of six. There is a general consensus among toxicologists that every increase in blood lead levels of 10 micrograms per deciliter (μg/dL) is associated with a one- to three-point drop in IQ. Although there is debate over the statistical validity of the association, a majority opinion holds that there is no threshold of effect in children, meaning that a level so low as to be without a measurable effect has yet to be identified. Lead-exposed children also exhibit behavioral problems and often have difficulty concentrating and staying focused. A study conducted by Herbert Needleman, a professor of psychiatry and pediatrics at the

University of Pittsburgh School of Medicine, found a dose-dependent relationship between lead exposure and heightened aggressive and delinquent behavior in 11-year-old boys. The study was published in the February 1996 issue of the *Journal of the American Medical Association.*

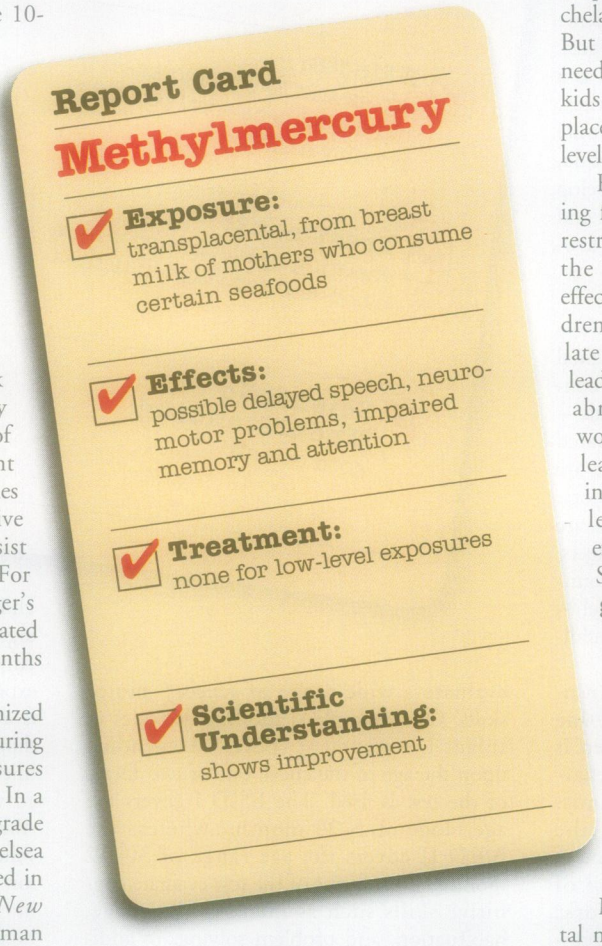
Although all children are potentially at risk for lead poisoning, the impact is greatest among the urban poor, who tend to live in older housing where lead-based paint and lead-contaminated soils and household dusts are a pervasive problem. Unfortunately, many children from poor urban neighborhoods are also saddled with parental drug and alcohol abuse, low parental IQ, excessive noise, and other neurobehavioral risk factors. Thus burdened, the additional contribution from low-level lead poisoning may be enough to nudge some children into the ranks of the severely intellectually impaired.

However, children from more advantaged backgrounds can also be at risk. Bellinger studied a cohort of middle- to upper-middle-class children from Cambridge, Massachusetts, during the 10-year period from 1983 to 1993. Of these children he says, "You might not notice lead effects in the high [socioeconomic status] group because the kids look okay. But when you test them you see that the performance of the [more] exposed kids is less than it otherwise might have been. No matter where they start out on the distribution [for developmental test scores], lead exposure pushes children toward lower performance."

Lead levels in children tend to peak at around two years of age, most likely due to high exposures from mouthing of toys (which can collect dust and paint chips) and other hand-to-mouth activities during this period. Effects on cognitive functioning have been found to persist into adolescence and early adulthood. For example, poor BSID scores in Bellinger's cohort at the age of two were still associated with reduced function at both 57 months and 10 years of age.

Whereas lead has long been recognized as a potent neurotoxicant, it is only during the last 20 years that low-level exposures have been linked to deficits in children. In a landmark study of first- and second-grade schoolchildren from the towns of Chelsea and Somerville, Massachusetts, published in the 29 March 1979 issue of the *New England Journal of Medicine*, Needleman found that behaviors such as distractibility, decreased persistence, dependence, and daydreaming were significantly correlated with elevated levels of lead in children's teeth. These findings contribute to a more recent hypothesis that in some cases lead may play a role in the development of ADHD. According to Bellinger, in the early 1990s the American Psychological Association refined the diagnostic criteria for ADHD to encompass two major categories: an impulsive hyperactive subtype and an inattentive subtype. Bellinger says that Needleman's findings closely parallel the criteria used to diagnose children with the inattentive subtype of ADHD. But lead's role in the etiology of ADHD is a subject of continuing investigation, he cautions, and it is likely that a host of other suspected risk factors, including genetic predisposition, maternal smoking and alcohol use, and complications during pregnancy, are also involved.

There is still much to be learned about ADHD, adds Andrew Rowland, an epidemiologist at the NIEHS. "A lot of basic information is missing. We need to understand more about the epidemiology of ADHD and how it distributes throughout the population." Rowland is conducting a two-year study of ADHD in a population of 8,000 children in North Carolina. This study will help to identify subpopulations in which the disorder is most prevalent and investigate possible causative factors, including reproductive problems such as preterm delivery and pregnancy complications and childhood blood lead levels. Needleman is also continuing to investigate lead's relationship with ADHD and is just beginning a clinical study that will assess lead exposures in 250 children already diagnosed with the disorder.



Children with clinical lead poisoning are usually treated with chelating agents that bind the metal and help flush it out of the body. Walter Rogan, medical research officer in the Epidemiology Branch of the NIEHS, is currently studying whether treatment with a chelating agent known as succimer can reduce or prevent lead-induced developmental delay [see NIEHS News, p. A298]. Prescribed for children poisoned at levels of 45 µg/dL or greater, this is the first study to evaluate lead's effects on neurological function following lower-dose exposures. "Treatment is a big question," says Bellinger. "Hopefully, Rogan's study will help us answer the question of whether chelating treatments have a beneficial effect. But all of these findings are pointing out the need for primary prevention. We don't want kids to get to 15 or 20 µg/dL in the first place. That's why screening for blood lead levels and abatement are so important."

Fortunately, the United States is benefiting from public health initiatives that have restricted most uses of lead and increased the public's understanding of its toxic effects. Mean blood lead levels in U.S. children have dropped from 13 µg/dL in the late 1970s to 3 µg/dL. But challenges in lead reduction efforts continue to be faced abroad, particularly in the developing world, where the continued presence of leaded gasoline, lead-based paints, and industrial discharges contributes to high levels of exposure. Mexico City, for example, is 15 years behind the United States in terms of its phaseout of leaded gasoline, and high body burdens of lead in the Mexican population are a continuing problem.

Methylmercury Raises Questions

Unlike lead, for which the critical window for exposure appears to occur postnatally, the fetal stage is considered to be the most sensitive period for methylmercury neurotoxicity.

Methylmercury is formed when elemental mercury forms complexes with organic molecules in the environment. Most people are exposed to methylmercury by eating contaminated fish. Fish advisories are common to many freshwater bodies in the United States, particularly in New England, which

lies in the path of airborne mercury emissions from industrial beltways in the Midwest. Advisories often target women of childbearing age, especially those who are already pregnant. At very high doses, methylmercury produces an illness similar to congenital cerebral palsy among children exposed *in utero*.

But methylmercury's effects at low doses are far more subtle and difficult to detect. Evidence is mounting that the brains of fetuses are exquisitely sensitive to methylmercury, and that low *in utero* exposures can produce symptoms in children that suggest neurodevelopmental delay. These symptoms are thought to include neuromotor problems, delayed speech, and problems with attention and memory. However, tests of prenatally exposed children often vary in their results, and no specific "behavioral signature" for methylmercury toxicity (or for any other neurotoxicant, for that matter) has yet been identified.

There is also a substantial database of evidence documenting persistent developmental effects of methylmercury exposure in animals. According to Deborah Rice, a toxicologist in the U.S. Environmental Protection Agency's (EPA) National Center for Environmental Assessment in Washington, DC, there is robust toxicological evidence for sensory and motor deficits in macaques exposed to methylmercury *in utero*. However, she adds that whereas epidemiologists have raised questions concerning cognitive effects from methylmercury in exposed children, the animal data are largely negative in this respect. "The evidence for cognitive effects from methylmercury in animal models is not compelling," she says.

Translating the available toxicology and epidemiology data to estimates of the amount of fish that can be eaten safely is a difficult task. Consumption of most store-bought fish is likely to be of minimal concern. According to the EPA document *Mercury Study Report to Congress*, released in December 1997, the top 10 seafood species that make up 80% of the seafood market all have methylmercury concentrations lower than 0.2 parts per million (ppm), which is considerably less than the action level of 1.0 ppm set by the Food and Drug Administration (FDA) (interstate sales of seafood with methylmercury concentrations above this limit are prohibited). Individual states set advisories for recreational fishing in specific waterbodies, but limits on consumption vary according to both the concentrations in the fish and the extent of recreational fishing on the given waterway. Currently, 41 states have issued waterbody-specific fish advisories for methylmercury.

For commercially bought fish, the greatest concerns center on top-level predator species such as tuna, shark, and swordfish, which can concentrate methylmercury to high levels. There is disagreement among the FDA and the states regarding safe consumption levels for these species. The FDA says that canned tuna, which usually contains an average of 0.17 ppm methylmercury, can be eaten safely by all segments of the population. On the other hand, a number of states have issued advisories recommending that both pregnant women and women of childbearing age who intend to become pregnant limit their intake of tuna. The New Jersey Department of Environmental Protection, for example, recommends that these women eat no more than eight ounces of tuna per week, and even less if they are eating other fish that may also contain methylmercury. There is also some discrepancy over consumption of shark and swordfish. The FDA recommends that women of childbearing age limit their consumption to one meal per month, while several states recommend a maximum of one meal every two months and no consumption of these species at all for children younger than seven.

The basis for these discrepancies lies with the uncertainty regarding the dose of methylmercury required to produce an adverse effect in exposed children. Exposures to methylmercury are often quantified by using measurements of the chemical in hair, which is generally considered to be an adequate measure of exposure. Since 1995, the EPA has regulated methylmercury on the basis of a study of 81 Iraqi children exposed *in utero* when their mothers ate methylmercury-contaminated bread. The elevated risk of neurobehavioral deficits in these children was associated with a lower-bound maternal hair concentration of 11 ppm. However, the Iraqi data had multiple shortcomings, not the least of which was the small sample size. Two additional studies—one conducted in the Seychelles in the Indian Ocean, the other in the Faroe Islands, located between the Shetland Islands and Iceland—used more refined tests to assess large cohorts of children exposed *in utero*. However, these studies have produced sharply conflicting results, and there is pointed disagreement over how such results should be used to set regulatory exposure limits.

The Seychelles study, led by Philip W. Davidson, a professor at the University of Rochester School of Medicine and Dentistry found no adverse outcomes in children evaluated at 66 months of age who were born to mothers with hair methylmercury concentrations averaging 6.8 ppm. The study was published as *Effects of Prenatal and Postnatal Methylmercury Exposure from Fish Consumption on Neurodevelopment* in the 26 August 1998 issue of the *Journal of the American Medical Association*. The exposure to methylmercury came almost entirely from the 25 different species of ocean fish commonly eaten in the Seychelles. Mothers reported consuming an average of 12 fish meals per week during pregnancy. Analyses conducted by the study team indicated that the average methylmercury concentration in these fish was less than 0.3 ppm, which is comparable to commercial fish sold in U.S. supermarkets.

Unlike the Seychelles study, positive results indicating adverse effects were observed during the course of the Faroese study, which was headed by Philippe Grandjean, a professor in the Department of Environmental Medicine at Odense University in Denmark. In this study, a dose-dependent relationship was seen for delayed acquisition of language skills, reduced memory and attention span, and effects on visual-spatial and motor functions in exposed children. Some of these effects were associated with average maternal methylmercury hair concentrations of slightly less than 5 ppm. Umbilical cord blood methylmercury levels in pregnant women were also measured, and were found to be an even better predictor of neuropsychological effects than maternal hair. This study was published as *Cognitive Deficit in 7-Year-Old Children with Prenatal Exposure to Methylmercury* in the November–December 1997 issue of *Neurotoxicology and Teratology*.

The principal source of methylmercury among the Faroese was a traditional diet that includes pilot whale meat as well as fish. PCBs were also present in the fish and whale blubber consumed by the Faroese, and, to a much more limited extent, in the diets of the Seychellois cohort as well. However, there is now a general consensus that PCBs did not influence the outcome of either study [see *EHP* 107(5):A236 (1999)].

Experts generally agree that both studies, which used substantially different test batteries to evaluate the children, were well designed and well executed. Says Rogan, who has been working on neurobehavioral toxicology issues in children for more than 20 years, "I can't come up with any obvious difference to account for the effects observed in one study and a lack of effects in another." Factors that may have influenced outcomes include the different sources of exposure or exposure measures, differences in the neurobehavioral tests used, influences of confounders or covariates, and biostatistical issues involved in the analysis of the data. Differing ages of the children at the time of testing is also believed to be an important factor. Some of the most significant effects in the Faroese cohort were observed in chil-

dren who were seven years old, which is a year and a half older than the children in the Seychelles study.

Both research groups are currently moving ahead with additional analyses to refine their conclusions. Roberta White, a professor in the Department of Neurology and Environmental Health at Boston University and a principle investigator of the Faroe Islands study, will be reanalyzing some of that study's data using the same scoring system used by the Seychelles researchers. Davidson and his colleagues have also recently completed an additional evaluation of eight-year-olds from the Seychellois cohort, which was finished in April 1999 (these data are still under review). "Many [skills] were assessed," says Davidson. "Our battery was very similar to the Faroes battery, in large part because at eight years we could use many of the tests they used."

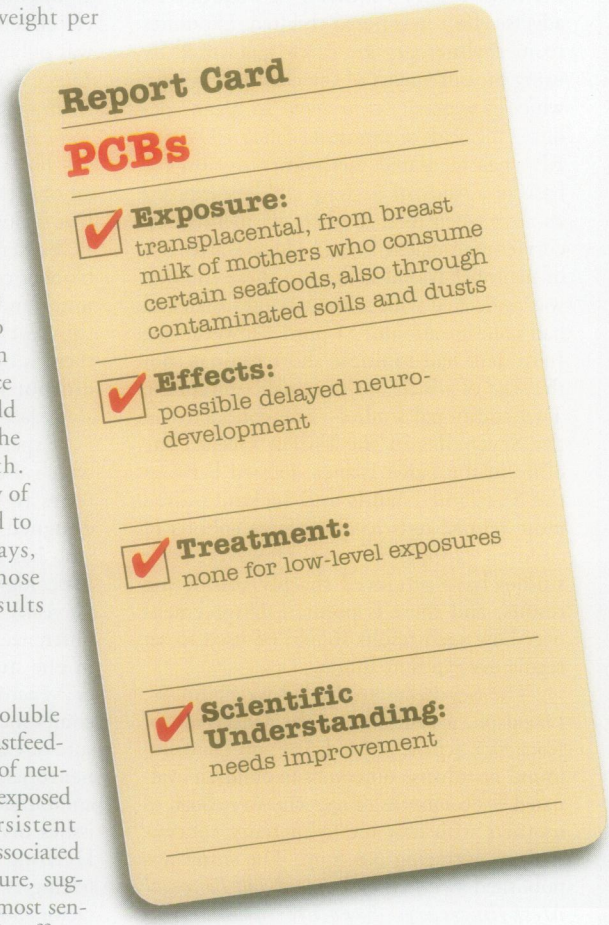
The conflicting results have sparked an ongoing debate within the federal government over whether the results of the Seychelles study should be used to establish revised standards for methylmercury in fish. On the one hand, the Agency for Toxic Substances and Disease Registry is relying on the Seychelles results as a basis for raising their minimum risk level from 0.1 microgram per kilogram body weight per day (µg/kg/d) to 0.3 µg/kg/d. This proposal was strongly opposed by the EPA, which favors waiting until a more definitive analysis of the data is completed. "We're taking a wait-and-see approach," says Kathryn Mahaffey, an environmental health scientist at the National Center for Environmental Assessment, who expresses the agency's opinion that regulatory actions in the face of conflicting study results should err on the side of caution with the aim to protect public health. "There's also a National Academy of Sciences committee being formed to review methylmercury," she says, "and we're going to wait for those results." That committee's results should be available in May 2000.

Neurotoxicity of PCBs

Despite the fact that more fat-soluble PCBs are transferred during breastfeeding than transplacentally, studies of neurobehavioral end points in PCB-exposed children have shown that persistent deficits during adolescence are associated mainly with transplacental exposure, suggesting that the fetal brain is the most sensitive target organ for neurotoxic effects. Sources of exposure to PCBs are varied, but the most important is consumption of contaminated foods, especially fish. PCB-contaminated soils and dusts are also potentially significant, as is consumption of fruits and vegetables grown in contaminated soils.

Joseph and Sandra Jacobson, both professors in the Department of Psychology at Wayne State University in Detroit, Michigan, are following a cohort of children who had both transplacental and breastfeeding exposures to PCBs through their mothers' consumption of Lake Michigan fish. In a study published in the 12 September 1996 issue of the *New England Journal of Medicine*, the Jacobsons found that adverse neurologic and intellectual effects observed during infancy and early childhood were still apparent at the age of 11. But these effects were only seen in the most highly exposed children, those who were born to mothers with PCB concentrations in cord and maternal blood of 4.7 and 9.7 nanograms per milliliter respectively, and 1.2 µg/g in maternal milk. Even though these were the highest concentrations observed in the study, the authors pointed out that they were only slightly elevated above those found in the general population. *In utero* exposures to PCBs in this group of children were associated with an average IQ score that was 6.2 points lower than that of less-exposed children within the same cohort. Furthermore, 8 of the 12 children in the highest exposure group were at least one year behind their peers in word or reading comprehension, and all but one lagged behind by at least six months.

Joseph Jacobson says these findings may be particularly worrisome because PCBs are ubiquitous in the environment, and maternal body burdens were similar to those of the general population in the United States. This widespread low-level contamination makes it difficult to find a suitable control study group, and Jacobson is quick to point out that in order to document effects, it is necessary to look carefully at children with the highest overall exposures. "Children at the upper end of the exposure distribution are at risk," he says, "but because of the way the food supply is distributed, these children are randomly distributed as well, and it's hard to identify a cohort." Jacobson is currently continuing his investigations of PCB exposures in children in a population of Inuits in the Arctic. "They eat a lot of fat from sea mammals that eat a lot of fish," he says. "PCBs accumulate to high levels, and we think we can learn a lot from studying [the Inuit population]."



Limited Data for Pesticides

The neurobehavioral effects of pesticides, particularly organophosphates, carbamates, and organochlorine pesticides, are also a subject of increasing concern, although there are currently few data available to estimate the magnitude of the problem. Despite compelling evidence for neurobehavioral effects from pesticides in animals (which is not surprising, considering that most synthetic insecticides are designed specifically to attack the central nervous system), human data remain exceedingly rare. Among the only human data currently available are those that have been generated by Elizabeth Guillette, an anthropologist and adjunct professor in the Bureau of Applied Research in Anthropology at the University of Arizona in Tucson. With the results of a simple test showing that young children exposed to pesticides were practically unable to draw a simple picture of a person, Guillette provided one of the most compelling illustrations to date of a possible neurodevelopmental effect of pesticides in children [see *EHP* 106(6):347–353 (1998)]. The random undifferentiated lines drawn by exposed children averaged only 1.6 body parts per figure, whereas nonexposed children produced reasonably lifelike figures averaging 4.4 body parts each. These results were part of a battery of developmental end points

evaluated in a study of indigenous children living in the Yaqui Valley of northwestern Mexico. Additional findings attributed to pesticide exposures included decreases in stamina, gross and fine eye–hand coordination, and 30-minute memory.

Criticisms of Guillette's data include the fact that they were not accompanied by corresponding tissue or environmental pesticide concentrations, but were instead assumed based on residential proximity to farms that used high quantities of organophosphate, organochlorine, and pyrethroid compounds. Furthermore, to identify developmental problems, Guillette used an anthropological technique known as rapid assessment, which is a broad approach designed to look for problems in a community and identify areas for future research, rather than to diagnose specific indicators of neurobehavioral dysfunction. Guillette admits that her results have been criticized by developmental psychologists, who questioned the validity of the results, given that she didn't use a full neurodevelopmental test battery. Nonetheless, her findings have received considerable attention within the scientific community, and many have applauded her work. "I think they're very interesting findings," says Virginia Moser, a toxicologist in the Neurotoxicology Division of the EPA's National Health and Environmental Effects Research Laboratory, who is conducting neurobehavioral studies of pesticides in animals. "The next step is to try to get pesticide exposure data," she says. "If we could get blood samples [of the subjects] and analyze for the pesticides [that were in use] at specific times of the year, we could see exactly what they're being exposed to. It would also be useful to find out exactly what the farmers are using and how much, but this information is hard to get in a lot of places."

According to Moser, the specific effects seen in animals depend in large part on the pesticides tested. "In some cases, activity is decreased and the first thing you see is increased lethargy," she says. These findings are interesting, because they corroborate the activity patterns that Guillette observed in the pesticide-exposed Yaqui children, whom she reported as appearing listless. "I thought there was more solitary play rather than group activities in the exposed children," Guillette says. "If prodded, they would play, but there was a noticeable lack of spontaneous creativity in their play habits."

As is the case in much of the developing world, several of the pesticides used in the Yaqui Valley, including lindane (sometimes used to treat head lice in children), endrin, and DDT, are banned in the United States and Canada. Many people in developing areas remain unaware of the toxic effects posed by pesticides at high rates of exposure (often unable to read the labels on pesticides, many farmers subscribe to the concept that more is better), let alone at the low levels described in these studies. According to Weiss, several populations within the United States are particularly at risk, including families of migrant agricultural workers, who continue to be highly exposed.

Ultimately, the challenges posed by neurobehavioral toxicology lie in refining tests of cognitive and developmental skill sets in exposed children, identifying additional contaminants and mechanisms for behavioral effects, and improving dose–response measures in a way that facilitates effective risk assessment. Epidemiology studies are also needed to integrate the results of psychological and toxicological testing with possible population-level effects. Many of these areas are currently active areas of research. According to Landrigan, research directions of particular interest include further investigations into possible links between chemical exposures and both autism and ADHD, expanding the focus of toxicity testing to include neurodevelopmental end points, and performing additional *in vitro* studies on the effects of chemicals on neuronal development.

Public sector groups are getting involved in the issue, as well. According to Gina Solomon, a physician with the Environmental Defense Fund in San Francisco, her organization will be focusing its efforts on quantifying the prevalence of mental health problems such as ADHD in children and developing partnerships with academia, government, and industry to continue gathering critical data. But, she adds, the effects posed by chemicals are likely only one part of a more pervasive onslaught faced by children in today's society. "Chemical exposures interact with family structure, television, violence, and other factors in complicated ways," she says. "This makes the issue very hard to study and correct. It's a daunting task."

Charles W. Schmidt