Toxic Threats to Neurologic Development of Children

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Learning disabilities, attention deficit hyperactivity disorder, developmental delays, and emotional and behavioral problems are among childhood disabilities of increasing concern. Interacting genetic, environmental, and social factors are important determinants of childhood brain development and function. For many reasons, however, studying neurodevelopmental vulnerabilities in children is challenging. Moreover, inadequate incidence and trend data interfere with full understanding of the magnitude of the problem. Despite these difficulties, extensive laboratory and clinical studies of several neurodevelopmental toxicants, including lead, mercury, polychlorinated biphenyls, alcohol, and nicotine, demonstrate the unique vulnerability of the developing brain to environmental agents at exposure levels that have no lasting effect in adults. Historically, understanding the effects of these toxicants on the developing brain has emerged slowly while generations of children are exposed to unsafe levels. Unfortunately, with few exceptions, neurodevelopmental toxicity data are missing for most industrial chemicals in widespread use, even when populationwide exposures are documented. The personal, family, and communitywide costs of developmental disabilities are profound. In addition to the need for more research, a preventive public health response requires mitigation of exposures to potential neurodevelopmental toxicants when available evidence establishes the plausibility of harm, despite residual toxicologic uncertainties. *Key words*: ADHD, attention deficit hyperactivity disorder, developmental disabilities, learning disabilities, metals, neurodevelopment, neurotoxicology, PCBs, pesticides, polychlorinated biphenyls. — *Environ Health Perspect* 109(suppl 6):813–816 (2001).
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Nature of the Problem

The unique vulnerability of the developing brain to environmental agents at exposure levels that have no lasting effect in the adult is well established. Long-lasting damage to brain development and function caused by prenatal alcohol exposure, for example, was recognized centuries ago. In the Old Testament (Judges 13:7) we find: "Behold, thou shalt conceive and bear a son; and now drink no wine or strong drink." In 1726, the College of Physicians Report to the British Parliament described parental drinking as a "cause of weak, feeble, and distempered children" (*1*).

Studying neurodevelopmental vulnerabilities in children, however, is challenging. Varying definitions of end points, nonspecific end points caused by multiple factors, lack of exposure and effect surveillance data, confounders and effect modifiers, and long latency periods between exposures and outcomes complicate attempts to reach definitive conclusions through epidemiologic studies. Even when a significant association is established, researchers often disagree about when causality has been demonstrated or what the shape of a dose–response curve might be. As a result, estimates of thresholds and reference or benchmark doses are often a matter of debate and vary as a function of the outcome of interest.

Considerable attention is being focused on the neurodevelopmental effects of prenatal and childhood exposures to a variety of contaminants in the ambient environment. This interest is sparked partly by a growing recognition of an apparent increase in the incidence of developmental disabilities. In the United States nearly 12 million children under 18 years of age (17%) suffer from deafness, blindness, epilepsy, speech deficits, cerebral palsy, delays in growth and development, emotional or behavioral problems, or learning disabilities (*2*). Learning disabilities alone affect 5–10% of children in public schools (*3*). Attention deficit hyperactivity disorder (ADHD) conservatively affects 3–6% of all school children and perhaps as many as 17% (*4*). The use of Ritalin for this disorder has doubled every 4–7 years since 1971 (*5*). The incidence of autism may be as high as 2 per 1,000 children. The number of children entered into the California autism registry increased by 210% between 1987 and 1998 (*6*). Improved reporting and differing diagnostic criteria may explain some but not all of these trends (*7*).

Genetic, environmental, and social factors interacting in complex ways are important determinants of cognitive development and behavior. None alone is sufficient to explain populationwide increases in neurodevelopmental abnormalities. Except for single-gene disorders, heredity accounts for, at most, about 50% of the variance of cognitive, behavioral, and personality traits among individuals (*8*). This, of course, implies that the other 50% of variability must be due to environmental influences.

Insights gained from molecular biology, chromosome analysis, and twin studies shed some light on genetic influences and gene–environment interactions. Phenylketonuria is an example of a single-gene disorder in which mental retardation results from an inherited inability to metabolize phenylalanine. In this disease an environmental intervention, removing phenylalanine from the diet, completely prevents the neurologic impacts. Is this a genetic or an environmental disorder?

More commonly, multiple subtly acting genes working together exert smaller influences over neurologic development. Genetic polymorphisms that influence metabolic enzyme levels help to explain some populationwide variance to susceptibility to toxic exposures such as, for example, exposure to organophosphate pesticides (*9,10*). A growing understanding of the syndrome called PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) suggests that some children with a particular antigenic marker on B lymphocytes are particularly susceptible to repetitive, obsessive–compulsive behaviors, tics, and Tourette syndrome after a streptococcal infection—another example of gene–environment interactions (*11*).

Among the problems that interfere with more complete understanding of the incidence and etiology of neurodevelopmental disorders is the inconsistent use of diagnostic labels that results when symptoms of concern are of variable severity and, collectively, only partially match diagnostic criteria. Behavioral problems, for example, may range from mild attention deficits to severe conduct disorders. Developmental problems may span a spectrum from mild impairment of social skills to severe and disabling autism. Learning-related disorders may be isolated or mild and specific, or associated with severe mental retardation. Moreover, some traits typical of one diagnostic category are likely to be found in another as well. For example, up to 30% of children

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with ADHD have a learning disability and 30–80% have a conduct disorder (*12*).

Toxicologic studies in laboratory animals or humans typically attempt to identify specific traits rather than syndromes that result from exposures. Conversely, healthcare providers and educators are more likely to search for diagnostic categories that best encompass the constellation of traits that they identify in an individual. ADHD, for example, is manifest as a mixture of attentional problems and impaired impulse control. Toxicologists are more readily able to study and report the impacts of chemical exposure on discrete tests of attention than on a mixture of attentional and behavioral problems. Differing disciplinary approaches contribute to a lack of communication, as well as complicating clinical or laboratory research and populationwide monitoring of trends. For the purposes of studying etiologies and opportunities for prevention of developmental disabilities, explicit consideration of traits, as well as diagnostic categories, will provide important insights.

Specific Developmental Toxicants

Brain development begins early in embryonic life and continues well beyond birth into adolescence. During development, brain cells divide, migrate, differentiate, establish synaptic connections, and undergo programmed cell death (apoptosis) in an orchestrated sequence of events controlled by neurotransmitters and other neurotrophic factors. Interference with any stage of this cascade of events may alter subsequent stages, so that even short-term disruptions may have long-term effects later in life.

Despite the challenges inherent in studying neurodevelopmental disorders in children, a large literature conclusively documents the effects of a few environmental agents (*7*). It is, for example, well established that fetal or infant exposure to lead, alcohol, or nicotine impairs normal neuropsychologic development. Fetal alcohol exposure causes hyperactivity and cognitive deficits (*13*). Maternal smoking causes intelligence quotient (IQ), learning, and attention deficits in offspring (*14*). Early-life lead exposure decreases learning, attention, and IQ and contributes to hyperactivity, impulsiveness, and aggression (*15,16*).

Mercury

Mercury (Hg) is a potent neurodevelopmental toxicant commonly encountered as dietary methylmercury, which adversely affects enzymes, cellular membrane function, and neurotransmitter levels (*17,18*). Mercury causes oxidative stress, lipid peroxidation, and mitochondrial dysfunction and disrupts synaptic transmission, microtubule formation, amino acid transport, and cellular migration in the developing brain (*19*). In a prolonged poisoning episode in Japan and a more acute episode in Iraq, large prenatal methylmercury exposures were associated with psychomotor retardation, seizures, developmental delays, and mental retardation (*20,21*). Much smaller prenatal exposures from maternal consumption of contaminated fish in New Zealand (mean maternal hair level Hg 8.3 ppm) and the Faroe Islands (mean maternal hair level Hg 4.3 ppm) adversely affected IQ, language development, visual–spatial skills, gross motor skills, memory, and attention in offspring (*22,23*). A study in the Seychelle Islands (mean maternal hair level Hg 5.9 ppm) showed no adverse effects on child neurologic development at 5 years of age (*24*).

As with lead, a historical review of our understanding of the neurodevelopmental toxicity of mercury shows that more refined testing has resulted in a steady decline in the exposure level thought to be "safe" and without adverse effects. The U.S. Environmental Protection Agency (U.S. EPA) has recently developed a reference dose for mercury of 0.1 μg Hg/kg/day and estimates that mercury exposures at this level are likely to result in hair mercury levels of about 1.0 ppm. Maternal exposures at or below this level are thought unlikely to increase the risk of harm to the developing fetal brain. A committee of the National Academy of Sciences has affirmed and supported the derivation of this reference dose (*25*). The U.S. EPA estimates, unfortunately, that 52,000–166,000 pregnant women in the United States consume fish contaminated with mercury at levels at or above this reference dose (*26*).

Manganese

The central nervous toxicity of manganese (Mn) due to occupational exposures is well characterized. Symptoms include gait and movement disorders, and in some cases, inappropriate behavior. More recently, the developmental neurotoxicity of manganese has emerged as a significant public health concern. In several small epidemiologic studies of children, manganese hair levels are associated with ADHD (*27–29*). Developmental exposure to manganese in laboratory animals is associated with hyperactivity (*30*).

At low levels, manganese is an essential dietary trace element necessary for critical enzymatic reactions. The concentration of manganese in human breast milk is about 6 μg Mn/L, whereas infant formula may contain 77–100 μg Mn/L, depending on whether it has been supplemented; soy formula may naturally contain as much as 200–300 μg Mn/L (*31,32*). Compared to adults, children and immature animals absorb more and excrete less manganese (*33,34*). Moreover, in infants, manganese easily gains access to the developing brain because of an immature blood–brain barrier.

These observations raise questions about the wisdom of supplementing infant formula with manganese and the widespread use of infant soy formula containing naturally high concentrations of manganese. They also further concerns about the use of gasoline supplemented with an organic manganese compound as an octane enhancer in the United States and Canada. The Ethyl Corporation (Richmond, VA, USA), the U.S.-based manufacturer of the additive, claims there is no evidence to support concerns that manganese in gasoline represents a threat to public health—an argument that is eerily reminiscent of their position on the use of tetraethyl lead many years ago. Under provisions of the North American Free Trade Agreement (NAFTA) (*35*), the Ethyl Corporation brought legal action against Health Canada for blocking access to Canada's gasoline market. Health Canada ultimately decided to settle, not only allowing the additive onto the market but also agreeing to pay Ethyl Corporation an estimated $10 million for legal costs and lost income (*36*). Meanwhile, available data indicate that the brain is vulnerable to long-lasting effects from developmental exposures to manganese.

Polychlorinated Biphenyls

The adverse neurodevelopmental impacts of polychlorinated biphenyls (PCBs) have been examined in several large epidemiologic studies. In humans, developmental exposures to PCBs at ambient environmental levels cause hyporeflexia, psychomotor delays, delayed cognitive development, and IQ deficits (*37–41*). Impaired learning, altered behavior, and hyperactivity have been demonstrated in laboratory animals (*42,43*).

PCBs are likely to exert their adverse effects through a variety of mechanisms. Co-planar PCBs may interact with the aryl hydrocarbon receptor and exert dioxinlike effects. PCBs also alter thyroid hormone metabolism and may interfere with thyroid hormone-induced gene transcription (*44*). In humans, seals, rodents, and birds, PCB exposure causes decreased thyroid hormone levels (*45,46*). Some PCBs also alter neurotransmitter levels (*47*). For example, *ortho*-PCBs decrease dopamine synthesis, whereas non-*ortho*-PCBs increase dopamine levels.

Because thyroid hormone is essential for normal brain development, the effects of PCBs and other chemicals that interfere with thyroid hormone homeostasis are of particular concern. A recent study by Haddow et al. (*48*) of women with hypothyroidism during pregnancy showed the extreme sensitivity of the developing brain to even mildly depressed or

low-normal thyroid hormone levels. At 7–9 years of age, offspring of these women were more likely than the offspring of mothers with normal thyroid function to perform poorly on tests of attention and word discrimination. Haddow and co-workers used elevated serum thyrotropin (TSH) levels to identify hypothyroid women. Elevated TSH levels correlated with lower total and free thyroxine levels.

In the study by Koopman-Esseboom et al. (*49*) of ambient environmental levels of PCBs on maternal and infant thyroid function, PCB exposures significantly correlated with decreased maternal triiodothyronine (T_3) levels but not with maternal thyroxine (T_4) or TSH (*49*). However, higher maternal PCB exposures significantly correlated with higher TSH levels in infants 2 and 3 months of age.

Polybrominated diphenyl ethers (PBDEs—widely used as flame retardants in consumer products and detected in increasing concentrations in human breast milk) and certain pesticides such as dicofol, pentachlorophenol, dinoseb, and bromoxynil, competitively bind with the thyroid hormone binding protein, transthyretin (*50*). Some bind more avidly than T_4, displacing T_4 and potentially interfering with its transport to the developing brain. The developmental neurotoxicity of these substances has not been studied to any appreciable degree, yet human exposures to PBDE and pentachlorophenol are widespread (*51,52*).

Pesticides

Limited data are available describing the effects of developmental exposures to neurotoxic pesticides on subsequent brain function. In rodents a single low-level exposure to an organophosphate pesticide or a pyrethroid on day 10 of life causes permanent decreases in brain cholinergic receptors and hyperactivity when the animal is tested at 4 months of age (*53,54*). A limited ecologic study of Mexican children exposed developmentally to a mixture of agricultural chemicals showed adverse effects on motor skills, memory, attention, and learning (*55*). The general lack of neurodevelopmental toxicity data for agricultural chemicals is of particular concern because of their widespread use and ubiquitous exposures. Population-based studies in the United States show that over 90% of children have detectable urinary residues of just one of the neurotoxic organophosphate pesticides. Specimens analyzed for residues of 30 pesticides showed that >50% of the population contained at least six (*53*).

Conclusions

Developmental delays, learning disabilities, ADHD, and behavioral disorders extract a terrible toll from children, families, and society (*56*). Children with ADHD are at risk for failure in the classroom and later in the workplace. Individuals with learning disabilities have a more difficult time keeping a job, learning new skills, and getting along with coworkers. Children with learning disabilities are often alienated, isolated, and misunderstood. Some developmental disabilities increase the risk of substance abuse, delinquency, criminal behavior, and suicide.

Families of children with learning, developmental, or behavioral disorders experience additional stress. The costs associated with caring for these children can be high for families and society. Special education programs and psychologic and medical services drain resources. When services are unavailable, children, families, and communities suffer in numerous ways.

As the science of neurodevelopment slowly evolves, questions about appropriate preventive actions deserve consideration. The neurodevelopmental effects of relatively few compounds encountered in the ambient environment are well characterized. Yet, even these limited data highlight the profound vulnerability of the developing brain. Moreover, comparisons of animal and human data for lead, mercury, and PCBs show that laboratory animal studies tend to underestimate human neurodevelopmental sensitivity by 2–4 orders of magnitude (*57*). In each case, reference or benchmark doses were continuously revised downward as human data were developed. Unfortunately, neurodevelopmental data are lacking for the large majority of known or suspected neurotoxicants. Regulatory agencies have generally failed to require neurodevelopmental testing of chemicals before they are marketed. None of the voluntary testing programs proposed by the chemical industry in the United States includes neurodevelopmental testing.

In its Sixth Biennial Report on Great Lakes Water Quality (*58*), the International Joint Commission (IJC) advocated a weight of evidence approach to the identification of substances that may cause harm. They found it disingenuous that science must prove with 100% certainty that an exposure will result in an adverse health effect before taking precautionary action. They concluded, ". . . the focus must be on preventing the generation of persistent toxic substances in the first place, rather than trying to control their use, release, and disposal after they are produced." They endorsed the precautionary principle that, with evidence of threats of significant harm, even in the face of scientific uncertainty, precautionary action should be taken to protect public health and the environment. However, Gordon Durnil, former chair of the IJC, described the response strategy of industry lobbyists as the three Ds—deny, divert, delay (*59*).

Although we can do little about genetic contributions to many of these developmental disorders, we have enormous opportunities to mitigate environmental factors. Sufficient evidence has been accumulated to permit better understanding of the hazards of exposure to neurotoxic chemicals. Clearly, more comprehensive pre- and postmarket neurodevelopmental testing of chemicals to which humans and wildlife are likely to be exposed is essential. Residual uncertainties, however, cannot be an excuse for avoiding precautionary action when available evidence establishes the plausibility of harm.

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