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# Behavioral Toxicology

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The new fields of behavioral toxicology and behavioral teratology investigate the outcome of specific toxic exposures in humans and animals on learning, memory, and behavioral characteristics. Three important classes of behavioral neurotoxicants are metals, solvents, and pesticides. The clearest data on the deleterious effects of prenatal exposure to toxicants comes from the study of two metals, lead and mercury, and from epidemiological investigations of the effects of alcohol taken during pregnancy. Less complete data are available for two other groups of agents, solvents and pesticides. What we do know about their effects on the fetal brain is convincing enough to make us demand caution in their distribution. —*Environ Health Perspect* 103(Suppl 6):77–79 (1995)

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## Behavioral Toxicology

Behavioral toxicology, the study of chemical toxicants and their influence on brain function, is a young field. The notion that a chemical can affect the brain and that the earliest expression of toxicity could be found in altered behavior, thinking, or mood is not new; it was voiced at least 2000 years ago by Dioscorides when he wrote, "Lead makes the mind give way." Despite this early warning, the scientific community has until recently paid little systematic attention to the impact of neurotoxicants on behavior. The first textbook on this subject was published in 1975 (1).

Behavioral teratology, the study of the effect on behavior of chemical exposure of the fetus *in utero*, is an even newer discipline. Until recently, the uterus had been visualized as a time capsule with a 9-month lease, sheltering the developing fetus from most adverse influences such as drugs, toxicants, or nutritional deprivation. The thalidomide and Minamata disasters quickly disabused scientists and laymen alike of this false comfort. It is now clear that many chemicals cross the placenta and impinge on the developing brain. Behavioral deficits have been shown for some agents at doses well below those that cause anatomical alterations.

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## Lead

Lead has been known to affect workers for millennia, and its hazards to the reproductive process have been known for at least a century. British factory inspectors at the turn of the twentieth century noted that women who were exposed to lead through working in the cottage ceramic industry tended to be barren and that children who were born to those women were often short-lived (2). Childhood lead poisoning was first described in Australia 100 years ago. For 50 years it was believed that if lead did not kill the child, he or she was left with no stigma of the exposure. Careful follow-up of children who had recovered from the disease showed that most had school failure or behavioral problems. For the past 20 years, epidemiologists and child development specialists have been investigating the effects of lead exposure in children with no clinical symptoms. This controversial issue has now been effectively settled. Almost all workers in the field agree that lead at silent doses produces deficits in psychological function; these include intelligence, perception, attention, language function, and perhaps social adjustment. The recently published report of the National Academy of Sciences provides a thorough summary of this issue (3).

In the late 1970s, attention began to shift to the question of intrauterine exposure to lead. Scanlon (4) measured umbilical-cord blood lead concentrations in new-

borns and showed that infants born to inner city mothers tended to have higher blood lead levels than those born to suburban mothers. The observation that lead crossed the placenta sparked studies of prenatal exposure on infant development. The first study examined a large cohort of births at the Boston Hospital for Women (5). Umbilical-cord bloods were obtained from almost 12,000 births over a 2-year period. Lead was found to be related to minor birth defects in a subsample of 5000 of these infants. A subsample of these subjects that was evenly divided among low exposure (<3 µg/dl), medium exposure (6–7 µg/dl), and high exposure (>10 µg/dl) was followed. Subjects were seen at 6, 12, 24, 57, and 120 months of age. Significant deficits in infant IQ scores were found in children in the high cord blood lead group as late as 24 months of age (6). At 57 and 120 months of age, the effect of umbilical-cord blood was no longer significant, but the effect of the 24-month blood lead level was statistically significant (7). Similar data have subsequently been reported from studies in Cincinnati (8) and Australia (9). It is clear that lead exposure during pregnancy is a behavioral teratogen.

## Mercury

Knowledge about the neurotoxicity of mercury dates from the 1950s. In Minamata, Japan, a chemical plant used the waters of Minamata Bay to discharge its wastes. One of the most important discharge products was mercury, mostly in its inorganic form. Aquatic bacteria transformed it to the organic form methylmercury. Because it enters the brain more readily, this form is much more toxic. It was taken up by the local fish and, in the 1950s, residents who ate fish from the bay were found to suffer

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severe organic brain damage. Most severely stricken were infants exposed *in utero*.

Another epidemic of mercury poisoning occurred in 1960. The U.S. government sent seed grain to Iraq as part of an international aid effort, intending for the grain to be planted and not eaten. The seed was treated with methylmercury to prevent fungal infestation and was dyed pink to indicate that it was unsuited for baking. The largely illiterate Iraqi peasants baked bread with it, and an outbreak of over 5000 cases of poisoning occurred. Infants were about 10 times more sensitive than adults.

An unexpected outbreak of acute mercury intoxication occurred in 1981 when a family repainted a large part of their home with water-soluble paint. This product contained phenylmercury added as an antifungal agent. Paint companies have voluntarily agreed to stop this practice, but no product recall was made.

## Alcohol

The toxic effects of alcohol on the fetal brain were first established in France in 1968 (10) and in the United States in 1973 by David Smith, a West Coast pediatrician (11). The unraveling of this relationship has followed a traditional history—the problem was first brought to attention when infants born to mothers with high alcohol intakes were noticed to have characteristic features: impaired growth, flat face, long upper lip, and mental retardation. This set of dysmorphic features was termed the fetal alcohol syndrome. Investigators then began to examine the effects of lower doses. This kind of question can only be addressed by following sizable samples of infants over long periods of time. The pioneer in this effort has been Dr. Anne Streissguth, whose studies have unequivocally established that small doses of alcohol taken during pregnancy are associated with cognitive and attention dysfunction in offspring in later life (12).

## Solvents

Alcohol, because it is a fat-soluble chemical, readily crosses the blood-brain barrier and enters brain cells. Many other solvents share this property and are found in the household in proximity to pregnant women and young children. Among the more common solvents found in households are paint thinners, degreasing and dry cleaning agents, and spot removers. Nearly all solvents can cause acute and chronic injury to the central nervous system. Inhalation of high doses of almost any

solvent (including gasoline) can cause dizziness, nausea, and hallucinations within a few moments. This can rapidly lead to unconsciousness. The only studies of long-term solvent exposure have been conducted in workers in whom chronic exposure causes vertigo, clumsiness, drowsiness, and often learning problems and memory and attention deficits. Although the literature on prenatal exposure to solvents is sparse, prudence dictates that pregnant women should avoid contact with these agents. One case of fetal solvent syndrome was reported in 1979 (13). The offspring closely resembled that of a mother who had abused alcohol. In this case the mother was addicted to sniffing toluene.

## Pesticides

Most pesticides poison insects by interfering with the metabolism of certain neurotransmitters. The human nervous system uses the same neurotransmitters to conduct signals between brain cells. This is the source of both the agents' benefits and their dangers to human health. Most pesticides poison the enzymes that break down acetylcholine, one of the most important and widely distributed neurotransmitters. As a result, the transmitter continues to stimulate the nerve and, in extreme circumstances, this can lead to convulsions or even death.

More than 1500 pesticides are currently in use in the United States. These are blended to produce 50,000 commercial products of varying toxicity. Two groups of pesticides, the organophosphates and the carbamates, are extremely toxic to acetylcholine-destroying enzymes and can lead to both acute and chronic symptoms. Organochlorine compounds such as DDT and Heptachlor have less acute toxicity, but many have been shown to resemble estrogen compounds; by binding to estrogen receptors in the body, they may have a host of unwanted effects. Most recently, increased levels of DDT were reported in the breast tissue of women with breast cancer.

The widespread use of pesticides has resulted in many opportunities for toxic or subclinical exposures. These can occur through contamination of drinking water, medical and veterinary applications, rodent control, mosquito control, and through residues on fruits and vegetables.

The National Academy of Sciences has recently completed a thorough review of the question of foodborne pesticides hazards to children (14). It notes the particular sensitivity of the developing brain to

these agents and calls for newer, more stringent standards to reduce childhood exposure to them.

## Measuring the True Costs of Pollutants

Economists have recognized that the true costs of a product or activity are rarely reflected in the price but are diverted to other objects. The price of a barrel of fuel oil in 1990 did not reflect the cost of the Persian Gulf War. That cost may have been as much as \$80 billion, or \$23 per barrel of oil. Instead of being attached to fuel costs, this was entered into the defense budget and passed on to the taxpayer. Economists call this practice "externalizing the costs." When we do this we often mislead ourselves about the real personal or societal costs of a given activity. To a considerable extent, the degree to which a society internalizes costs is a measure of its civility. There were, and are, societies that externalized the costs of labor—they held slaves. Internalizing the cost of workplace safety resulted in regulations and actions that have reduced morbidity and mortality on the job.

Similarly, we have externalized to a considerable degree the costs for producing commercial products. The cost of not making houses safe is externalized to the health of children who are exposed to lead and other toxicants. The U.S. Public Health Service estimated the cost of deleading the dangerous housing stock in the United States at \$28 billion (15). This is what it would take to reduce the number of houses bearing large amounts of lead. The Public Health Service took this one step further and calculated the money that would be saved by taking this expensive action. To do this, they estimated the societal costs that accrue from money spent on medical care for lead-exposed children, the amount spent on remedial education, and the lost tax revenues that ensue when IQ is lowered. The economists concluded that deleading the houses would result in a monetized benefit of \$60 billion, a net return of \$28 billion. We may ask, can we afford not to delead houses?

Similar analyses could be applied to any neurotoxicant. What is required is a metric for lost cognitive and behavioral function. Only when we attach all of the costs of production and consumption of commercial products will we be in a position to make informed judgments about their use and control.

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