Chemical Wastes, Children's Health, and the Superfund Basic Research Program

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Three to 4 million children and adolescents in the United States live within 1 mile of a federally designated Superfund hazardous waste disposal site and are at risk of exposure to chemical toxicants released from these sites into air, groundwater, surface water, and surrounding communities. Because of their patterns of exposure and their biological vulnerability, children are uniquely susceptible to health injury resulting from exposures to chemical toxicants in the environment. The Superfund Basic Research Program, funded by the U.S. Environmental Protection Agency and directed by the National Institute of Environmental Health Sciences, is extremely well positioned to organize multidisciplinary research that will assess patterns of children's exposures to hazardous chemicals from hazardous waste disposal sites; quantify children's vulnerability to environmental toxicants; assess causal associations between environmental exposures and pediatric disease; and eluciudate the mechanisms of environmetal disease in children at the cellular and molecular level. *Key words*: environmental health, pediatric environmental disease, Superfund. *Environ Health Perspect* 107:423–427 (1999). [Online 20 April 1999]
http://ehpnet1.niehs.nih.gov/docs/1999/107p423-427landrigan/abstract.html

Millions of tons of hazardous wastes have been produced in the United States since World War II and have been dispersed into the air, into water, and on and under the ground. Much of this waste has accumulated in uncontrolled hazardous waste sites, and these sites are widespread across the nation. The U.S. Environmental Protection Agency (EPA) has identified more than 15,000 such sites; 1,371 are proposed for listing or are listed already on the National Priorities List (NPL). Assessment and remediation of these sites is proceeding under the direction of the U.S. EPA, with support of the national Superfund Trust.

The majority (65–70%) of uncontrolled waste sites in the United States are waste storage and treatment facilities (including landfills) or former industrial properties. Many of these properties have been abandoned, and most have more than one major chemical contaminant. Less common are waste recycling facilities and mining sites, which may be active, inactive, or abandoned. Another group of hazardous waste sites is associated with federal government facilities, such as military facilities and nuclear energy complexes. The National Research Council has identified 17,482 contaminated sites at 1,855 military installations and 3,700 sites at 500 nuclear facilities. Some of these sites cover large geographic areas and are contaminated with very complex mixtures of wastes. The substances most commonly released into environmental media from uncontrolled hazardous waste sites are heavy metals and organic solvents: lead (59% of sites), trichlorethylene (53%), chromium (47%), benzene (46%), and arsenic (45%) (*1*).

Children are a group within the population who are at particular risk of exposures to chemicals released into the environment surrounding Superfund hazardous waste sites. Approximately 11 million Americans live within 1 mile of a Superfund NPL site, and between 3 and 4 million of these persons are children under 18 years of age (*2*).

The Superfund Basic Research Program (SBRP) is a university-based grant program managed by the National Institute of Environmental Health Sciences (NIEHS) and supported through the Superfund Trust. The mission of SBRP is to support prevention-oriented research that increases understanding of the effects of toxic environmental exposures on human health and that provides a scientific basis for prevention of those exposures and their associated health effects. The multidisciplinary research teams supported in universities across the United States by this program are undertaking a range of studies relevant to children's environmental health, including *a*) studies to define routes of children's exposures to environmental toxicants, *b*) epidemiologic investigations into the health effects of environmental exposures, *c*) studies of the etiologic mechanisms of environmentally induced diseases, and *d*) community-based intervention trials. These university-based programs are very well positioned to build further upon this research base in pediatric environmental health, to educate communities about toxic hazards to children, about approaches to disease prevention and health promotion, and to serve as credible sources of information.

This report reviews current information on environmental threats to children's health, summarizes pediatric environmental health research currently under way in university-based Superfund Basic Research Programs across the United States, and offers suggestions for future directions in prevention-oriented research within the SBRP.

Children's Vulnerability to Toxicants in the Environment

Children are uniquely vulnerable to environmental toxicants. This heightened susceptibility appears to arise from several sources (*3*).

Children have disproportionately heavy exposures to environmental toxicants (*3*). Pound for pound of body weight, children drink more water, eat more food, and breathe more air than adults. Children in the first 6 months of life drink seven times as much water as the average American adult. One- to 5-year-old children eat three to four times more food. The air intake of a resting infant is twice that of an adult. The implication of these findings for health is that children will have substantially heavier exposures than adults to any toxicants that are present in water, food, or air. Two additional characteristics of children further magnify their exposures: their hand-to-mouth behavior, and their play close to the ground.

Children's metabolic pathways, especially in the first months after birth, are immature. Children's ability to metabolize, detoxify, and excrete many toxicants is different from that of adults (*4*). In some instances, children are actually better able than adults to deal with environmental toxicants (*3*). More commonly, however, they

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The authors acknowledge the generous assistance of S. Carroll, M.M. Mount Sinai School of Medicine, and B.E. Anderson and C. Thompson, National Institute of Environmental Health Sciences.

Received 16 July 1998; accepted 22 October 1998.

are less well able to deal with toxic chemicals and thus are more vulnerable to them.

Children undergo rapid growth and development, and their developmental processes are easily disrupted. Many organ systems in infants and children undergo very rapid change prenatally, as well as in the first months and years after birth. These developing systems are very delicate and are not well able to repair damage that may be caused by environmental toxicants. Thus, if cells in an infant's brain are destroyed by chemicals such as lead, mercury, or solvents, or if false signals are sent to the developing reproductive organs by endocrine disruptors, there is high risk that the resulting dysfunction will be permanent and irreversible (*5–7*).

Because children have more future years of life than most adults, they have more time to develop chronic diseases triggered by early exposures. Many diseases that are caused by toxicants in the environment require decades to develop. Many of those diseases, including cancer and neurodegenerative diseases, are now thought to arise through a series of stages that require years or even decades to evolve from earliest initiation to actual manifestation of disease. Carcinogenic and toxic exposures sustained early in life, including prenatal exposures, appear more likely to lead to disease than similar exposures encountered later (*8,9*).

The Range of Environmental Disease in Children

The spectrum of pediatric disease has changed profoundly in the United States over the course of the twentieth century. Smallpox is gone, and measles, rubella, cholera, and poliomyelitis have virtually disappeared. Today, the major pediatric diseases are complex, chronic conditions that frequently are associated with long-term disability. This pattern of illness has been termed "the new pediatric morbidity" (*10*).

Toxicants in the environment are now recognized, or at least suspected, to cause a wide array of disease, dysfunction, and disability in children and thus to contribute significantly to the new pediatric morbidity (*2*). Examples are as follows.

Asthma. Asthma now affects 5 million children in the United States. Incidence and mortality have doubled in the past decade (*11*). Approximately 600 children die annually and 150,000 are hospitalized. Asthma is the leading cause of admission of children to hospitals. Ambient and indoor air pollution are major exacerbating factors (*12–14*).

Childhood cancer. The reported incidence of childhood cancer has increased substantially in the United States in the past two decades (*15*). Although death rates are down because of spectacular advances in treatment, incidence rates for leukemia, brain cancer, Wilms tumor, and testicular cancer are all reported to have increased. In part, these increases may be due to improvements in diagnosis, but environmental factors are also suspected to have contributed (*16*).

Neurodevelopmental impairments. These disorders, including learning disabilities, dyslexia, intellectual retardation, attention deficit hyperactivity disorder, autism, pervasive developmental disorder, delinquency, and violence, are widespread. These disorders are estimated to affect approximately 3% of all American children (*17,18*). Neurodevelopmental impairments produce lifelong needs for special education; they lead to increased risk of hospitalization, institutionalization, and incarceration; they diminish lifetime productivity and earning capacity; they create enormous personal, familial, and economic burdens; and they engender family and societal disruption. Toxicants in the environment such as lead (*5*), mercury, polychlorinated biphenyls (PCBs) (*19*), and certain pesticides are important factors even at relatively low levels of exposure in the causation of some types of neurodevelopmental impairment.

The diseases of tobacco. These conditions are widespread; they include otitis media, pneumonia, bronchitis, and other respiratory infections, which result from residential exposure of more than 30% of American preschool children to environmental tobacco smoke (ETS) (*20*).

Disorders of endocrine and reproductive development. These disorders are common and appear to be increasing in frequency. They include hypospadias, for which incidence has doubled since 1972 (*21*); testicular cancer in young men (15–29 years of age), for which incidence has increased by 68% (*15*); and the increasingly early occurrence of menarche among young girls (*22*). Colborn et al. (*23*) have suggested that estogenic chemicals in the environment may play a causal role.

The Preventability of Environmental Disease in Children

Disease of environmental origin in children is, in theory, preventable (*24*). Toxic environmental diseases arise as a direct consequence of human activity. They can therefore be prevented through modification of that activity, particularly through the containment of common sources of exposure. Research is the essential prerequisite to effective prevention (*25*). Examples are as follows:

- Reduction of children's blood lead levels following removal of lead from gasoline (*26*), an action driven by documentation of the toxicity of lead to children at low levels of exposure.
- Adoption of state and local ordinances to reduce exposures to ETS following recognition of the respiratory and developmental hazards of ETS (*20*).
- Reduction in use of diagnostic X rays during pregnancy and early infancy following recognition of the greatly increased risk of childhood leukemia associated with early exposure to ionizing radiation (*27*).
- Revision of federal pesticide law in the United States with passage in 1996 of the Food Quality Protection Act (*28*) following recognition of infants' and children's unique susceptibility to pesticides in the diet (*3*).

Gaps in Previous Research

Despite children's extensive exposures and heightened vulnerability to environmental toxicants, until very recently there has been no coherent research agenda in the United States directed toward understanding and preventing the environmental causes of childhood illnesses. Research into the causes of pediatric disease, in general, and into pediatric disease of environmental origin, in particular, has been seriously underfunded. Too few of the high-volume chemicals to which children are at risk of exposure have been tested for their possible developmental or pediatric toxicity (*29,30*). Less than 0.4% of the $500 billion spent on children in the United States each year is directed toward research, and only a fraction of that sum goes toward research on the causes of pediatric environmental disease (*31*). Specific gaps in knowledge that urgently need to be closed include the following:

- There is inadequate knowledge of patterns of exposure. In recent years exposures to lead have decreased sharply because of the phase-down of leaded gasoline (*26*). Also exposures to PCBs have fallen since the cessation of PCB manufacture. But preliminary data suggest that use of residential pesticides has increased (*32–34*). The possible impact of these changing exposures to environmental neurotoxicants on children's development are entirely unknown.
- Information on mechanisms of toxicity is insufficient. Recent data in experimental models suggest that certain pesticides and chlorinated compounds may disrupt development by disrupting hormonal signaling during critical phases of organogenesis (*35*) or by interfering with early neural development (*36–40*). But knowledge is almost completely lacking as to which pesticides in current use are of concern, relevant dose levels, cellular

or molecular loci of effect, or relevance or experimental date to human development.
- There is insufficient data on long-term developmental and functional consequences of early exposures. Data from studies of lead exposure in early life suggest that the resulting developmental deficits are permanent and irreversible (*5*), but it is not known whether similar lifelong persistence characterizes the deficits that may result from other early exposures in childhood.
- Knowledge of which strategies are most effective in prevention is inadequate.

The Superfund Basic Research Program

Current Pediatric Research Portfolio

The NIEHS/EPA SBRP has traditionally focused on understanding the impact of toxic environmental exposures on the health of adults. However, it has become apparent that this database of information is not necessarily applicable to children. The program recognized this deficit early and, accordingly, has directed over 10% of its diverse research efforts toward understanding the effects of environmental exposures on children's health.

Table 1 presents a brief description of the various research projects that the SBRP supports in the area of children's health. These studies in universities across the United States include fetal, infant, childhood, and adolescent research. Research in exposure assessment is of particular interest. Other research projects that are more closely aligned with women's health issues, although they may ultimately impact fetal health, have not been included.

Further information on these university-based programs may be obtained from the SBRP Web site maintained by the NIEHS (*36*).

Table 1. University-based research in pediatric environmental health supported by the Superfund Basic Research Program.

Program	University	Program director
Factors Modifying Behavioral Toxicity of Lead	Cornell University	Barbara Strupp
Developmental Immunotoxicologic Appraisal of DMSA	Cornell University	Rodney R. Dietert
In Utero PCB and Metal Exposures and Infant Development	Harvard University	Susan Korrick
Human Cell Culture Studies of Mutagens in the Aberjona Basin	Massachusetts Institute of Technology	William G. Thilly
Lead Mobilization during Pregnancy and Lactation in Urban Women	Mount Sinai School of Medicine	Gertrude Berkowitz
Detection, Prioritization, and Detoxification of Developmental Toxicants Associated with Chemical Wastes	Texas A&M University	Timothy D. Phillips
PCBs and the Well-being of Mohawk Children and Youth, Growth, Development, and Cognitive Behavioral Functioning	University of Albany, SUNY	Lawrence Schell
Determination of Toxic Metal Species in Environmental and Biological Matrices with High Energy Ion Beams	University of Arizona	Quintus Fernando
Cardiac Teratogenicity of Halogenated Hydrocarbons	University of Arizona	Paula D. Johnson
Dichloroacetate Kinetics, Metabolism, and Human Toxicology	University of Florida	Peter W. Stapool
Biomarkers of Cancer Susceptibility in Human Populations	University of California at Berkeley	John K. Wiencke
Biomarkers of Genetic Damage in Human Cells	University of California at Berkeley	Martyn T. Smith
Molecular Epidemiology of Childhood Leukemia	University of California at Berkeley	Patricia A. Buffler
Children's Environmental Health Network	University of California at Berkeley	Joy Carlson

Options for the SBRP

The multidisciplinary research programs supported in universities across the United States by the NIEHS SBRP have an opportunity to build on this excellent base in pediatric environmental medicine and to contribute further to the understanding and prevention of the diseases in children that are known or suspected to be of toxic environmental origin. Also, these programs are able to contribute to efforts to study and prevent the adverse effects on children's health that may result from exposures near hazardous waste sites or sources of toxic emissions.

The following are a series of recommendations for prevention-oriented research on diseases of environmental origin in children. These recommendations were summarized from a larger compilation of research recommendations developed in 1997 by the Children's Environmental Health Network (*41*).

Childhood asthma. Research is needed to understand why rates of asthma are increasing in American children (*11*). Studies are needed to understand why incidence and mortality rates are increasing so much more rapidly in urban minority children than in children of other sectors of society. Studies are also needed to assess the relative contribution of outdoor and indoor air pollution to exacerbations of asthma.

Childhood cancer. It is important to understand why reported incidence rates of certain cancers are rising in American children (*15,16*). It is unlikely that there is one specific cause responsible for increases in leukemia, brain cancer, Wilms tumor, and testicular cancer. These diseases need to be studied, employing well-designed epidemiologic studies that test specific hypotheses.

Neurobehavioral toxicants. Research is needed to better characterize the potential neurologic toxicity of environmental chemicals to which children are frequently exposed. Basic research is needed to define how toxicants in the environment may disrupt development in the brains of infants and children at different stages of development. The possible late neurodegenerative consequences of early exposures to neurotoxicants should also be studied. Such studies should be multidisciplinary in design. Some studies could be undertaken in experimental animals dosed early and followed over a lifetime, and other such studies would require long-term prospective follow-up of exposed human populations (*42*).

Endocrine and sexual disorders. Few chemicals have been tested for their ability to mimic hormonal activity (*35*). Many pesticides and other chemicals may act as endocrine disruptors; thus, they should be appropriately tested. Estrogenic, androgenic, thyroid, and other hormonal effects should all be considered. Specific recommendations include the following:
- Studies should be undertaken on patterns of children's exposure to endocrine-disrupting chemicals.
- Studies should be conducted to assess the possible role of environmental estrogens in the etiology of hypospadias, cryptorchidism, and testicular cancer.
- Studies of the possible relationship between premature onset of menarche in girls and exposure to environmental disruptors should be supported.

Some of these research questions might most efficiently be answered through prospective longitudinal studies of large populations of children.

Environmental justice. Environmental injustice is all too common in the vicinity of Superfund sites. African Americans, Native Americans, and people of Hispanic origin

comprise a disproportionately large proportion of residents living near these sites. Children of color are at greater risk of toxic exposure than children from other sectors of society (*43,44*). Environmental justice issues should be consciously addressed in SBRP programs.

Conclusion

Children are not little adults (*2,3*). Their tissues and organs are rapidly developing and growing, and at various stages these growth processes create windows of great vulnerability to environmental toxicants. Children's patterns of consumption and exposure are very different from those of adults. The combination of disproportionately heavy exposure plus biologic vulnerability makes children very susceptible to injury caused by toxicants in the environment. Superfund hazardous waste sites are important potential sources of children's exposure to environmental toxicants.

To address the issue of children's exposure to environmental toxicants, it appears logical and in the national interest to develop a new child-centered, prevention-oriented agenda for research, risk assessment, and formulation of health policy in the United States (*41*). A guide to developing such a program may be found in the work of the Agency for Toxic Substances and Disease Registry (ATSDR), an agency deeply involved in conducting health assessments of populations living near hazardous waste sites (*1*). The ATSDR conducts health consultations and issues public health advisories when site conditions warrant, and maintains surveillance systems and registries of people exposed to toxic substances to aid in assessing the health consequences of low-level, long-term exposures. The ATSDR also conducts public health promotion activities in communities near hazardous waste sites. The ATSDR has recently developed guidelines to encourage the systematic consideration of children's health issues in all health assessments of populations near Superfund sites. The following guidelines were graciously provided by the ATSDR:

- Are children exposed to potentially harmful substances?
- Are any exposure pathways unique to children?
- Do children differ from adults in their weight-adjusted intake of toxicants?
- Do pharmacokinetic or pharmacodynamic parameters of adults and children differ?
- What are the effects of multiple and cumulative exposures? Are latent or delayed effects of early exposure possible?
- At what stage of development is the child exposed? Could any developmental processes be altered by the toxicant?
- Are there adequate animal models for exposure after birth? What do these models indicate about adverse effects on exposed children?
- Are effects seen in more than one generation of a family?
- Are there ethical and cultural consequences unique to children? If children are not included in an agency activity, why are they excluded?

These guidelines may serve as a useful orientation for site-specific research activities in the SBRP.

Cleanup and remediation of hazardous waste sites across the United States is proceeding under the leadership of the EPA, with the support of the Superfund Trust. A close historical and administrative link exists between the EPA Superfund Program, the ATSDR, and the SBRP. This link creates the opportunity for university-based SBRP grantees to collaborate with the EPA, the NIEHS, and the ATSDR in studying the adverse effects on children's health of exposures to environmental toxicants associated with hazardous waste sites.

Development and adoption of a child-centered agenda is necessary if disease of toxic environmental origin in children is to be controlled, prevented, and eventually eradicated. This agenda should be multidisciplinary, and it should include epidemiology, pediatrics, exposure assessment, toxicology, and health economics. It is essential that the agenda be developed in close consultation with those who represent the interests of children and the other vulnerable groups within our society. The NIEHS Superfund Basic Research Program has contributed already to development of this agenda, and it is in an excellent position to continue this leadership in the future.

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