COMMENTARY

Children's Health and the Environment: A New Agenda for Prevention Research

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Patterns of illness in American children have changed dramatically in this century. The ancient infectious diseases have largely been controlled. The major diseases confronting children now are chronic and disabling conditions termed the "new pediatric morbidity" — asthma mortality has doubled; leukemia and brain cancer have increased in incidence; neurodevelopmental dysfunction is widespread; hypospadias incidence has doubled. Chemical toxicants in the environment as well as poverty, racism, and inequitable access to medical care are factors known and suspected to contribute to causation of these pediatric diseases. Children are at risk of exposure to over 15,000 high-production-volume synthetic chemicals, nearly all of them developed in the past 50 years. These chemicals are used widely in consumer products and are dispersed in the environment. More than half are untested for toxicity. Children appear uniquely vulnerable to chemical toxicants because of their disproportionately heavy exposures and their inherent biological susceptibility. To prevent disease of environmental origin in America's children, the Children's Environmental Health Network (CEHN) calls for a comprehensive, national, child-centered agenda. This agenda must recognize children's vulnerabilities to environmental toxicants. It must encompass *a*) a new prevention-oriented research focus; *b*) a new child-centered paradigm for health risk assessment and policy formulation; and *c*) a campaign to educate the public, health professionals, and policy makers that environmental disease is caused by preventable exposures and is therefore avoidable. To anchor the agenda, CEHN calls for long-term, stable investment and for creation of a national network of pediatric environmental health research and prevention centers. — *Environ Health Perspect* 106(Suppl 3):787–794 (1998). *http://ehpnet1.niehs.nih.gov/docs/1998/Suppl-3/787-794landrigan/abstract.html*

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Introduction

The protection of children against chemical toxicants in the environment is a major challenge to modern society (*1*). Children in America today inhabit a world vastly different from that of generations past (*2*). Most children in the United States in 1998 are better fed and better educated than children of earlier generations. Thanks to public health-based prevention strategies that have encouraged good housing, safe drinking water, and sanitary waste disposal and employed vaccines, antibiotics, and improved nutrition, once-lethal infectious diseases such as measles, smallpox, poliomyelitis, and cholera have been conquered. The predicted life span of an infant born today is more than two decades longer than that of a baby born at the beginning of the twentieth century (*3*).

Yet, children today face hazards that were neither known nor imagined a few decades ago. They are at risk of exposure to nearly 15,000 high-production-volume synthetic chemicals, nearly all of which have been newly developed in the past 50 years. Many of these materials are contained in household products and are dispersed widely in the environment (*4*). More than half have never been tested for their potential toxicity, and thus their potential dangers to children are substantially unknown (*5,6*). Children's exposures to chemicals are compounded by continuing widespread child poverty, by violence, and by inequitable and increasingly restricted access to basic medical care. The health and economic consequences of children's exposures to environmental toxicants will be experienced by our society throughout much of the length of the twenty-first century.

The challenge to society in this context is 2-fold: to determine what causal associations exist between children's environmental exposures and disease, and to develop a science-based strategy that will prevent hazardous exposures and control environmental disease and disability (*1*).

This report from the First Research Conference of the Children's Environmental Health Network* examines data on the susceptibility of children to toxicants in the

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Abbreviations used: CDC, Centers for Disease Control and Prevention; ETS, environmental tobacco smoke; NAS, National Academy of Sciences; NHANES, National Health and Nutrition Examination Survey; PCBs, polychlorinated biphenyls; SEER, Surveillance, Epidemiology and End Results; SIDS, sudden infant death syndrome.

*The Children's Environmental Health Network is a national project whose mission is to promote a healthy environment and to protect the fetus and the child from environmental hazards. For more information call (510) 450-3818, or E-mail cehn@aimnet.com

environment. It reviews current epidemiologic information on the rising incidence of diseases in children known or suspected to be of environmental origin. It considers the evidence that environmental toxicants are contributing to changing patterns of pediatric illness. It highlights gaps in that knowledge. And most importantly, it presents a blueprint for a new agenda in pediatric environmental health, an agenda with the ultimate goal of preventing and controlling environmental illness in America's children.

Children's Vulnerability to Toxicants in the Environment

Children are highly vulnerable to environmental toxicants. This susceptibility was recognized in the creation of the discipline of pediatrics and was underscored through Byers' (*7*) and Needleman's (*8*) seminal studies on pediatric lead toxicity. On the basis of a detailed analysis undertaken by the National Research Council, this susceptibility is now recognized to be based on the following factors (*9*):

- Children have greater exposures to environmental toxicants than adults.

  Pound for pound of body weight, children drink more water, eat more food, and breathe more air than adults. For example, children in the first 6 months of life consume 7 times as much water per pound as does the average American adult. Children 1 through 5 years of age eat 3 to 4 times more food per pound than the average adult. In addition, children have unique food preferences. For example, the average 1-year-old drinks 21 times more apple juice and 11 times more grape juice and eats 2 to 7 times more grapes, bananas, pears, carrots, and broccoli than the average adult. The air intake of a resting infant is twice that of an adult per pound of body weight. Two behavioral characteristics of children further magnify their exposures to toxicants in the environment: their hand-to-mouth activity, which increases their ingestion of any toxicants in dust or soil; and their play close to the ground (*9*).
- Children's metabolic pathways, especially in the first months after birth, are immature compared with those of adults.

  A child's ability to metabolize, detoxify, and excrete many toxicants is different from that of an adult. In some instances, children are actually better able than adults to deal with environmental toxicants. More commonly, however, they are less able to deal with toxic chemicals and thus are more vulnerable to them (*10,11*).
- Children are growing and developing very rapidly, and their delicate developmental processes are easily disrupted.

  Many organ systems in young children—the nervous system in particular, but also the lungs, the immune system, and the reproductive organs—undergo extensive growth and development throughout pregnancy and in the first months and years of extrauterine life. During this period, structures are developed and vital connections established. These systems are not well adapted to repair any damage that may be caused by environmental toxicants. Thus, if cells in the developing brain, immune system, or reproductive organs are destroyed by neurotoxicants, or if development is diverted by endocrine disruptors, there is high risk that the resulting dysfunction will be permanent and irreversible. Depending on the organ damaged, the consequences can include loss of intelligence, immune dysfunction, or reproductive impairment.
- Because children have more future years of life than most adults, they have more time to develop chronic disease that may be triggered by early exposures.

  Many diseases that are triggered by toxicants in the environment require decades to develop. Examples include mesothelioma caused by exposure to asbestos, leukemia caused by benzene, breast cancer that may be caused by intrauterine exposure to DDT (*12*), and certain chronic neurologic illnesses (*13*). Many of those diseases are now thought to be the products of multistage processes that require many years to evolve from initiation to manifestation of illness. Toxic exposures sustained early in life appear more likely to lead to disease than similar exposures encountered later (*9*).

The New Pediatric Morbidity

The combination of children's exposures to newly developed chemical toxicants coupled with the triumphs of vaccines and antibiotics have changed the face of childhood illness in the industrially developed nations. For a series of diseases known or suspected to be of toxic environmental origin, incidence has increased over the past two decades. The following are examples of this new pediatric morbidity (*3*).

Asthma and Air Pollution

Asthma is a multifactorial disease that has a genetic basis and is exacerbated by a wide range of factors including infections, allergens, tobacco smoke, and environmental toxicants. Mortality among children from asthma has doubled over the past decade (*14*). Approximately 200 children die annually of asthma in the United States, more than 150,000 are hospitalized, and 5 million suffer from the disease. Increases in asthma are particularly evident in urban localities, and rates are highest in African-American and Latino children. In New York, Chicago, Los Angeles, Atlanta, and other major cities, asthma has become the leading cause of children's admissions to hospitals (*15*).

Ambient air pollution is an important trigger of asthma attacks in children. Air pollution is of special significance because it is preventable. Recent epidemiologic data indicate that ozone, oxides of nitrogen (NO_x), and fine particulates—the bulk of them from automobile, truck, and bus exhaust—are the components of urban outdoor air pollution most directly associated with pediatric asthma (*16,17*). In asthma attacks provoked by exposures in indoor air, important contributors include environmental tobacco smoke (ETS), mites, molds, and cockroach allergens (*18*).

Fine particulate air pollution, in addition to contributing to exacerbations of asthma in children, has been linked to increased rates of mortality in young infants (*19*) and in the elderly (*20*). A recent study of neonatal mortality found an association between elevated concentrations of airborne fine particulates and neonatal deaths, including the sudden infant death syndrome (SIDS) (*19*).

Childhood Cancer

Each year in the United States an estimated 8000 children are diagnosed with cancer (*21*). Leukemia and brain are the most common malignancies in childhood. After injuries, cancer is the second most common cause of death in American children beyond the first year of life.

Although the death rate from childhood cancer has declined markedly in recent years, thanks to vastly improved approaches to cancer treatment, cancer incidence has increased. Data from the National Cancer Institute Surveillance, Epidemiology and End Results (SEER)

Program indicate that incidence of acute lymphocytic leukemia increased by 27.4% from 1973 to 1990, from 2.8 cases per 100,000 children to 3.5 per 100,000. Since 1990, all incidence has declined in boys, but continues to rise, albeit more slowly, in girls. From 1973 to 1994, incidence of childhood brain cancer increased by 39.6%, with nearly equal increases in boys and girls. Wilms tumor incidence in these years rose by 45.6%. And in young men, 20 to 39 years of age, incidence of testicular cancer increased by 68% from 1973 to 1994 (*21*).

These increases in the incidence of childhood cancer have not been explained (*22*). They may in part reflect better diagnostic detection, in particular the introduction of magnetic resonance imaging for detection of brain cancer. Changes in lifestyle, particularly in diet, need to be considered and may play some role. Viruses are another possibility, although evidence to support the viral hypothesis is scant. The increases are too rapid to be the consequence of genetic alteration. Finally, the strong probability exists that environmental factors are involved, at least to some extent, and that intrauterine as well as postnatal exposures to environmental toxicants are etiologically important.

Tobacco

Active smoking among children typically begins early; 90% of smokers begin smoking before 18 years of age (*23*). More than 70% of all American high school students have tried cigarettes, and 17% are regular smokers. Over the past decade, the number of boys who have started smoking has declined. But tragically, there has been a steady increase in the number of girls and young women who have begun to smoke.

Passive smoking is also a hazard to children (*24*). Children exposed to environmental tobacco smoke have more bronchitis, pneumonia, otitis media, and viral respiratory infections than unexposed children. Children who live with two smoking parents have more respiratory illnesses than children who have only one smoking parent. Maternal smoking has a stronger effect on children's respiratory illnesses than smoking by the father.

Smoking during pregnancy poses a serious danger for the unborn child. Among women who smoke the likelihood of giving birth to a low birth weight infant is substantially increased (*25*). Women who smoke are at increased risk of miscarriage. Women who smoke require more months to conceive a pregnancy than nonsmoking women of the same age (*26*). Infants with pulmonary hypertension of the newborn are 6 times more likely to have been exposed *in utero* to the products of tobacco smoke. Finally, children of parents who smoke are at elevated risk of SIDS (*28,29*).

Neuropsychiatric Dysfunction and Environmental Exposures

Children are exposed to many neurotoxic substances in the environment, including lead, solvents, mercury, pesticides and polychlorinated biphenyls (PCBs) (*13*). These exposures have been shown to produce acute outbreaks of devastating neurologic illness such as the epidemic of Minamata disease in Japan caused by methyl mercury, and a statewide outbreak of carbamate pesticide poisoning in California caused by illegal contamination of Fourth of July watermelons. More recently, concern has arisen that chronic, lower-dose exposures of children to environmental neurotoxicants including lead, PCBs, and certain pesticides may produce more subtle but nonetheless permanent and irreversible learning deficits and behavioral dysfunctions.

Lead is of particular importance, both historically and currently, among environmental neurotoxicants, and studies of lead provide the paradigm for the concept of subclinical neurotoxicity. Despite the 94% decline in exposure that followed removal of most lead from gasoline, the Centers for Disease Control and Prevention (CDC) estimates currently that blood lead levels are elevated to levels of 10 µg/dl or above in approximately 940,000 preschool children (*30*).

The principal source of lead exposure is lead-based paint, which is found in approximately 60 million housing units. Elevated blood lead levels are most highly concentrated among poor, minority children living in inner cities, and the toxic effects of lead may be most severe in these children (*30*). But lead is no respecter of social station, and approximately 10 of all cases of childhood lead poisoning occur as the result of house renovation; most typically these cases occur in middle- and upper-class families (*31*).

Exposure of children to lead at current levels has been shown to produce impairment in brain function in children. This possibility was first recognized in 1979 when Needleman et al. (*8*) in a pioneering study of subclinical lead poisoning found that asymptomatic children with elevated body lead burdens and blood lead levels of 30 to 50 mg/dl had a 4.5-point deficit in mean verbal IQ scores compared to socioeconomically similar children with lower lead burdens. This early observation has been confirmed by subsequent longitudinal epidemiologic studies in children with blood lead levels in the range of 10 to 25 µg/dl (*32–35*). Moreover, the lead-induced deficit in intelligence appears to be permanent. An 11-year follow-up of the children in Needleman's original study found that those who had higher lead burdens in early life were more likely to experience persistent reading difficulty and to fail to graduate from high school (*36*). Thus early subclinical exposure to lead appears to result in lifelong disability. Multiplied by the tens of thousands of children at risk, the societal and fiscal impact of this disability is enormous (*37*).

Early exposure to lead may additionally be associated with increased risk in adult life for violent behavior. A recent study by Needleman et al. (*38*) has reported a link between body lead burden and adolescent delinquency. Further research is needed on these issues, extending beyond lead to examine both the short- and long-term consequences of children's exposures to a range of environmental neurotoxicants. Moreover, studies are needed of possible interactions and synergies between environmental toxicants and social and economic factors in the genesis of violent asocial behavior.

Endocrine and Sexual Disorders

Evidence is accumulating that environmental contaminants, particularly chlorinated hydrocarbon compounds, can exert adverse effects on health through their ability to disrupt estrogen function and other signaling functions within the human body (*39*). Some of these materials have been used as pesticides; others have industrial applications or are incorporated into plastics. DDT is a well-known example. DDT was banned, in part, because it interfered with estrogen metabolism in pelagic birds, resulting in thin-shelled, unhatchable eggs. Certain PCBs appear able to occupy thyroid hormone receptor sites; DDE can block the androgen receptor. Effects resulting from these exposures have been observed in experimental animals, in wildlife populations within several broadly contaminated ecosystems such as the Great Lakes and central Florida, and to a more limited extent in humans (*40*).

The embryo, fetus, and young child appear to be at particularly high risk of adverse consequences following early exposure to endocrine disruptors (*39*). Early exposure to endocrine-disrupting compounds can interfere with reproductive development (*41*). The developing nervous system appears also to be highly vulnerable to these chemicals, and early exposure to PCBs has been linked to persistent neurobehavioral dysfunction (*42*). Endocrine-disrupting compounds may be responsible, at least in part, for increases over the past two decades in incidence of testicular cancer (*21*), for a recently reported doubling in incidence of hypospadias in the United States (*43*), and for the increasingly early onset of puberty in young girls (*44*).

The Preventability of Pediatric Environmental Disease

Disease and dysfunction of environmental origin in children are preventable (*45*). Toxic environmental diseases that arise as a consequence of human activity can be prevented through modification of that activity. This principle has been illustrated by the tremendous reduction in children's blood lead levels that followed removal of lead from gasoline (*28*). Other recent successes are the following:

- Recognition of the vulnerability of children's lungs to ambient air pollutants triggered promulgation in 1997 of new federal air standards on ozone and fine particulates (*20*).
- Recognition of the vulnerability of children to ETS has been critical to recent revisions of national and local tobacco policy (*24*).
- Recognition of the special vulnerability of children to pesticides was critical to passage in 1996 of the Food Quality Protection Act (*9*).
- Recognition of the widespread exposure and heightened vulnerability of children to pesticides has led to restructuring of federal regulatory policy on food crop pesticides (*9*).
- Recognition of the very great susceptibility of fetuses to radiation (*46*) resulted in substantial reduction of prenatal use of medical x-rays and also to recommendations to reduce x-ray exposure of premature infants.

Prevention requires research. Research is needed to identify patterns and biologic mechanisms of environmental disease in children; to assess children's exposures to environmental toxicants and to quantify dose–response relationships; and to provide a blueprint for prevention (*47*).

Gaps in Previous Research

Despite children's extensive exposures and heightened vulnerability to environmental toxicants, until very recently there has not been a coherent research or policy agenda in the United States in children's environmental health. Research on pediatric disease, in general, and on pediatric disease of environmental origin, in particular, is seriously underfunded. According to a recent report from the White House Office of Science and Technology Policy, less than 0.4% of the $500 billion total spent on children in the United States each year is directed toward research, and only a fraction of that sum goes toward research on environmental illness (*48*). This report also found that 96% of the pediatric research budget comes from the federal government; nongovernmental organizations have not in recent years been a major force in research against environmental disease in children. At the present time there does not exist a single academic center in the United States dedicated to assessing and preventing the environmental health problems that confront children.

In the past year, fundamental change has occurred in the policy of ignoring children's vulnerability to environmental toxicants. The Food Quality Protection Act passed in August 1996 mandates that children's health be specifically considered in setting all standards for food crop pesticides. In September 1996, the Administrator of the U.S. Environmental Protection Agency (U.S. EPA) made a commitment that protection of children against health threats in the environment will be a major policy goal of the agency, a goal to be reflected in all future U.S. EPA research and regulation (*4*). Similar actions have been taken by the Administrator of the Agency for Toxic Substances and Disease Registry and the Director of the National Institute of Environmental Health Sciences. Most recently, in April 1997, President Clinton issued an executive order making the protection of children's health a major objective of the current federal administration (*49*).

These developments are very good news for pediatric environmental health. They hold forth the promise that investment in research against pediatric disease of environmental origin will be substantially increased and that findings from this research will have an enhanced impact on health policy and disease prevention.

A New Child-Centered Agenda for Research, Risk Assessment, Health Policy Formation, and Education

To confront the widespread and inadequately controlled exposure of America's children to toxicants in the environment, and to address rising rates of diseases in children that are known or suspected to be of environmental origin, the Children's Environmental Health Network calls for development of a comprehensive, national, child-centered agenda in environmental health. It must encompass research, risk assessment, health policy formation, and education. Commitment to this agenda must be sustained in a broad-based, nonpartisan fashion throughout the coming decades.

Research Recommendations

The Children's Environmental Health Network considers the following specific areas of research to be of critical national priority. These are areas of substantial need. They are areas where acceleration of research will likely lead to breakthroughs in current knowledge of pediatric environmental disease and to more effective prevention.

Childhood Asthma. Research is needed to understand why rates of asthma are increasing in America's children (*14*). Studies must be designed to understand why mortality rates are increasing so much more rapidly in urban minority children than in children of other sectors of society. Is the increase due to changes in the ambient environment, changes in the indoor environment, socioeconomic factors, or a combination of all of these?

Research is specifically needed to address the following issues:

- to more precisely characterize the linkages between air pollution and asthma, and to examine interactions among components of air pollution in the exacerbation of asthma;
- to assess the role of indoor air pollutants, including bioaerosols, in exacerbating respiratory disease. This research needs to direct careful attention to exposure assessment. It is particularly important because children today spend so much time indoors;
- to study synergies between indoor and outdoor air pollution and risk of asthma;

- to examine individual differences among children in their susceptibility to air pollutants;
- to examine factors in the environment that may be altering children's susceptibility to allergens and chemicals that alter the threshold for airway reactivity, thus contributing directly to the etiology of asthma (*50*);
- to evaluate primary prevention strategies that may be employed during pregnancy and early life to reduce incidence of asthma;
- to conduct large prospective population-based studies of children who live in the inner city and in affluent environments, to assess interactions among infection history and environmental exposures in the development of allergy, asthma, and airway reactivity; and
- in all of these studies, detailed assessment must be made of the impact of good medical care on the course and severity of the disease.

Childhood Cancer. It is essential that research to identify the specific environmental and other preventable causes of childhood cancer be accelerated (*51*). A major, unresolved question is why incidence rates of cancer in American children appear to be rising (*21,22*). Some approaches that might be applied are the following:

- Develop geographic maps showing patterns of incidence and changes in incidence for each type of childhood cancer in the United States. Although such maps cannot test causal hypotheses, they are effective generators of hypotheses.
- Initiate large biomarker-based epidemiologic studies to evaluate the role of suspect exposures in the genesis of childhood cancer.
- Initiate prospective longitudinal studies of children exposed to known or suspected carcinogens, including children with exposures *in utero.*
- Study of cancer susceptibility in children with focus on interactions between genetic polymorphisms and environmental exposures in etiology of cancer.

Neurobehavioral Toxicants. Research is needed to better characterize the potential neurological toxicity of environmental chemicals to which children are exposed. Both acute and delayed consequences of these exposures need to be assessed (*13*).

Specific research recommendations include *a*) to explore mechanisms of action of neurotoxicants; *b*) to examine the health effects of mixtures of neurotoxicants, especially pesticides; *c*) to develop multigenerational assays of neurotoxicity; *d*) to devise techniques to study gene–environment interactions in neurotoxicity; *e*) to continue studies of the neurotoxicity of mercury and PCBs in some children using sensitive outcome measures; and *f*) to undertake further studies of the long-term social and behavioral consequences of early exposure to lead and other neurotoxicants, including drug abuse and criminal behavior. Such studies must explore possible synergies between toxicants and sociocultural factors.

Finally, efforts must be made to prevent further introduction of neurotoxicants into the environment of children. For example, a proposal has recently been made by The Ethyl Corporation to add manganese to gasoline. Manganese is a known neurotoxicant that in adults causes a syndrome similar to Parkinson's disease; the pediatric toxicity of organic manganese is not known (*52*). It has been only a few decades since lead, a potent neurotoxicant, was removed from gasoline with the outstanding public health effect of lowering blood lead levels in children. Introducing yet another known neurotoxicant is at best imprudent and must seriously be questioned.

Endocrine and Sexual Disorders. Research recommendations to assess the impact of endocrine disruptors on children's health include

- studies to better define patterns of exposure to endocrine-disrupting chemicals
- studies to assess the possible contribution of environmental estrogens to rising incidence of hypospadias, cryptorchidism, and testicular cancer
- epidemiologic and toxicologic studies to examine possible linkages between *in utero* exposure to endocrine disruptors and later risk of breast and prostate cancer
- studies of the possible relationship between premature onset of menarche in girls and exposure to environmental endocrine disruptors
- studies of the hazards of pediatric exposure to dioxins, particularly dioxins released into the environment through incineration of hazardous waste
- studies into the possible relationship between endometriosis and early exposure to environmental endocrine disruptors

Some of the above objectives might most efficiently be achieved by undertaking large prospective longitudinal studies in children.

Intervention Studies. Studies are needed to assess the efficacy of proposed interventions against environmental disease (*45*). Approaches to prevention against pediatric environmental illness include pollution prevention, behavioral modification, and secondary prevention. For example, prevention might include introduction of integrated pest management in urban housing, or the administration of medication to children who have already been exposed to carcinogens, with assessment of subsequent biochemical changes, dietary modification, and efforts to reduce body burdens of toxicants (*51*). These approaches require careful assessment of their efficacy and cost-effectiveness, and outcomes need to be rigorously assessed.

Economic Studies. Studies are needed to assess the costs of pediatric environmental disease (*37*). Both the direct costs of illness and the indirect costs that result from loss of education, foregone future achievement, and familial disruption need to be examined in these analyses. The life-long consequences of each toxic exposure as well as possible transgenerational effects need to be considered. Calculation of these costs will permit assessment of the benefits that will accrue to American society through prevention of pediatric environmental disease.

Cross-Cutting Issues in Research

In addition to research into specific exposures and diseases, the Children's Environmental Health Network has identified five cross-cutting approaches that need to be integrated into future research into children's health and the environment:

Exposure Assessment. In epidemiologic analyses, exposure assessment is traditionally the most difficult and most neglected component. Inadequate characterization of exposure usually tends to bias the results of epidemiologic studies towards the null and thus to obscure true causal associations. In the planning of population-based studies of disease in children, specific attention and adequate budgets must be directed toward assessments of exposures. Biomarkers of exposure may prove useful. It is important to recognize that the patterns of children's exposures to toxicants in the environment vary over time and with developmental stage.

Windows of Vulnerability. Historical episodes such as the thalidomide tragedy and the epidemic of adenocarcinoma of the vagina caused by diethylstilbestrol illustrate clearly that there exist windows of vulnerability in early life during which embryos, fetuses, infants, and children are extraordinarily susceptible to environmental toxicants (*53*). In some instances this

vulnerability is qualitative; in other instances it is quantitative and becomes manifest as vulnerability to toxicants at relatively low doses of exposure. Increasingly, approaches to assess such vulnerabilities need to be incorporated into toxicology testing paradigms (*53*).

Heretofore, most toxicologic testing has administered toxic chemicals to adolescent animals and then followed the animals into middle adult life or early old age. Increasingly, there is a need to administer toxic chemicals to infantile animals or even *in utero* and then to follow the animals across the entire span of their lives. This approach would more nearly mimic the human condition in which early exposures may be followed by appearance of disease only decades later. Adoption of testing paradigms that could assess the long-term effects of early exposures was a specific recommendation of a National Academy of Sciences (NAS) committee report titled *Pesticides in the Diets of Infants and Children* (*9*).

The NAS Committee recommended studies to fulfill the following objectives and the Network concurs in their recommendations: *a*) to identify developmental periods of vulnerability; *b*) to study developmental processes during critical periods of vulnerability; *c*) to develop new approaches to toxicity testing that have the capacity to detect unanticipated outcomes of early exposures; and *d*) to study environmental exposures in early life and their relationship to risk of adult disease as well as transgenerational effects.

Gene–Environment Interactions and Genetic Susceptibility

Epidemiologists and laboratory scientists are working together on studies that seek to understand the extent of gene–environment interactions in the etiology of diseases (*54*). More work is needed to assess important genetic polymorphisms and to identify the genes that control enzymatic activity, endocrine regulation, immunologic status, and a variety of other host factors, and that may influence disease susceptibility during developmental periods. Much can be learned from mechanistic, genetic, and epidemiologic investigations of environmental carcinogens, and the multistep/multievent process refined through carcinogenesis research can be used as a paradigm for study of other environmentally induced diseases.

Biomarkers in Pediatric Environmental Health Research. Epidemiology, the study of diseases in populations, has long played a central role in pediatric environmental health research. Traditionally, epidemiology seeks to delineate patterns of disease and death, to identify populations at high risk, and to discover causal factors and routes of exposure. Additionally, epidemiologic research seeks to integrate population data with clinical and laboratory insights to develop an understanding of mechanisms of disease causation.

Classical epidemiology, however, is limited in the study of diseases caused by environmental hazards by frequent lack of exposure assessment data and the typically long delay between exposure and appearance of symptoms.

Also, because diseases of environmental origin usually are rare events, analyses of their links with toxic exposures may require the evaluation of very large populations.

Many of these limitations could be overcome by the incorporation in epidemiologic studies of powerful biochemical, molecular, and cytogenetic probes termed biological markers (*54*). These markers can be divided into three categories: markers of exposure, markers of effect, and markers of susceptibility (*55*). Markers of exposure permit precise assessment of past exposures and internal biological dose and thus allow sharper delineation of exposure–effect relationships. They also permit identification of exposed individuals within a larger population, enabling classical epidemiology to be more readily applied to this smaller group of individuals with higher risk of disease. Some common biological markers of exposure are blood lead levels for lead exposure, and serum/urine cotinine (a metabolite of nicotine) for ETS.

Biological markers constitute an extraordinarily promising means for objectively quantifying the effects of environmental justice on children's health. For example, the National Health and Nutrition Examination Survey (NHANES) surveys of children's blood lead levels in the United States conducted by the CDC demonstrate clear disparities in children's blood lead levels along racial and economic lines, with the highest prevalence of elevated blood lead levels occuring among poor, minority children living in inner cities (*30*).

Child-Centered Risk Assessment. The current paradigm of risk assessment places the toxicant or hazard at the center of the discussion; it then examines data on effects, exposures, and mechanisms of action. This paradigm focuses almost exclusively on adults; children are considered only incidentally. The current approach examines chemicals only one at a time; yet typically, exposures in the real world occur simultaneously to multiple chemicals.

What is needed is a new paradigm of risk assessment in which children, not toxicants, are placed at the center of the paradigm (*56*). With this paradigm in place, a host of new questions can be asked: What is the child exposed to? How is the child exposed and at what stage of development? What are the effects of acute exposures or long-term, low-level exposures? What are the delayed effects? What are the effects of multiple cumulative exposures? What are the transgenerational effects?

Using this new paradigm, data would need to be collected and analyzed based on children's exposures and not extrapolated from adult data. The development of such a new approach to risk assessment is an essential prerequisite to the development of child-protective public policies.

Collaboration between Scientists and Communities at Risk. Too often in our society, the children most heavily exposed to environmental toxicants are poor children in minority communities. This pattern of disproportionate exposure is termed environmental injustice (*57*). To address this issue, President Clinton, on February 11, 1994, signed Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-income Populations." This order established strategic elements for achieving environmental justice that must be implemented by all federal agencies.

The environmental justice paradigm emphasizes community-based and community-driven prevention/intervention models. Communities must become involved as active practitioners of science, as co-investigators collaborating with academic scientists concerned with design of study instruments and protocols, data collection, and interpretation. The populations most impacted should have a seat at the planning and decision-making table (*57–60*).

Specific recommendations include

- development of research agreements that incorporate respect, equity, and empowerment of communities;
- involvement of the community in research at every stage including selection of topics, implementation and evaluation
- assurance that studies seek not only to fulfill scientific goals, but also to further community objectives;
- training and guidance that enables members of the community to become investigators.

Conclusions

In February 1997, the Children's Environmental Health Network convened a group of internationally recognized experts to discuss the status of research, practice, prevention, and policy in children's environmental health. The amount of new information and the rate of new discoveries in the last decade have been staggering. The successes of our medical technologies are impressive. Yet, in spite of our extraordinary accomplishments, we are currently unable to reassure ourselves and our society that our most precious resource, our children, are adequately protected by the policies that derive from our science. We lack a coordinated program.

To address these issues, the Children's Environmental Health Network urges development of a new child-centered, prevention-oriented agenda for research, risk assessment, education, and formulation of environmental health policy in the United States. Adoption of such an agenda is urgently needed if childhood diseases of environmental origin are to be controlled, prevented, and eventually eradicated. This agenda will need to be multidisciplinary and include pediatrics, epidemiology, exposure assessment, toxicology, and health economics. It is essential that the agenda be developed in close consultation with those who represent communities and the interests of children.

The Children's Environmental Health Network recognizes clearly that environmental toxicants are not the only hazard confronting American children. Children, and especially poor, minority children living in inner city communities, are beset by violence, poverty, and inadequate access to medical care. A child-centered agenda for research, education, and community empowerment in children's environmental health must be coordinated with important and valid efforts that are underway to address those problems.

A new child-centered agenda in pediatric environmental health will require adequate and substantial funding. Far too few resources in the United States are directed at present toward children's environmental health (*48*). The Children's Environmental Health Network calls for substantial and sustained investment by federal and state governments to establish a children's environmental health agenda. Also, we encourage foundations and other components of the private sector to become increasingly involved. There is a critical need for the creation of a national network of prevention-oriented Children's Environmental Health Centers that encompass etiologic research, training of the next generation of leaders in the field, provision of clinical services, and participatory public education in partnership with communities. These Centers will anchor the agenda that the network envisions.

The ultimate vision of the Children's Environmental Health Network is of a world in which preventable diseases of toxic environmental origin in America's children are controlled and eradicated.

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