Children's Health and the Environment: Public Health Issues and Challenges for Risk Assessment

Philip J. Landrigan,[1] Carole A. Kimmel,[2] Adolfo Correa,[3] and Brenda Eskenazi[4]

[1]Department of Community and Preventive Medicine, Mount Sinai School of Medicine, New York, New York, USA; [2]National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC, USA; [3]National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia, USA; [4]Maternal and Child Health and Epidemiology, Berkeley School of Public Health, University of California, Berkeley, California, USA

Infants and children are not little adults. They are uniquely vulnerable to environmental toxicants. To protect infants and children against toxicants, the National Research Council in 1993 called for development of an approach to risk assessment that considers children's unique patterns of exposure and their special vulnerabilities to pesticides. Many aspects of that call were codified into federal law in the Food Quality Protection Act (FQPA) of 1996. This report highlights the central elements needed for development of a child-protective approach to risk assessment: *a*) improved quantitative assessment of children's exposures at different life stages, from fetal life through adolescence, including acute and chronic exposures, exposures via multiple routes, and exposures to multiple agents; *b*) development of new approaches to toxicity testing of chemicals that can detect unanticipated and subtle outcomes and that evaluate experimental subjects over the entire life span from early exposure to natural death to replicate the human experience; *c*) development of new toxicodynamic and toxicokinetic models that account for the unique physiologic characteristics of infants and children; *d*) development of new approaches to assessment of outcomes, functional, organ, cellular and molecular, over the entire life span; these measures need to be incorporated into toxicity testing and into long-term prospective epidemiologic studies of children; and *e*) application of uncertainty and safety factors in risk assessment that specifically consider children's risks. Under FQPA, children are presumed more vulnerable to pesticides than adults unless evidence exists to the contrary. Uncertainty and safety factors that are protective of children must therefore be incorporated into risk assessment when data on developmental toxicity are lacking or when there is evidence of developmental toxicity. The adequate protection of children against toxic agents in the environment will require fundamental and far-reaching revisions of current approaches to toxicity testing and risk assessment. *Key words:* children's environmental health, developmental toxicology, risk assessment, safety factors, toxicity testing. *Environ Health Perspect* 112:257–265 (2003). doi:10.1289/ehp.6115 available via *http://dx.doi.org/* [Online 25 November 2003]

Protection of human health against disease and injury caused by toxic chemicals in the environment is the ultimate goal of risk assessment and risk management. Historically, risk assessment focused on adult exposures and toxicities and gave little consideration to vulnerable life stages such as fetal development and early childhood. An emphasis on adult cancer risk and the evolution of methodologies for estimating cancer risks that are different from the methods used to assess other health effects tended to further diminish the importance for risk assessment of children's exposures and outcomes. In addition, the use of default factors based on the healthy young adult did not account adequately for the unique exposures and sensitivities of fetuses, infants, and children (Landrigan and Carlson 1995).

In the past decade, stimulated especially by the 1993 National Research Council (NRC) report on Pesticides in the Diets of Infants and Children [NAS (National Academy of Sciences) 1993], recognition has grown that children are a group within the population who have unique exposures and special vulnerabilities to environmental toxicants. It is now understood that children require an approach to risk assessment that considers their particular characteristics. The present report, developed by the International Life Sciences Institute (ILSI) with support from the U.S. Environmental Protection Agency (U.S. EPA), is intended to consider the elements and structure of a child-protective approach to risk assessment.

The purpose of this article is to introduce a series of reports from an ILSI Workshop on Risk Assessment and Children's Health held in July 2001. This article begins the discussion of child-protective risk assessment by *a*) summarizing information on the vulnerability of children to agents in the environment; *b*) presenting a rationale, based on considerations of public health and preventive medicine, for developing an approach to risk assessment that considers the unique exposures and special sensitivities of infants and children; and *c*) highlighting elements of great importance for a child-protective approach to risk assessment.

The word "children" is used throughout this paper to include all stages of development (fetuses, infants, and children) from conception to 21 years of age.

The Historical Development of Child-Protective Risk Assessment

The National Research Council report on Pesticides in the Diets of Infants and Children. Publication in 1993 of the NRC report on Pesticides in the Diets of Infants and Children (NAS 1993) was critical in raising awareness of the importance for risk assessment of children's environmental health. This report elevated concern on a broad national level about children's special vulnerabilities to environmental agents. It made clear that protection of the health of vulnerable populations would require a new approach to risk assessment.

The NRC report recommended an approach to risk assessment that moved beyond consideration of average exposures based primarily on adult characteristics to one that accounted for the heterogeneity of exposures and for potential differential sensitivities at various life stages, particularly during prenatal development, infancy, and childhood. The NRC report built on guidelines that the

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Address correspondence to P.J. Landrigan, Dept. of Community and Preventive Medicine, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1057, New York, NY 10029 USA. Telephone: (212) 241-6173. Fax: (212) 996-0407. E-mail: phil.landrigan@mssm.edu

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U.S. EPA had published for developmental toxicity risk assessment in 1986 and revised in 1991 (U.S. EPA 1986, 1991). It also built on other published documents such as the ILSI report on Similarities and Differences between Children and Adults: Implications for Risk Assessment (Guzelian et al. 1992).

Infants and children were identified in both the NRC and ILSI reports as groups within the population who require special consideration in risk assessment because of their unique patterns of exposures to environmental hazards and their special vulnerabilities. The NRC report noted that "children are not little adults." It called for the development of new risk assessment methods that would incorporate better data on children's exposures to pesticides along with improved information on the potentially harmful effects of pesticides during fetal development, infancy, and childhood (NAS 1993).

To "provide a more complete characterization of risk," the NRC committee recommended use of exposure distributions rather than point estimates. It noted that levels of exposure could differ by several orders of magnitude between children and adults. The NRC report recommended also that exposure assessment methods be expanded to consider exposures to multiple chemicals with multiple routes of exposure (NAS 1993).

To enhance characterization of the susceptibility of children, the NRC committee recommended the development of physiologically based pharmacokinetic models that could describe the unique features of young, developing humans. To assess the long-term and delayed effects of early exposures, the committee recommended that "it would be desirable to develop bioassay protocols that provide direct information on the relative contribution of exposures at different ages to lifetime risks." The committee called for further development of "appropriate toxicological tests for perinatal and childhood toxicity" to address issues not addressed in current testing guideline protocols (NAS 1993).

The NRC committee concluded that "in the absence of data to the contrary, there should be a presumption of greater risk to infants and children. To validate this presumption, the committee recommended that "the sensitivity of mature and immature individuals should be studied systematically to expand the current limited database as to relative sensitivity."

To provide enhanced protection to children during vulnerable periods of early development, the NRC committee recommended that a child-protective safety factor of up to 10-fold be considered in risk assessment "when there is evidence of developmental toxicity and when data from toxicity testing relative to children are incomplete." The committee noted that it had long been standard practice at the U.S. EPA and U.S. Food and Drug Administration to divide the no-observed-effect-level (NOEL) obtained in animal test results by an uncertainty factor of 100-fold in establishing a reference dose (RfD) for toxic effects other than cancer or heritable mutation. The committee noted that this 100-fold factor comprises two separate factors 10-fold each: one allows for uncertainty in extrapolating data from animals to humans; the second accommodates variation within the human population. The committee acknowledged that "this latter uncertainty factor generally provides adequate protection for infants and children."

Nevertheless, the committee expressed concern that the standard 100-fold safety factor may not always be sufficient to account for unique susceptibilities at particularly sensitive stages of early development. The committee was also concerned about the great gaps that currently exist in developmental toxicity testing data for many chemicals. It was for these reasons that the NRC committee recommended consideration of a third child-protective safety factor in risk assessment.

Food Quality Protection Act of 1996. After publication of the NRC report, the concept that children should be considered more vulnerable to pesticides than adults in the absence of evidence to the contrary was adopted by the U.S. Congress. In 1996, by unanimous vote of both Houses of Congress, the concept was incorporated into the Food Quality Protection Act of 1996 (FQPA 1996), the principal federal statute governing the use of pesticides in agriculture. Major provisions of this act are as follows:

- Standards for pesticide residues in food must be health based. They must be set at levels that ensure a "reasonable certainty of no harm."
- Exposure and vulnerabilities of infants and children must be specifically considered in establishing pesticide residue standards.
- When insufficient data exist to assess the special exposures and/or vulnerabilities of infants and children, an additional 10-fold safety factor must be considered in setting standards.
- Consideration of the potential benefits of pesticides must be limited.
- All pesticide standards must be reviewed every 10 years.
- Endocrine effects of pesticides must be systematically evaluated in toxicity testing.

FQPA incorporates most of the recommendations of the NRC report. It requires that standards for agricultural pesticides be set at levels sufficiently strict to protect the health of infants and children. It directs the U.S. EPA to use an additional 10-fold margin of safety in assessing the risks to infants and children to take into account the potential for prenatal and postnatal toxicity, particularly when the toxicology and exposure databases are judged to be incomplete. The statute authorizes the U.S. EPA to replace this default 10-fold FQPA safety factor with a different factor only if, based on reliable data, the resulting margin would be adequate to protect infants and children. The requirement for the FQPA safety factor was intended by Congress to be a stimulus to the generation of data on developmental toxicology and on early life exposures.

Recently, the U.S. EPA published its final guidance on the application of the additional FQPA safety factor in risk assessment (U.S. EPA 2002a). The agency will apply the additional factor at the beginning of the risk assessment process but recognizes that the intent of the FQPA safety factor overlaps with several uncertainty factors traditionally used to account for data gaps and concerns in the risk assessment process. These include default 10-fold factors to account for: *a*) the lack of a no observable adverse effect level (NOAEL) (lowest observable adverse effect level to NOAEL factor); *b*) the lack of chronic exposure data for setting the chronic RfDs and reference concentrations (RfCs) (subchronic to chronic factor); and *c*) inadequacies or gaps in the database considered minimal for setting RfDs/RfCs (database factor). In most cases, the U.S. EPA has expressed the opinion that these factors will be sufficient to account for the concerns related to children's health. If, however, the adequacy and appropriateness of the toxicity assessment or the exposure assessment are judged by the U.S. EPA's risk assessors to be insufficient, a part or all of the child-protective FQPA factor is applied to the RfD. The resulting FQPA-adjusted RfD is termed the population-adjusted dose.

According to a report issued by Consumers Union in February 2000, the U.S. EPA had applied one or more additional safety factors for 104 of 273 (38%) pesticides evaluated between August 1996 and March 2001. For the organophosphorus insecticides, one of U.S. EPA's high priority categories for review, additional safety factors were applied for 26 of 49 substances (Consumers Union of the United States Inc. 2001).

Children's Unique Vulnerability to Toxicants in the Environment

The detailed analysis of children's exposures to environmental chemicals undertaken by the NRC established that children's heightened vulnerability to chemicals arises from four sources described below (NAS 1993).

Children have disproportionately heavy exposures to many environmental agents. Children drink more water, eat more food, and breathe more air pound-for-pound of body weight compared with adults. For example,

children in the first 6 months of life drink seven times as much water, whereas children ages 1 through 5 years eat 3 to 4 times more food on a body-weight basis than the average adult. 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 environmental contaminants present in water, food, and air (NAS 1993). Two additional characteristics of children magnify their exposures: their hand-to-mouth behavior and their play close to the ground.

Children's metabolic pathways, especially in fetal life and in the first months after birth, are immature. Children's ability to metabolize, detoxify, and excrete environmental agents is different from that of adults. In some instances, children are better able than adults to deal with environmental agents (NAS 1993; Spielberg 1992) because they cannot make the active metabolite required for toxicity. In other instances, children are less able to deal with toxic chemicals and thus are more vulnerable to them (NAS 1993; Spielberg 1992). Differences in metabolism exist also between prenatal and postnatal life and may vary over the course of pregnancy. An additional source of vulnerability in fetuses and young children is that the blood–brain barrier is not fully developed, and therefore xenobiotics may be more easily able to enter the central nervous system (Rodier 1995).

Developmental processes are easily disrupted during rapid growth and development before and after birth. Rapid growth and development occur during embryonic and fetal life as well as in the first years after birth. In the brain for example, billions of cells must form, move to their assigned positions, and establish precise connections with other cells (Rodier 1995). Development of the endocrine and reproductive organs is guided by a complex and precisely timed sequence of chemical messages. If cells in an infant's brain are destroyed by chemicals, if connections between neurons fail to form, or if false signals are sent to the developing reproductive organs by endocrine disruptors (EDs), neurological or reproductive dysfunction may result (Bellinger et al. 1987; Needleman et al. 1990; Jacobson and Jacobson 1996). Because children have more future years of life than most adults, they have more time to develop chronic diseases that may be triggered by early exposures. Many diseases caused by toxic agents in the environment require decades to develop.

Children have more years of future life and thus more time to develop diseases initiated by early exposures. Many of those diseases, including cancer and neurodegenerative diseases, are thought to arise through a series of changes within cells that require many years to evolve from initiation to actual manifestation of illness. Exposures to environmental agents early in life, including prenatal exposures, appear more likely to produce chronic disease than similar exposures encountered later (Ekbom et al. 1997; Gray et al. 1991). Thus, there are likely to be critical windows of exposure, even for these chronic diseases, that need to be further explored.

Risks at Different Ages

Children are exposed to toxic agents through the air they breathe, the water they drink, the foods they eat, the medications they consume, and the wide variety of environments they inhabit, including their homes, day care centers, schools, and motor vehicles. Children have unique routes of exposure that have no parallel among adults, and the routes of exposure and the resulting risks to health differ in different stages of childhood. Contact with toxic agents can occur *in utero* through transplacental transfer of chemicals from mother to fetus; it can occur via breast milk in nursing infants; and it can occur in early childhood via hand-to-mouth transfer of toxic chemicals. Analysis of children's varying patterns and pathways of exposure to environmental agents and the resulting health effects at various stages of development is an essential prerequisite to formulation of a child-protective approach to risk assessment.

Early examples of unique vulnerability to pharmaceuticals during pregnancy. In pregnancy, especially in the first trimester, maternal use of certain medications has been linked to a number of adverse effects in humans. The first of these outcomes to be recognized were anatomical birth defects. Examples of these unique risks include the following:

- In 1961 a sudden increase in the frequency of limb reduction defects, phocomelia in particular, in West Germany and Australia was shown to have been caused by maternal prenatal use of the sedative-hypnotic thalidomide (Lenz 1962; McBride 1961; Taussig 1962). Removal of the drug from the market led to a substantial decrease in the frequency of limb reduction defects.
- *In utero* exposure to aminopterin, an antagonist of folic acid, has been associated with anencephaly, meningocele, hydrocephalus, and cleft lip and palate (Thiersch 1952; Warkany et al. 1959).
- *In utero* exposure to the anticonvulsant diphenylhydantoin has been associated with a broad spectrum of abnormalities, including orofacial clefts, nail and digital hypoplasia, growth abnormalities, and mental deficiency (Fedrick 1973; Monson et al. 1973).
- *In utero* exposure to valproic acid, another anticonvulsant, has been associated with neural tube defects and heart, craniofacial, and limb anomalies (Kallen et al. 1989).
- *In utero* exposure to the anticoagulant coumadin has been associated with hypoplasia of the nasal cartilage, chondrodysplasias, and atrophy of the optic nerves (Warkany 1976).
- *In utero* exposure to isotretinoin (13-*cis*-retinoic acid), an analog of vitamin A used to treat cystic acne, is associated with a characteristic pattern of malformations, including abnormal ear development, a flat nasal bridge, mandibular hypoplasia, cleft palate, hydrocephalus, neural tube defects, and conotruncal heart defects (Lammer et al. 1985).
- Administration of diethylstilbestrol (DES) to pregnant women to prevent miscarriage has been shown to cause various genital abnormalities in their offspring (Bongiovanni et al. 1959; Gill et al. 2002) as well as the development of adenocarcinoma of the vagina of their daughters in their late teens and early twenties (Herbst et al. 1971; O'Brien et al. 1979).

Many teratogenic agents were also found to cause neurological and other functional disorders in children that are not necessarily associated with gross structural alterations. For example, isotretinoin causes profound mental retardation in many children, and about half those children do not have any major malformations (Adams and Lammer 1993, 1995). DES causes a variety of reproductive problems in addition to vaginal adenocarcinoma, including infertility and poor pregnancy outcomes (Kaufman et al. 2000). Most recently, exposures to thalidomide and valproic acid in early pregnancy have been linked to autism (Moore et al. 2000; Stromland et al. 1994).

Examples of unique vulnerabilities to environmental agents. **Heavy metals.** Despite a decline in exposures over the past two decades (American Academy of Pediatrics Committee on Environmental Health 1998; Brody et al. 1994), resulting principally from removal of lead from gasoline, lead exposure continues to occur *in utero* and among children of preschool age in the United States. A national survey (conducted from October 1991 to September 1994) indicated that an estimated 940,000 preschool children had blood lead levels above the Centers for Disease Control and Prevention (CDC) intervention level of 10 μg/dL; nearly 275,000 had blood lead levels greater than 15 μg/dL, and nearly 85,000 had greater than twice the CDC intervention level (20 μg/dL) (CDC 1997). Today, lead-based paint in older homes is the most common source of lead exposure in children (CDC 1997). Exposures can occur through ingestion of paint chips or dust from deteriorating surfaces, from chewing on painted cribs, or through inhalation of lead paint dust, as can occur during home renovation. Children exposed prenatally to blood lead levels as low as 10 μg/dL, and possibly even as low as 5 μg/dL (Lanphear et al. 2000), may have delayed early mental development. Further, chronic low-level lead exposure during childhood may result in a decreased IQ,

reading and learning disabilities, attention deficits, and persistent behavioral problems (Bellinger et al. 1987; Needleman et al. 1990, 2002). The fact that toddlers are an age group at high risk of lead poisoning is a direct consequence of their unique hand-to-mouth behavior, coupled with the fact that their brains are still undergoing growth, development, myelination, and differentiation.

Prenatal exposure to methyl mercury has been shown to have adverse effects on neurodevelopment. This is an age-specific, unique risk that results from transplacental transfer of mercury from maternal blood to the fetal brain. Mercury deposited from the atmosphere into lakes, streams, and oceans can be converted into organic mercury compounds that accumulate in fish and biomagnify as they move up the food chain to reach highest levels in top predator fish species and marine mammals. These compounds are lipid soluble and are well absorbed from the gastrointestinal tract (Clarkson 1972). Methyl mercury crosses the placenta and is excreted in breast milk. Consumption of fish with high levels of methyl mercury by pregnant women in Minamata Bay, Japan, in the 1950s was associated with cerebral palsy in their offspring (Harada 1968). When people in Iraq consumed grain treated with a methyl mercury fungicide between 1959 and 1972, thousands were poisoned (Bakir et al. 1973). In both of those episodes, mothers who were asymptomatic or showed mild toxic effects gave birth to infants who appeared normal at birth, but in whom psychomotor retardation, blindness, deafness, and seizures developed over time (Amin-Zaki et al. 1979). For further assessment of the susceptibility of the fetus and infants to the neurotoxic effects of methyl mercury, three longitudinal studies are being undertaken to evaluate the long-term subclinical effects among children whose mothers' diets during pregnancy included large amounts of fish or marine mammals containing methyl mercury (Crump et al. 1998; Davidson et al. 1998; Grandjean et al. 1997). A report from the NAS based on an analysis of these three studies has concluded that low-level exposures to methyl mercury *in utero* can have adverse effects on neurobehavioral development (NAS 2000). The U.S. EPA has issued a new risk assessment for methyl mercury, setting the chronic oral RfD at 0.01 μg/kg/day (U.S. EPA 2001). This RfD is based principally on the finding of developmental neuropsychological impairments in children from the Faroe Island epidemiology study and on supporting data from the New Zealand study.

Environmental tobacco smoke. Environmental tobacco smoke (ETS) is a complex mixture of chemicals generated during the burning and smoking of tobacco products. Chemicals present in ETS include irritants and systemic toxicants such as hydrogen cyanide and sulfur dioxide (SO_2), mutagens and carcinogens such as benzo[*a*]pyrene, formaldehyde, and 4 aminobiphenyl, and the reproductive toxicants nicotine, cadmium, and carbon monoxide (CO) (Jenkins et al. 1992). Of children in the United States 11 years of age and younger, 43% live in a home with at least one person who smokes (Pirkle et al. 1996). Exposures of children to ETS produce a range of effects, some of which are unique to early life, and others that are analogous to the effects produced by ETS in adults.

Prenatal exposure to ETS affects fetal growth and is associated with a 20–40% elevated risk of low birth weight or "small for gestational age" [CEPA (California Environmental Protection Agency) 1997; Eskenazi et al. 1995; Haddow et al. 1988; WHO 1999]. The primary effect observed, reduction in mean low birth weight, is small in magnitude (25–50 g). However, if the distribution of birth weight in a population of babies is shifted downward by ETS exposure, infants who are already compromised may be pushed into higher risk categories. Because low birth weight is associated with increased infant morbidity and mortality, exposure to ETS is likely to augment such burden. Exposure to ETS during infancy has been associated with an increased risk of sudden infant death independent of low birth weight or prematurity (Klonoff-Cohen et al. 1995; Taylor and Sanderson 1995).

In children ETS exposure affects the upper and the lower respiratory tract. Infants and young children are at particular risk of exposure to ETS because of the small diameter of their airways and because pound-for-pound they breathe more air than adults. Infants exposed to ETS in their home environment have a 1.5- to 3-fold increased risk of lower respiratory infection compared with unexposed children (McConnochie and Roghmann 1986; Ogston et al. 1987;). The risk of lower respiratory infection associated with ETS is highest among infants under 3 months of age (Wright et al. 1991). Children whose parents smoke also are more likely to develop middle ear effusion, as measured by tympanometry (Reed and Lutz 1988; Strachan et al. 1989), and chronic respiratory problems (cough, phlegm, or wheezing) (Mannino 1996). Children exposed to ETS are at elevated risk of developing asthma, and those with asthma are more likely to experience more severe disease (Chilmonczyk et al. 1993; Martinez et al. 1992; Weitzman et al. 1990). Childhood exposure to ETS affects lung growth and development, as measured by small but significant decrements in pulmonary function tests (Cullinan and Taylor 1994; Cunningham et al. 1994; Lebowitz et al. 1992; Wang et al. 1994). Because early lung development is important in terms of future respiratory health, these results suggest that ETS may have adverse long-term effects on children's respiratory health that warrant further investigation through longitudinal studies.

Air pollutants. Various indoor air pollutants are associated with respiratory disorders in children, and these pollutants include particles, gases, vapors, allergens, and molds (Lambert and Samet 1996; Spengler 1991; U.S. EPA 1994). In the home, common sources of air pollutants other than tobacco smoking include gas and wood stoves and furnishings and construction materials that release organic gases and vapors, some of which contain formaldehyde. Combustion of natural gas results in the emission of nitrogen dioxide (NO_2) and CO. Cooking or heating with wood results in the emission of several substances in the form of liquid (suspended droplets), solids (suspended particles), and gases such as NO_2 and SO_2 (Lambert and Samet 1996). The aerosol mixture of very fine solid and liquid particles or "smoke" contains particles in the inhalable range [i.e., < 10 μm in aerodynamic diameter (PM_{10})]. Exposure to CO disrupts oxygen transport and may result in symptoms that mimic influenza, including fatigue, headache, dizziness, nausea and vomiting, cognitive impairment, and tachycardia (Lambert and Samet 1996). Exposure to high levels of NO_2 and SO_2 may result in acute mucocutaneous irritation and respiratory effects, and chronic exposure to relatively lower levels has been linked to asthma and respiratory irritation (Morrow 1984; Neas et al. 1991). Exposure to particles in wood smoke may result in irritation and inflammation of the respiratory tract, manifested as rhinitis, cough, wheezing, and worsening of asthma (Morris et al. 1990; Robin et al. 1996). Whether adults exposed to similar levels of wood smoke have a different probability of severe lower respiratory illnesses is unclear.

Indoor environments also contain a number of aeroallergens that trigger asthma episodes in children, including allergens of house dust mites, cats, and cockroaches (Cullinan and Taylor 1994). In urban dwellings, house dust mite and cockroach allergens are important in both onset and worsening of asthma symptoms (Cullinan and Taylor 1994). Cockroach allergens are common in the homes of inner-city children with asthma (Call et al. 1992; Rosenstreich 1997). Recent clinical and epidemiologic studies indicate that exposure to molds or dampness may increase the risk of respiratory symptoms among children (Dales et al. 1991; Delfino et al. 1997; Verhoeff et al. 1995). It is unclear whether the increasing prevalence of

asthma morbidity in children in recent years is due to an increased prevalence of exposure to aeroallergens, molds, or dampness, or to a combination of those indoor factors with changing patterns of ambient air pollution.

Ambient air pollution levels are also associated with asthma and other respiratory morbidity in children. Daily fluctuations in PM_{10} have been associated with increased emergency room visits for childhood asthma (Rennick and Jarman 1992; Schwartz et al. 1993), hospital admissions for asthma (Montealegre et al. 1993), decrements in peak flow rates in normal children (Neas et al. 1995), increased respiratory symptoms (Forsberg et al. 1993), and increased medication use in children with asthma (Pope 1991). Ozone has been of particular concern, as it provokes airway inflammation at very low levels (Aris et al. 1993). In addition, ozone increases airway reactivity (Horstman et al. 1990; Kreit et al. 1989), and there is evidence to suggest that ozone may potentiate the effects of allergens (Molfino et al. 1991). Ozone levels have been related to increases in asthma admissions and emergency room visits among children in Atlanta, Georgia (White et al. 1994), New Jersey (Cody et al. 1992), and Mexico City (Romieu et al. 1995). A study of the effect of increases in ambient ozone levels on children and workers in summer day camp in New Jersey suggests that children may be more sensitive than adults to increases in ambient ozone levels (Cody et al. 1992). In this study, increases in ozone concentrations above 120 ppb were associated with an increase in respiratory symptoms and a decline in peak expiratory flow rate among children but with no change in respiratory symptoms or pulmonary function among camp workers.

The potential impact of air pollution on childhood asthma morbidity in a community is exemplified by a report from CDC that examined hospitalizations for asthma in the Atlanta metropolitan area during the summer of 1996 in the weeks before, during, and after the summer Olympic Games. This analysis found that the rate of asthma hospitalization declined during the 2 weeks of the games, when citizens of Atlanta heeded an advisory from the mayor to improve air quality by not driving and by using public transportation instead. Emergency room visits for nonrespiratory conditions in children remained constant, indicating that diminished access to emergency rooms did not account for the decline in emergency room visits for respiratory problems. After the Games ended, motor vehicle traffic increased, air quality deteriorated, and childhood asthma hospitalization rates rebounded (Friedman et al. 2001).

Finally, ambient air pollutants, especially fine particulates, CO, and diesel exhaust, have been linked in epidemiologic studies to low birth weight, prematurity, and increased risk of birth defects (Ashworth 1998; Bobak 2000; Bobak et al. 2001; Dejmek et al. 1999; Gold et al. 1999; Ha et al. 2001; Perera et al. 2003; Ritz and Yu 1999; Ritz et al. 2000, 2002; Wang et al. 1997; Wilhelm and Ritz 2003).

Diseases and Outcomes in Children of Known or Suspected Environmental Origin

Patterns of disease among children in industrially developed nations today are quite different from those of generations past (Haggerty and Rothman 1975). Many of the traditional infectious diseases have been controlled: smallpox is eradicated, polio is nearly gone, measles is under control, diphtheria and tetanus are rarities, and cholera has virtually disappeared. Although AIDS and tuberculosis remain very much with us, the impact of the infectious diseases upon childhood mortality is greatly diminished. The expected life span of a baby born in the United States today is more than two decades longer than that of an infant born at the beginning of the twentieth century (Haggerty and Rothman 1975). Similar epidemiologic transitions from infectious to noninfectious diseases are occurring at various rates today in many nations around the world as those countries strengthen public health programs, control the classic infectious diseases, and move toward industrial development. In other countries, sadly, the increasing incidence of HIV positivity and of AIDS threatens to undo those gains.

Children today are at risk of disease caused by environmental hazards not encountered by previous generations. Over 85,000 synthetic chemical compounds, most of which have been developed since World War II, are now registered for commercial use in the U.S. EPA's Toxic Substances Control Act inventory. There are currently 2,800 chemicals produced in quantities of one million pounds or more per year (Goldman and Koduru 2000). These high-production-volume (HPV) chemicals are those with the potential to be most widely used in foods and consumer products and to be most widely disseminated in the environment. Fewer than half of these HPV chemicals have been tested for their potential toxicity to humans, and fewer still for their toxicity to children (Goldman and Koduru 2000; NAS 1984). Thus, their potential hazards to children's health and development are mostly unknown (Schaefer 1994).

Diseases of great importance to children in America today that are thought, or at least suspected, to be caused or aggravated by chemicals in the environment include the following:

Asthma. A recent study by the National Center for Health Statistics that surveyed data on self-reports of asthma, physician's office visits for asthma, emergency room visits for asthma, and hospitalizations for asthma provides evidence for increases in prevalence of asthma in the United States during the past 15 years, particularly among children (CDC 1995a). Estimates of the average rates of asthma prevalence increased over time across all age groups. Asthma mortality also increased. Children experienced some of the higher rates of morbidity as measured by self-reports, office visits, emergency department visits, and hospitalizations for asthma. These increases were particularly evident in urban localities. In New York and in other major cities, asthma has become the leading cause of admission of children to hospitals and the leading cause of school absenteeism (CDC 1995b). The increasing prevalence of asthma and the higher asthma morbidity among children in the United States, albeit still unexplained, suggest that, compared with adults, children are more likely to develop asthma and asthma exacerbations and/or be exposed to chemical or other factors that cause or trigger asthma episodes.

Childhood cancer. The reported incidence of childhood cancer has increased substantially in the United States in the past two decades (Devesa et al. 1995). Although death rates are down as a consequence of early detection and vastly improved treatment, data from the National Cancer Institute show that the reported incidence of acute lymphoblastic leukemia (ALL) 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 in girls (Robison et al. 1995). From 1973 to 1994, the incidence of brain cancer increased by 39.6%, with nearly equal increases in boys and girls (Schechter 1999).

Neurodevelopmental disorders. Neurodevelopmental disorders, including learning disabilities, dyslexia, mental retardation, attention deficit disorder, and autism, are widespread and affect 5–10% of the four million babies born in the United States each year. Some clinical investigators have reported that prevalence is increasing, but existing data are not of sufficient quality to either sustain or refute that position (American Academy of Pediatrics 2001). Causes are mostly unknown, but *in utero* and early-life exposures to lead (Bellinger et al. 1987; Needleman et al. 1990), mercury (NAS 2000), polychlorinated biphenyls (PCBs) (Jacobson and Jacobson 1996), certain pesticides (Campbell et al. 1997; Eskenazi et al. 1999; Whitney et al. 1995; Wiles and Campbell 1993), and other environmental neurotoxicants are known or thought to contribute to the burden of disorders (NAS 1992). A recent report from the NRC concluded that 3% of developmental disabilities are the direct consequence of neurotoxic environmental exposures, and that another 25% arise out of the interplay of environmental

factors and individual genetic susceptibility (environment was defined broadly in this report and included diet, alcohol, tobacco and other lifestyle factors, as well as toxic chemicals) (NRC 2000).

Endocrine disruption. Endocrine disruptors are chemicals that have the capacity to interfere with the body's hormonal signaling system (Harrison 2001; Longnecker et al. 1997). Effects of these chemicals, which have been hypothesized to include cancer (Kogevinas et al. 1997), decreased fertility (Peterson et al. 1993), birth defects of the reproductive organs (Longnecker et al. 2002; Paulozzi et al. 1997), altered sex ratios (Mocarelli et al. 2000), neurodevelopmental impairment (Jacobson and Jacobson 1996), thyroid dysfunction, and diabetes (Longnecker and Daniels 2001), have been observed *in vitro* in cell systems (Birnbaum 1994) and *in vivo* in experimental animals exposed to specific chemicals in the laboratory (Gray et al. 2000) as well as in wildlife populations in several broadly contaminated ecosystems such as the Great Lakes (Colborn et al. 1996) and in Lake Apopka in Florida (Guillette et al. 1994).

On the basis of animal studies, the embryo, fetus, and neonate, and the child in the prepubertal period appear to be at particularly high risk of adverse consequences after exposure to EDs (Selevan et al. 2000). Early exposures to these compounds have the potential to alter anatomic structures and may influence the subsequent course of endocrine functioning (Longnecker et al. 2002; Peterson et al. 1993), neurological development (Jacobson and Jacobson 1996), and sexual development over the life span (Birnbaum 1994; Blanck et al. 2000a, 2000b; Colborn et al. 1996; Euling and Kimmel 2001; Gray et al. 2000; Guillette et al. 1994; Longnecker and Daniels 2001; Selevan et al. 2000; Wu et al. 2003).

Evidence for the effects of EDs on human health is less abundant than evidence for effects *in vitro* and in wildlife, but data on human developmental effects of EDs are accumulating. These effects involve the reproductive organs as well as the brain. The first report of an effect of an ED on human development was the seminal observation by Herbst (Herbst and Bern 1981) of eight cases of clear cell adenocarcinoma (CCA) of the vagina in young women who had been exposed *in utero* to DES. Ultimately, more than 300 cases of CCA were documented in women exposed *in utero* to DES (NAS 1999) Other examples of the human developmental toxicity of the organochlorine EDs are reduced intelligence and sperm abnormalities in Taiwanese boys after prenatal exposure to PCBs and furans (Guo et al. 2000); reductions in intelligence in U.S. and German children after prenatal exposure to PCBs (Jacobson and Jacobson 1996; Winneke 1995); alterations in gender-related play behavior in Dutch children exposed prenatally to PCBs (Weisglas-Kuperus et al. 2000); altered sex ratio at birth in infants in Italy and Russia after prenatal exposure to dioxins (Mocarelli et al. 2000); and accelerated onset of puberty in Michigan girls exposed prenatally to polybrominated biphenyls (Blanck et al. 2000b).

Through the FQPA, Congress has mandated more extensive screening of chemical compounds to assess their potential for endocrine disruption (FQPA 1996).

Critical Issues for Improved Assessment of Environmental Health Risks to Children

Protection of children's health against the adverse effects of exposures to toxic environmental agents will require an approach to risk assessment that moves beyond consideration of average levels of exposure and risk and beyond consideration of only the 60–70 kg average adult (U.S. EPA 1999, 2002b). This new approach must account for children's exposures to multiple chemicals and must be based on better developmental toxicity data than currently exist for most chemicals. To account for the unique exposures and special vulnerabilities of infants and children (NAS 1993), this new child-protective approach to risk assessment will need to include the elements described below.

Improved exposure assessment. Additional data are needed on children's patterns and levels of exposures to chemicals in the environment. Because exposures vary by age, this information will need to be collected for different age groups, from the nursing infant through the adolescent.

Accurate and frequently updated information is needed on children's diets at different ages and on the concentrations of xenobiotics in those diets. Surveys should regularly be conducted also of levels of chemical contaminants in breast milk. Better data are needed on the extent of exposure that results from children's unique mouthing behaviors.

All sources of exposure need to be considered in evaluating the potential risks of environmental chemicals to infants and children (NAS 1993). Models need to be developed that can account for children's simultaneous exposures to multiple chemicals of differing potency via multiple routes of exposure. These models need to be able to assess the cumulative effects of chemicals that may have either synergistic or antagonistic actions. The U.S. EPA's recent work in assessing exposures to multiple organophosphate pesticides is a useful first step in this direction.

Exposure estimates need to be constructed differently, depending on whether acute or chronic effects are of concern. The incorporation of biomarkers into data collection may be useful.

Most important, it is essential to examine the full distribution of children's exposures to chemicals in the environment. Point estimates of average exposure are no longer sufficient. The actual distribution of the range of children's exposures across the population needs to be determined through field studies. Appropriate mathematical models must be constructed, such as Monte Carlo models, that can permit the combining of various data sets and thus permit examination of full exposure distributions (NAS 1992). Of special concern are children whose exposures fall into the top 10, 5, or 1% of the population.

Enhanced toxicity testing. New, more sensitive approaches to chemical toxicity testing are needed that can reliably detect the unanticipated developmental consequences of exposures during critical windows of prenatal and postnatal vulnerability (Selevan et al. 2000). These new models of developmental toxicity testing need to generate data on organ systems that have not been adequately addressed in the past, for example, the nervous, immune, respiratory reproductive, cardiovascular, and endocrine systems.

A shortcoming with much current toxicity testing is that test chemicals are administered to experimental animals in adolescence, and the animals are subsequently sacrificed at a point in life that corresponds roughly to a human age of 60–65 years (Mehlman et al. 2002). Thus, both the unique impacts of early exposures and any late effects of early exposures are not captured (U.S. EPA 2002b), including cancer, heart disease, neurological disorders, or diabetes. To improve current toxicity testing, for certain classes of chemicals investigators may need to undertake studies in which chemicals are administered to experimental animals either *in utero* or shortly after birth and the subjects then followed over their entire natural life span. For other classes of compounds, it may be necessary to expose animals throughout the life span. The approach should attempt to replicate the human experience and may enhance detection of delayed effects (NAS 1992).

Too much reliance on anatomical observation of readily observed anomalies as well as insufficient testing of the functioning of organ systems have been features of much traditional toxicity testing. To improve the situation, enhanced functional tests of neurobehavioral, immune, endocrine, and reproductive toxicity will be of great importance (U.S. EPA 1986, 1991, 2002b). These functional assessments need to be applied on a more routine basis, especially when data from other studies, for example, adult target organ toxicity, or multigeneration studies, raise concerns about possible developmental effects.

New toxicodynamic and toxicokinetic models. The physiological and biochemical characteristics of children that influence metabolism and disposition of chemicals at different stages of development need to be considered in risk assessment. Physiological parameters, such as tissue growth rates, and biochemical parameters, such as enzyme induction, may differentially affect the responses of infants and children to environmental chemicals at different developmental stages (Cresteil 1998; Ginsberg et al. 2002). Physiologically based pharmacokinetic models can be used to estimate the dose of toxic metabolites reaching target tissues at different developmental stages (O'Flaherty 1997; Welsch 1995).

A mechanistically based approach to hazard assessment. The pathogenic mechanisms of environmentally induced disease in children need to be elucidated at functional, organ, cellular, and molecular levels (Birnbaum 1994; Campbell et al. 1997; Whitney et al. 1995). These assessments could be undertaken in conjunction with toxicity testing of chemicals and also in the context of epidemiologic studies. Clinical and epidemiologic studies are of proven value for studying etiologic associations between environmental exposures and pediatric disease (Bellinger et al. 1987; Jacobson and Jacobson 1996; Needleman et al. 1990). A strong argument can be made for the need to establish a major multiyear prospective epidemiological study of children's health, the National Children's Study, as a means of identifying and characterizing the consequences of multiple, early, low-level exposures, as called for in the Children's Health Act 2000 (Berkowitz et al. 2001; The National Children's Study Interagency Coordinating Committee 2003). The advantages of such a study would be its great statistical power, coupled with the ability to examine prospectively the impact of a variety of environmental factors, their interactions, and interaction with genetic factors on children's health and development.

Application of uncertainty and safety factors that specifically consider children's risks. Children must be presumed to be more vulnerable to environmental toxic agents than adults in the absence of data to the contrary, as was specifically recommended by the NRC Committee on Pesticides in the Diets of Infants and Children (NAS 1993). That committee called for the incorporation of an additional child-protective uncertainty factor into risk assessment to account for this greater vulnerability, particularly in the absence of data, and the FQPA mandated the application of an additional margin of safety for children's risk in the case of pesticides (FQPA 1996). Traditional approaches to risk assessment are now being modified to more carefully and explicitly account for risks to children (U.S. EPA 2002a). However, a number of data gaps in exposure assessment and in developmental toxicity must be addressed through the development and implementation of additional testing guideline protocols (U.S. EPA 1999, 2002b), the acquisition of better information on children's exposure patterns and sources, and the undertaking of basic research both on mechanisms of underlying development and on chemical interactions of environmental agents with developing organ systems (NRC 2000).

Conclusion

The protection of children against toxic chemicals in the environment is a major challenge to modern society (Schaefer 1994). Children are not merely a special vulnerable group within our population but rather the current inhabitants of a developmental stage through which all future generations must pass. Protection of the health of fetuses, infants, and children is essential for sustainability of the human species.

The current challenge to risk assessment stems from two facts: *a*) hundreds of new chemicals are developed every year, released in varying quantities into the environment, and absorbed into the bodies of many American children (CDC 2003); and *b*) the majority of these chemicals are not adequately evaluated prior to commercial introduction for their potential toxicity, their potential effects on development, or their possible interactive effects with other chemicals (Goldman 2000; Landrigan and Goldman 2003; NAS 1984). The need, in this context, is to design approaches to risk assessment that account for the unique exposures and sensitivities of children and that also will stimulate enhanced research in developmental toxicity. The ultimate goal is to formulate policies that will protect children against potential toxic agents and allow them to grow, develop, and reach maturity without incurring neurobehavioral impairment, immune dysfunction, reproductive damage, or increased risks of cancer as a consequence of environmental exposures in early life.

The protection of children against toxic chemicals in the environment will require fundamental and far-reaching revisions of current approaches to surveillance, toxicity testing, and risk assessment. No guidance document on risk assessment that fails to consider the unique exposures and special susceptibilities of fetuses, infants and children can today be considered adequate to protect human health.

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