CHILDHOOD CANCER AND THE ENVIRONMENT

Testimony before the President’s Cancer Panel

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East Brunswick, New Jersey
September 16, 2008
Distinguished Chairman and Member of the President’s Cancer Panel,

I am pleased to testify before you on the role of chemical and physical environmental factors in cancer incidence and mortality. Thank you for having convened this special hearing.

We have a unique opportunity today to review the scientific evidence for environmental and occupational causation of cancer. We have opportunity through this review to begin to build the foundation for a new national cancer policy – a policy that will open a second front in the War on Cancer – a policy that will direct appropriate focus and allocate sufficient resources to understanding and preventing the environmental and occupational causes of cancer. Such a prevention-oriented policy, if properly designed and executed, has potential to save the lives of millions of Americans.

Environmental and occupational exposures have been recognized to be potent causes of human cancer for more than two hundred years. Asbestos, benzene, the benzidine-based dyes, beryllium, 1,3-butadiene, chromium, ethylene oxide, ionizing radiation, nickel, nitrosamines, polycyclic aromatic hydrocarbons (PAHs), plutonium, radium, 2,3,7,8-tetrachlorodibenzo-dioxin and wood dust are among the environmental and occupational carcinogens that have been identified through astute clinical observation and confirmed through toxicological and epidemiological research.

Cancer caused by environmental and occupational exposures is in virtually all cases a consequence of human activity. It is therefore preventable. Some of the greatest victories in the War on Cancer have resulted from actions taken to control exposures to carcinogens in the environment and in the workplace. These include reductions in the use of asbestos, virtual elimination of the benzidine-based dyes, imposition of controls on exposures to chromium, nickel and wood dust in the workplace, and reductions in occupational, environmental and medical exposures to ionizing radiation.

Our challenge today is to develop visionary policy that will enable our nation to discover the still undiscovered environmental and occupational causes of cancer and then to move boldly against them. We must replicate the successes of the past if we are to prevent cancer and save lives in the future.

Environmental Exposures and Childhood Cancer. I will focus my testimony today on childhood cancer, specifically on:
1. Data on the rising incidence of child cancer
2. Evidence for the environmental origins of childhood cancer.

Increasing Incidence of Cancer in Children and Young Adults. In the past half century, mortality from childhood cancer has declined dramatically. This decline is the consequence of spectacular advances in medical and surgical treatment that, in turn, are based on great increases in understanding of cancer biology and therapeutics.

But in this same time span the incidence of childhood cancer has increased significantly and has offset the declines in mortality. Cancer is now the second leading cause of
death among children under age 15 in the United States. Mortality from childhood cancer is exceeded only by deaths from injury and violence.

Increases in incidence have occurred for three major malignancies of children and young adults, according to SEER data from the National Cancer Institute:

1. **Leukemia.** Leukemia is the most common childhood cancer. Incidence of leukemia in 0-14 year-old US children increased from 3.3 per 100,000 in 1975 to 5.1 per 100,000 in 2005, **55% increase.** Acute lymphocytic leukemia increased in the same years from 2.2 to 4.0 per 100,000, **81% increase.**

2. **Primary Brain Cancer.** This is the second leading cancer of children. Incidence of cancer of the brain and nervous system in 0-14 year-old children increased from 2.3 per 1000,000 in 1975 to 3.2 per 100,000 in 2005, **39% increase.**

3. **Testicular Cancer.** Incidence of testicular cancer in white men (most of them adolescents and young adult males) increased from 4.3 per 100,000 to 7.0 per 100,000 in 2005, **51% increase.** Among black men in the same years, both the absolute incidence and the rate of increase were much lower – from 0.9 to 1.3 per 100,000.

The cause of these reported increases in incidence is not known. They are certainly too rapid to be of genetic origin. Some have argued that they reflect improved access to medical care or the increasingly widespread availability of newer diagnostic technologies such as MRI and CAT scan. But while those explanations might explain a one-time “bump” in reported incidence around the time that Medicaid was introduced or newer imaging techniques became available, they fail to account for the consistent increase in incidence of three different types of childhood and young adult cancer observed in the United States over a span of three decades.

An unresolved question is whether these increases in incidence of childhood cancer could be due, at least in part, to exposures to carcinogens in the environment.

**Children’s Unique Vulnerability to Toxic Chemicals in the Environment.** Children are exposed to toxic and carcinogenic chemicals through many routes - the air they breathe, the water they drink, the foods they eat, the medications they consume, and the environments they inhabit, including their homes, day care centers, schools, and motor vehicles. Children have unique routes of exposure with no parallel among adults, for example, exposure in utero through transplacental transfer, and exposure postnataally via breast milk.

An analysis undertaken by the National Academy of Sciences (*Pesticides in the Diets of Infants and Children*, 1993) established that children are uniquely vulnerable to toxic exposures in the environment. The NAS found this vulnerability to have four sources:

- Children have disproportionately heavy exposures to many chemicals.
- Children’s metabolic pathways, especially in fetal life and in the first months after birth, are immature. Infants and children are therefore slow to detoxify and excrete many environmental chemicals and thus more vulnerable to them.
- Human development is complex, delicate and therefore all too easily disrupted by environmental exposures.
- Children have many years of future life and thus time to develop disease of long latency initiated by early exposures.
This understanding that children are uniquely vulnerable to toxic exposures had its origins in studies of major disease outbreaks. Notable among these were:

- **The Thalidomide Tragedy.** In the early 1960s, there occurred a sudden increase in incidence of limb reduction deformities, phocomelia in particular, that was first recognized among babies born in Europe. This epidemic was shown to have been caused by maternal use of the sedative thalidomide to control “morning sickness” during the first trimester of pregnancy. Thalidomide was kept out of the United States by action of the FDA, but worldwide more than 15,000 babies were affected. The babies’ mothers were physically untouched.

- **Minamata Disease.** A report from Japan, also in the 1960s, described an epidemic of cerebral palsy, profound mental retardation, microcephaly and convulsions among children living in a remote fishing village on Minamata Bay in southern Japan. The epidemic was traced to ingestion by pregnant women of fish and shellfish that had been contaminated by methylmercury. The source was a plastics factory that had discharged mercury into Minamata Bay. Mothers who ate contaminated seafood were spared, but the effects among children exposed in utero were devastating.

These tragic episodes destroyed forever the myth of the “invulnerable placenta”. They opened the possibility that exposures to toxic chemicals in utero and in the first years after birth might be responsible for a range of chronic diseases in children – cancer among them.

**Emerging Evidence for Environmental Causation of Childhood Cancer.** Clinical, epidemiological and toxicological studies spanning the past 60 years support the hypothesis that early exposures to environmental carcinogens can cause childhood cancer and that infants and children are uniquely vulnerable to certain environmental carcinogens. This evidence includes the following:

- **Radiation Leukemia.** An epidemic of leukemia was noted in the 1940s and early 1950s among young children who had been exposed in utero and in the first years after birth to ionizing radiation in the atomic bombings of Hiroshima and Nagasaki. Careful reconstructions of radiation dose in Hiroshima and Nagasaki and subsequent studies by Alice Stewart of fetuses exposed to X-rays in utero established that infants are significantly more sensitive to radiation–induced leukemia than adults.

- **Adenocarcinoma of the Vagina and DES.** The report of a series of cases of adenocarcinoma of the vagina in young women who had been exposed in utero to the synthetic estrogen, diethylstilbestrol (DES), established the plausibility of transplacental carcinogenesis. These young women’s mothers had been administered DES during pregnancy in an effort to prevent miscarriage. The mothers were unaffected, and the baby girls appeared normal at birth, but they went on to develop adenocarcinoma at the time of puberty or in early adult life. Many of these young women also had a variety of other reproductive problems, including Mullerian duct anomalies, an observation that suggests a possible linkage between chemical carcinogenesis in utero and teratogenesis.

- **Prenatal Occupational Exposures and Childhood Cancer.** Parental occupation before or during pregnancy in occupations that involve workplace exposure to volatile organic solvents, such as the painting and printing trades, has been associated in several retrospective studies with increased incidence of childhood leukemia.

- **Pesticides and Childhood Cancer.** Each year in the United States more than 1 billion pounds of synthetic pesticides - insecticides, herbicides, rodenticides and fungicides - are applied in agriculture, homes, schools, parks, playgrounds and daycare
centers. The National Toxicology Program has found in animal bioassays that a number of widely used pesticides are carcinogenic. Case-control epidemiologic studies, most of them relatively small in size, have found consistent, modest associations between pesticide exposures in utero and in early childhood and acute lymphocytic leukemia, childhood brain cancer and childhood non-Hodgkin’s lymphoma. These associations have tended to be strongest when exposures where characterized in greatest detail. There is some evidence for greater sensitivity of children as compared to adults. Rates of childhood leukemia are consistently elevated among children who grow up on farms, among children whose parents used pesticides in the home or garden, and among children of pesticide applicators.

- **Chemoprevention of Childhood Cancer.** Two environmental factors have been shown to reduce risk of childhood cancer. Breast feeding markedly reduces risk of childhood leukemia. Maternal consumption during pregnancy of a diet rich in vitamins C, E and folic acid reduces risk of childhood brain cancer. These hopeful findings provide further evidence of the sensitivity of the fetus and young infant to environmental factors that influence carcinogenesis.

### A National Strategy for Discovery of New Knowledge about the Environmental Origins of Childhood Cancer

The time has come when we must confront the rising incidence of childhood cancer. The time has past when we could dismiss rising trends in childhood cancer as diagnostic artifacts. We must carefully and deliberately consider the possibility that chemical and physical exposures in the environment are contributing to the rising incidence of childhood cancer in the United States.

We must therefore put in place a national program of prevention-oriented cancer research, and we must develop a new national cancer policy that focuses on prevention – a Second Front on the War on Cancer. Three key elements are these:

**Enhanced toxicity testing of commercial chemicals.** The goal of toxicity testing is to discover the still undiscovered chemical causes of cancer and other diseases. Fewer than 50% of the synthetic chemicals most widely used in American commerce have been tested for toxicity. Fewer than 20% have been examined for potential developmental toxicity. Several hundred new chemicals come to market each year, too often with little or no premarket toxicity testing. Pregnant women and young children in the United States are exposed daily to hundreds of chemicals of unknown toxic and carcinogenic potential. The risks of these exposures are largely unknown.

To rectify this situation, America needs legally mandated and strictly enforced testing of all commercial chemicals – old and new – for toxicity and carcinogenicity. America also needs a new, more sensitive strategy for chemical toxicity testing. A major shortcoming in most current testing is that chemicals are administered to experimental animals in adolescence, and the animals sacrificed at a point in life that corresponds to a human age of 60-65 years. This approach fails to capture the unique impacts of early exposures – cancer among them, and it misses the late effects of early exposures. To improve this situation, lifetime toxicity studies are needed. In lifetime studies, chemicals are administered to animals in utero or shortly after birth, and the animals followed over their entire natural life span. Such studies are currently undertaken in the laboratories of the Ramazzini Foundation. These studies have documented that exposures to vinyl acetate monomer, to ethyl alcohol and to aspartame that began during pregnancy are...
significantly more potent causes of cancer than similar exposures in adult life. The implications for understanding and prevention of childhood cancer are strong.

**Epidemiological Investigations - The National Children’s Study.** Most previous studies of the environmental origins of childhood cancer have been small case-control studies of limited statistical power and severely constrained ability to assess environmental exposures. To overcome those limitations and to discover the preventable causes of cancer in children, we need large, prospective epidemiologic studies.

The US National Children’s Study (NCS) is such a study. It was authorized through the Children’s Health Act of 2000 and will be directed by the National Institute of Child Health and Human Development (NICHD). It is a prospective study of 100,000 children who constitute a population-representative sample of all babies born in the United States. The children will be followed from conception to age 21 years. Environmental exposures will be assessed through multiple evaluations of the external environment as well as through measurements of biomarkers at multiple points in pregnancy and childhood. Information on individual susceptibility will be obtained though genetic evaluation of each child. To further increase the power of the NCS to detect the environmental causes of childhood cancer, NICHD plans to partner with the World Health Organization to pool data internationally. The NCS has been termed the “Children’s Framingham Study”. It will launch in January, 2009.

**Protection of Children in Risk Assessment and Regulation through Application of Uncertainty Factors.** If they are to prevent the environmental exposures that cause childhood cancer, risk assessment and regulation must incorporate approaches that account for and protect the unique exposures and heightened sensitivities of children.

Children must be presumed more vulnerable than adults to toxic chemicals. The NAS Committee on Pesticides in the Diets of Infants and Children specifically recommended this approach. When data on the susceptibility of children to a particular chemical are lacking, the NAS called for incorporation of child-protective uncertainty factors into risk assessment. This is a deliberately precautionary approach that gives the benefit of doubt to protection of the fetus, infant and child against chemical carcinogens.

I strongly recommend, when data on developmental toxicity and potential developmental carcinogenicity are absent, that child-protective safety factors be incorporated into all carcinogenic risk assessment and regulation.

**Conclusion – Need for a New Paradigm.** The rising incidence of childhood cancer poses a major challenge to our society. It demands reconsideration of our strategies and priorities for cancer research and prevention. It demands reassessment of the current paradigm of chemical carcinogenesis. Until now, we have considered dose-response to be the prime determinant of cancer risk. Dose-response is indeed a powerful unifying concept, but now we need to expand our paradigm to consider also the developmental stage in which an exposure occurs. We must expand our thinking on environmental carcinogenesis to encompass the concept of windows of developmental vulnerability. We must act as wise guardians of our children.

Thank you.