The U.S. EPA Conference on Preventable Causes of Cancer in Children: A Research Agenda

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On 15–16 September 1997, the U.S. Environmental Protection Agency sponsored the Conference on Preventable Causes of Cancer in Children. The conference was convened to examine rising trends in reported incidence of childhood cancer and the association of these trends with environmental exposures. This paper summarizes recommendations for future research offered by participants. These recommendations included more collaborative research integrating epidemiology, molecular biology, toxicology, and risk assessment; the development of better protocols for toxicologic testing including carcinogenicity using young animals; and research focused on specific periods of development during which susceptibility to environmental agents may be enhanced. Also recommended was enhanced use and development of molecular biomarkers for identification of susceptible populations, and documentation of exposures and effects in epidemiologic and toxicologic studies. Although toxicologic testing is considered essential to determine the effects of potential carcinogens on biological organisms, participants emphasized the need to link these findings with epidemiologic and exposure assessment research. — *Environ Health Perspect* 106(Suppl 3):867–873 (1998). *http://ehpnet1.niehs.nih.gov/docs/1998/Suppl-3/867-873carroquino/abstract.html*

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Introduction

Each year in the United States, about 8000 new cases of cancer are reported among children under 15 years of age. Although childhood cancer is a rare disease and medical advances have resulted in dramatic reductions in the death rate from childhood cancer, the occurrence of new cancer cases among children has continued to rise during the last two decades. Reported incidence rates for all cancer sites combined in children have risen by about 10% in the 1974 to 1991 compiling period (*1*), representing an average rate increase of about 1% (95% confidence interval, 0.6–1.3) per year (*2*). The reported incidence of gliomas and acute lymphocyte leukemia, the two most common forms of cancer, rose by about 40 (*3*) and 5% (*4*), respectively, for children in the under-15 age group. For a number of cancers (astroglial tumors, retinoblastomas, neuroblastomas, rhabdomyosarcomas, and acute lymphocytic leukemia), the reported increases in incidence appeared strongest for young children, especially those in the first through third years of life (*2*). For other types of cancer, for which the number of cases is small, such as Wilms tumors and non-Hodgkin lymphoma, the trends in incidence are difficult to quantify. Wilms tumor increased by about 46% (*3*) for the same age group, and bone and joint cancers were up by about 16% in the 0 to 19 age group (*3*). The causes of these reported increases in childhood cancer incidence have not been identified.

Most cancer results from the interaction between genetic factors and the environment (*5,6*). In this context, environment is defined broadly and includes diet, alcohol, drugs, tobacco, and all other nongenetic factors as well as classic environmental toxins. It has been estimated that about 80 to 90% of all cancers are attributable to environmental factors acting in conjunction with both genetic and acquired susceptibility (*7*); in infants and children the fraction of cancers due to environmental factors is probably somewhat lower than in adults. Most research efforts in recent years have been dedicated to the study of mechanisms of action of chemical carcinogens (*8*). A major challenge of environmental cancer prevention is to document environment susceptibility interactions and then to translate this knowledge into public health interventions (*7*).

In September 1997 as a consequence of the Clinton administration's commitment to reduce environmental health and safety risks to children, the U.S. Environmental Protection Agency (U.S. EPA) convened the Conference on Preventable Causes of Childhood Cancer. Leading cancer and environmental research experts along with members of the public discussed what is

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Abbreviations used: AFB_1, aflatoxin B_1; CYP1A1, cytochrome P4501A1; PAH, polycyclic aromatic hydrocarbon; PAH-DNA adduct, polycyclic aromatic hydrocarbon–DNA adduct; U.S. EPA, U.S. Environmental Protection Agency.

known about preventable causes of cancer and worked together to formulate a blueprint for childhood cancer research for the next decade.

Participants worked in groups that made recommendations for research in four areas: *a*) susceptibility factors, *b*) epidemiologic and risk factors, *c*) biologic markers of exposure and effects, and *d*) quantitative measurements of exposure.

This report summarizes the recommendations of the conference and presents the arguments supporting these recommendations.

Establish a National Childhood Cancer Registry

The strongest and virtually unanimous recommendation from conference participants was that a national childhood cancer registry be established.

A national children's cancer registry would serve as the nation's largest available data resource for quantification and evaluation of child-specific risks of cancer. The registry would *a*) collect and maintain detailed exposure information on all children in the United States who are diagnosed with cancer; *b*) support broader epidemiologic investigations of children's cancer than are currently possible; and *c*) communicate findings and timely updates to families, communities, investigators, and agencies. Registry data could be combined with other data and incorporated into maps to show geographic distribution of cases and generate hypotheses. Data from the National Health and Nutrition Examination Survey (NHANES) and from the U.S. Department of Agriculture might be employed as a source of population-based referent exposure markers. In addition, combined use of the Agency for Toxic Substances and Disease Registry's hazardous waste site location data and childhood cancer occurrence data could point to valuable research hypotheses.

Efficiency of case identification by the registry would be improved by collaboration with existing state tumor registries, Native–American health committees, clinical oncology treatment study groups (Children's Cancer Group, Pediatric Oncology Group), and collaboration with affected communities and families.

An active communications program would be required to provide families of participating children with timely reports of peer-reviewed research findings and any other information of clinical or personal significance.

Evaluate Children's Special Susceptibilities to Cancer

To identify and characterize the preventable causes of childhood cancer, research programs are required that evaluate the role of physiological, biochemical, and developmental factors in children's susceptibility to cancer. Children may be at disproportionate risk of developing cancer because of their increased absorption and retention of environmental agents, reduced detoxification and repair during the early stages of development, their higher rate of cell proliferation, and the fact that cancers initiated in the womb and in the early years have the opportunity to develop over many decades (*7*). In addition, children may be at greater risk by virtue of their nutritional and health status. The following recommendations were made:

a) Develop animal models to assess toxicologic differences between children and adults and to evaluate toxicity to developing organ systems.

New toxicologic protocols and models using young animals to predict childhood risk of cancer are needed. The use of young animals to predict effects on children requires additional validation. For example, rodents are less mature at birth than humans. Thus, more pronounced age-related differences would be anticipated in rodents than in humans during the neonatal period. Rodents and most other commonly used test animals mature very rapidly during this time, so that differences of even a few days in age can profoundly affect susceptibility to the toxicity of xenobiotic compounds (*9*). Thus, studies need to be conducted to determine the parallels and differences in development between test animals and humans.

b) Conduct research to study developmental changes in metabolism, immune function, and proliferative activity, and how these changes may affect susceptibility to cancer.

Chemical carcinogenesis is a multistep process involving genetic and epigenetic changes in susceptible cells that gain a selective growth advantage and undergo clonal expansion as the result of activation of protooncogenes and/or inactivation of tumor-suppressor genes (*10*). The occurrence of these events is modulated by several factors that themselves change in the course of development. Thus, DNA damage may be repaired by the action of DNA repair enzymes, whose presence and activity may change with age. Similarly, changes in metabolism will determine whether carcinogenic metabolites are formed, thus allowing for the initiation of the cancer process. The higher rate of cell proliferation of certain tissue during development may also contribute to the development of cancer.

c) Study changes in carcinogen-metabolizing capacity during development, from gestation through adulthood, to evaluate the role of metabolism in prenatal and postnatal susceptibility to carcinogens.

The susceptibility of children to cancer can be influenced by the presence and activity of metabolizing enzymes. The absence of or lower activity of enzymes that are required to metabolize carcinogens to their active form can reduce a child's risk of cancer following exposure. By contrast, decreased enzymes that detoxify carcinogens can increase cancer risk. Many enzyme systems change greatly in activity during early development, and a number of metabolic pathways responsible for bioactivation or detoxification are not present in the fetus or are less developed in the infant. For example, glucouronic acid conjugation is significantly depressed at birth, although a well-developed capability for sulfate conjugation exists (*11*). Studies are needed to determine which specific enzymes lead to changes in susceptibility in children to carcinogens and which of these enzymes are good predictors of children's susceptibility to cancer. The presence and activity of carcinogen-metabolizing enzymes during development from conception through adulthood should be studied.

d) Study the variability in carcinogen-metabolizing enzymes in childhood populations and the role of genetic polymorphisms in children's susceptibility to cancer.

There is great interindividual variability in the amounts and types of metabolizing enzymes, some of which are under direct genetic control (*12–14*). For example, CYP1A1, whose product metabolizes polycyclic aromatic hydrocarbons (PAH) such as benzo[*a*]pyrene is a polymorphic enzyme. About 10% of the Caucasian population has a highly inducible form of the enzyme that is associated with increased lung cancer in smokers (*7*). PAH–DNA adducts are also elevated in umbilical cord blood and placenta of newborns, with the CYP1A1 MSP1 polymorphisms, which suggests that the genetic polymorphism may increase risk from transplacental PAH exposure (*15*). Greater understanding of interindividual variations is key to understanding childhood susceptibility to cancer.

e) Study the role of gestational and preconception exposures that may result in

increased exposure and/or susceptibility of the fetus to carcinogens.

More information is needed on the ability of certain carcinogenic compounds and/or their metabolites to cross the placenta. In addition, little information is available on the metabolic changes that occur during pregnancy and how they can affect the accumulation of carcinogens in the mother or the production of carcinogenic metabolites that could be transferred to the fetus. The metabolic capacity of the placenta also needs to be evaluated, as it can result in exposure of the fetus to toxic metabolites. Metabolizing enzymes can be induced by exposure to structurally related chemicals (*16*), dietary factors (*12–14*), and disease states (*17,18*). Furthermore, maternal exposure to environmental carcinogens can result in enzyme induction to the fetus (*12–14*).

f) Evaluate the contribution of cell proliferation to different types of childhood cancer, paying special attention to specific periods of organ and tissue development during which accelerated cell proliferation may increase susceptibility to cancer.

Cell proliferation can contribute to an increased likelihood of carcinogenesis. For example, PAHs and aflatoxin B_1 (AFB_1) produce liver tumors when administered to newborn rodents but not when administered to older animals, presumably because the liver proliferates rapidly in the developing system but more slowly in older animals (*19*). Women who were in their teens at the time of the atomic bombings had the greatest risk of radiation-induced breast cancer (*20*). Because cells proliferate faster in children's bodies than in adults, cell proliferation may be a significant risk factor in childhood cancer. Some organs, such as the brain, are fully developed in early childhood, whereas others such as the skeletal system do not achieve maturity until adolescence (*19*). This may be the reason why osteosarcoma, the most common bone cancer, peaks in late adolescence, a period of rapid bone growth (*21*). More information is needed on the growth and maturation of different organs during development, so that the role of cell proliferation in childhood cancer can be evaluated.

g) Study the differences in DNA repair mechanisms between children and adults.

DNA repair mechanisms play an important role in cancer protection. For example, the *p53* encodes a protein that modulates DNA repair and cell division and mutations of the *p53* genes are involved in at least 50% of all cancers (*22*). *p53* mutations have been linked with tobacco smoking (*23–25*), and it is possible that *p53* mutations occur in the offspring of smoking mothers. More information is needed about the differences in DNA repair mechanisms between children and adults and the susceptibilities of genes such as *p53* in children to deleterious mutations.

h) Study the effects of carcinogens on the developing immune system, from conception to puberty. Evaluate the protective role of the mother's immune system in modulating prenatal and infant response to carcinogens.

Better information is needed on the effectiveness of the fetal and childhood immune system in modulating cancer response. The extent of maternal monitoring of fetal, transformed cells is unknown. It is also not known whether immune monitoring systems that detect transformed cells, such as T cells, function in children as effectively as in adults. Because infants depend on maternal antibodies that they receive through the placenta and later from breast milk for their immunity, greater understanding is needed on the protective role of the mother's immune system in modulating prenatal and infant response to carcinogens. Chemicals that affect the immune system, such as halogenated aromatic hydrocarbons that bind to the Ah receptor (*26*), may modify the host defense mechanism against infection and cancer (*27*). Some participants indicated that a lack of previous immunologic challenge to the child might affect the immune system's ability to detect cancerous cells. Study of the potential use of immune stimulators such as BCG4 in stimulating an immune defense mechanism against cancer was recommended.

i) Continue research efforts on the dietary factors that affect susceptibility to cancer. Assess whether the diets of infants and children provide adequate amounts of nutrients that are known to be cancer protective, including the evaluation of the diet of children in poverty. Conduct epidemiologic studies to determine the association between obesity in children and cancer.

Dietary factors such as animal fat intake and the levels of certain vitamins and micronutrients have been shown to influence susceptibility to cancer (*19*). Epidemiologic studies have identified multiple known or potential protective agents in the diet such as vitamins A, C, and E, various carotenoids, and selenium (*28,29*). Although substantial research has been dedicated to evaluate the role of diet in cancer prevention, little information is available on the role of children's diets in preventing cancer. Children's nutritional requirements are different from those of adults, and the effects of diet in childhood cancer prevention may be different from what would be expected by extrapolating from adult data. The protective role of antioxidant and micronutrient exposure needs to be investigated in children. Also, because some population subgroups such as people in poverty (*30*) and Hispanics (*31*) are more likely to suffer form certain nutrient deficiencies, children of these subgroups may be at greater risk of developing cancer. Cultural differences in diet may also contribute to differences in cancer risk among cultural groups. The use of data from the National Health and Nutrition Evaluation Survey is recommended to conduct such studies.

j) Evaluate the role of maternal nutrition and nutrient supplementation with individual micronutrients during pregnancy and lactation in cancer prevention.

Several studies, including a study reported in this issue (*32*) have shown a reduced risk of childhood brain cancer associated with maternal vitamin supplementation during pregnancy (*33,34*). This demonstrates the importance of pursuing this line of research further. More information is needed on the protective role of other micronutrients during pregnancy. The role of micronutrient supplementation during lactation and the first years of life in cancer prevention also needs further evaluation. To evaluate the diet of pregnant women, the use of data from NHANES is recommended.

Improve Epidemiologic Methods and Increase Use of Epidemiologic Data in Risk Assessment

Epidemiologic study of childhood cancer is difficult because of the rarity of the disease and the broad array of environmental, viral, and genetic risk factors potentially involved in pediatric carcinogenesis. Environmental exposures are usually low, and associations between environmental exposures and disease are often weak. Clustering of childhood cancer in communities has been the impetus for many studies, but such studies have rarely, if ever, clearly identified a cause. These cluster analyses have many limitations. They usually involve a small number of cases and a large number of potential environmental factors. Exposures can rarely be quantified and confounding factors are difficult to

control. Although cluster analysis has limitations, the group suggested and space associations may yield associations between environmental factors and disease that were previously undetected.

k) Facilitate cooperation among different countries to conduct large epidemiologic studies.

The infrequent occurrence of childhood cancer and the large numbers of potential factors involved make it difficult to conduct studies with acceptable epidemiologic power. Low exposure levels and the difficulty of finding unexposed control population make it difficult to establish cause-and-effect relationships. To overcome these limitations, conference participants recommended the design of large international collaborative studies. Such studies would increase statistical power and allow for multifactorial analysis. Because the degree of chemical exposure varies widely among countries, international studies would also allow examination of a large range of exposures and disease outcomes.

l) Examine the association between childhood cancer incidence and birth defects.

Many forms of childhood cancer such as early brain cancer can be thought of as terminal cell differentiation, a developmental process that can start prenatally or very early after birth and culminate in the formation of a tumor in early childhood. Thus, cancers that are viewed as a type of terminal differentiation and that appear as a result of risk factors during gestation may be considered birth defects. A relationship may exist between birth defects and early childhood cancer. For example, a negative correlation exists between the intake of folate in pregnancy and the occurrence of neural tube defects and certain malignant brain tumors in children (*35*). The distribution of childhood cancers with respect to birth defects and environmental risk factors should be examined. Chromosomal alterations in the fetus and newborn should be evaluated in relation to childhood cancer and birth defects.

Develop and Validate Biomarkers for Childhood Cancer and Increase Use of Biomarkers in Risk Assessment

Biomarkers have been used in clinical and epidemiologic research to document toxic exposures and to investigate genetic susceptibility to environmental toxins, but little environmental research has been performed using biomarkers to identify affected children. Except with radon, asbestos, and some pesticide exposures, there have been very few attempts to develop new biomarker techniques to identify toxic exposures in children.

It is recommended that significant efforts be dedicated to develop new sensitive biomarkers for childhood exposures and susceptibilities and that these are validated in laboratory and epidemiologic studies. The use of biomarkers in hypothesis-testing studies in conjunction with exposure assessment, personal monitoring, and validated questionnaires is also recommended. The following specific recommendations were made:

a) Study and validate the linkages between exposure biomarkers and biomarkers of effect and between biomarkers of effect and clinical outcome. Develop intermediate markers (surrogate markers) that can assist in linking exposure to disease outcomes.

Research to validate biomarkers includes determining the relationship between the biologic parameter measured and both upstream and downstream events in the exposure–effects continuum (*36–38*). For example, a hemoglobin (Hb) adduct considered for use as an exposure biomarker for a xenobiotic should exhibit a predictable relationship to ambient exposure level (*39*). By validating markers in this fashion, it becomes possible to use biomarkers in risk assessment to predict specific health effects. Because of the physiologic, metabolic, and developmental differences between children and adults, the relationship of exposure and effect biomarkers to other events of the continuum may be different between adults and children and should be evaluated. For example, newborns at delivery were found to have higher levels of PAH–DNA adducts in the blood than the mothers, despite the fact that transplacental exposure to the PAHs is estimated to be an order of magnitude or more lower than maternal exposure (*40*). More importantly, the relationship between early effects and appearance of a disease may be different from adults. The potentially shorter latency period for childhood cancer in comparison to adult cancer suggests that the clinical significance of exposure or early effect biomarkers varies with age.

b) Develop and validate susceptibility biomarkers such as the presence and activity of enzymes involved in carcinogenic bioactivation or detoxification through stages of development, DNA adducts, and biomarkers for nutritional status. Use susceptibility biomarkers to determine the range of susceptibility in the population and identify subpopulations at risk.

Studies of susceptibility biomarkers such as the presence or absence of metabolic enzymes would provide information on the differential susceptibility of children versus adults. Because polymorphisms exist for many of the enzymes involved in carcinogen metabolism, biomarkers for these polymorphisms could potentially be used to identify subgroups of infants with greatest potential risks. Biomarkers for the presence of chemically inducible enzymes may also serve as indicators of multiple exposures. In addition, other types of susceptibility biomarkers such as the levels of certain nutritional elements can be used to identify subsets of infants at risk. Susceptibility biomarkers can potentially provide information on a wide range of susceptibility factors related to age, gender, ethnicity, degree of exposure, and health and nutritional status.

c) Develop biomarkers that would detect maternal preconception exposures, transplacental exposures to the fetus, and early childhood exposures, e.g., biomarkers for passive smoking during these periods.

The reported increase in childhood cancer rates at younger ages suggests that environmental exposure during gestation and preconception may be involved. Experiments with a number of carcinogens (including PAHs, nitrosamines, and AFB_1) show that the risk of cancer is heightened if exposure begins *in utero* or in infancy rather than in adulthood (*9,41*). Therefore, it is necessary to emphasize the study of biomarkers that would detect maternal preconception exposures and transplacental exposures to the fetus. Biomarkers for early childhood exposures are also needed.

d) Increase the use of biomarkers in qualitative and quantitative aspects of risk assessment.

Biomarkers can be used in several aspects of risk assessment. Sensitive biomarkers can be employed to assess early indicators of harm in human populations with suspected environmental exposure (*39*). In hazard identification, the use of sensitive biomarkers can substitute for the need to use end points located at the extreme right of the exposure–disease continuum such as disease or tumor formation. Biomarkers can also provide information on the metabolic and physiologic differences between animals and humans, potentially eliminating the need for uncertainty factors. They can also be used for low-dose extrapolation. By utilizing validated and

sensitive exposure and effect biomarkers that show strong correlation with tumor development, it is possible to characterize dose–response relationships at response rates orders of magnitude lower and over a much greater dose range than is currently possible. Finally, incorporating exposure and effect biomarkers in the characterization of interindividual variability will allow protection of vulnerable individuals (*39*), while avoiding the need to use uncertainty factors to account for this variability. The use of biomarkers in all four steps of risk assessment is recommended.

e) Incorporate the use of biomarkers in clinical settings and develop protocols for collection of specimens.

Despite the importance of exposure assessment epidemiologic studies, exposure data is not developed at clinical centers as part of a primary health evaluation or at cancer childhood centers when new cases appear. Although a few epidemiologic studies have been conducted on children living near toxic dump sites, application of biomarkers to detect environmental toxic exposures in the clinical setting has been primarily used for lead poisoning and passive exposure to environmental tobacco smoke. The use of biomarkers in a clinical setting could facilitate the diagnosis of conditions in children that occur as a result of exposure to specific toxic substances. The identification of a specific biomarker should help to confirm that a child has been exposed to a particular toxin and may provide a tool to monitor either the effects of the toxin or the effects of therapy. For biomarkers to be used in a clinical setting, methods to collect samples will need to be appropriate to the child's age. Methods for intrauterine analysis of toxic exposures are also needed. New, less invasive, and painless methods for collecting biologic materials from children are needed.

Exposure Assessment

The National Research Council report *Pesticides in the Diets of Infants and Children* (*9*) found that infants and children differ from adults in their exposures and susceptibilities, both qualitatively and quantitatively. The report indicated that children's exposure to pesticides are greater than those of adults because they eat more food, drink more water, and breathe more air per unit of body weight than adults do. For instance, the air intake of a resting infant is twice that of an adult under the same conditions. Infants and children drink more than 2.5 times as much water daily as adults do, relative to body weight (*42*). During the first 6 months of life, children drink 7 times as much water per pound, and between the ages 1 through 5 years eat 3 to 4 times more food per pound than the average American adult (*9*). In addition, their activity patterns and location further magnify exposure to pollutants. Hand-to-mouth behavior increases their ingestion of toxins in dust or soil and because they play close to the ground, they are exposed to toxins that form low-lying layers in the air, such as certain pesticide vapors, radon, and particulate matter.

f) Develop a national database for exposure data.

A national IRIS-type (U.S. EPA's Integrated Risk Information System) database for exposure data is needed to compile chemical-specific exposure information. This database would include environmental fate and transport information on the chemical, information on its potential for bioaccumulation, and critical pathways that would result in exposure to children.

g) Define and characterize the child's environment by studying exposure patterns.

To understand children's exposures, it is first necessary to define their environment and then link children's environment to their behaviors. Children's micro- and macroenvironments are different from adults and change through development. The time spent at home, daycare, or school will result in completely different exposure scenarios. In addition, children's environments may vary demographically and across cultural groups. For example, children in different cultures experience a variety of different foods and lifestyle exposures. Thus, exposure research efforts should be dedicated to studying how children's characteristic environments differ from adults, what contaminants are found in their environment, and how their environment changes with age, gender, and culture background.

Studies of children's activity patterns are an essential component of estimating their exposures, and research efforts should be dedicated to this task. We need to know more about the activities that children engage in, and how to quantify exposures arising from children's activities. For example, how often does a child bring a toy to his/her mouth that has touched a contaminated surface? What is the distribution of ingestion rates of soil and dust among children in various age ranges? Little information is available on the exposures derived from dermal contact, ingestion, and inhalation of pollutants on floors, in household dust, and in the small child's indoor breathing zone. Research on activity patterns would include studies of behavior and activities for evaluating the duration, frequency, and extent of exposure, dietary intakes, physiologic parameters, and other relevant factors. Participants suggested that an interdisciplinary team be formed to research children's activities, behavioral development periods, environments, and exposures. This team would identify applicable categories for children by behavior, age, functionality and biology, and determine the average and range of variance in behaviors among children within agreed-upon groups. Cross-cultural differences in dietary patterns through development should also be studied.

h) Evaluate exposures to the fetus during gestation.

Maternal preconception exposure to a potential carcinogen may result in fetal exposure to the parent chemical or to any of the toxic metabolites produced by the mother. In addition, the metabolic capacity of the placenta may contribute to the bioactivation or detoxification of chemicals. Research is recommended to study the role of the placenta in protecting the fetus from carcinogenic compounds and to evaluate the contribution of the metabolic capacity of the placenta to fetal exposures.

i) Evaluate the contribution of paternal exposures to children's exposures.

Children's exposures through the father must also be studied. Exposure to pesticides in children of farmers occurs when pesticides are carried by the parents from the field into the home. Buckley et al. (*43*) found an association with acute lymphoblastic leukemia when both mother and father had been exposed to pesticides. The father's exposures may also contribute to the genetic syndromes that result in cancer, such as certain forms of retinoblastoma or Wilms tumor (*22*). Animal studies suggest that paternal exposures to rats can affect subsequent cancer risk without altering fertility (*44*). Thus, more information is needed on the role of paternal exposure in childhood cancer.

j) Characterize exposures that occur during critical periods of development.

Special attention should be given to exposures during specific periods of development during which susceptibility to cancer may be enhanced. For example, if contraceptives are used during adolescence, their contribution to outcomes such as breast cancer may be different than what is expected from adult users. For some types

of cancer, exposures at critical periods of development, such as when a tissue or system is rapidly developing, may greatly increase the child's susceptibility to cancer.

k) Determine whether the techniques currently used to measure contaminant concentration and collect environmental samples that are representative of a child's exposure. Develop protocols for environmental sampling that take into account the characteristics of the child's environment.

Environmental data is often the only available information to estimate exposures. It is necessary to determine whether the techniques currently used to measure contaminant concentrations and collect environmental samples are representative of a child's exposure. For example, air-monitoring measurements are currently taken at adult heights. These measurements may not be representative of the air quality closer to the ground, where children breathe. Thus, environmental sampling should take into consideration the specific characteristics of children's environments.

l) Identify highly exposed populations.

It is also recommended that research is done to target populations of children who are suspected to be more highly exposed (e.g., children of migrant farm workers). Collecting information from these research studies may help to identify some exposure factors from other chemicals. Information from unique cancer clusters (e.g., DES) could be better utilized to determine some children's exposure factors.

Summary

Preventable causes of childhood cancer were the focus of the conference. This is an area in which we still have much to learn. We do not yet know what fraction of childhood cancers are due to preventable causes. We are only beginning—on the basis of imperfect knowledge—to develop strategies for prevention. The recommendations that were made at this conference and that are summarized in this report are intended to provide a blueprint for closing gaps in knowledge and thus for guiding prevention of childhood cancer. We aim for future progress in prevention equal to the progress in treatment of childhood cancers.

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