Childhood Leukemia and Primary Prevention

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Leukemia is the most common pediatric cancer, affecting 3800 children per year in the United States. Its annual incidence has increased over the last decades, especially among Latinos. Although most children diagnosed with leukemia are now cured, many suffer long-term complications, and primary prevention efforts are urgently needed. The early onset of leukemia—usually before 5 years of age—and the presence at birth of "pre-leukemic" genetic signatures indicate that pre- and postnatal events are critical to the development of the disease. In contrast to most pediatric cancers, there is a growing body of literature—in the United States and internationally—that has implicated several environmental, infectious, and dietary risk factors in the etiology of childhood leukemia, mainly for acute lymphoblastic leukemia, the most common subtype. For example, exposures to pesticides, tobacco smoke, solvents, and traffic emissions have consistently demonstrated positive associations with the risk of developing childhood leukemia. In contrast, intake of vitamins and folate supplementation during the preconception period or pregnancy, breastfeeding, and exposure to routine childhood infections have been shown to reduce the risk of childhood leukemia. Some children may be especially vulnerable to these risk factors, as demonstrated by a disproportionate burden of childhood leukemia in the Latino population of California. The evidence supporting the associations between childhood leukemia and its risk factors—including pooled analyses from around the world and systematic reviews—is strong; however, the dissemination of this knowledge to clinicians has been limited. To protect children's health, it is prudent to initiate programs designed to alter exposure to well-established leukemia risk factors rather than to suspend judgment until no uncertainty remains. Primary prevention programs for childhood leukemia would also result in the significant co-benefits of reductions in other adverse health outcomes that are common in children, such as detriments to neurocognitive development.

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Introduction

Cancer is the second most common cause of death in children 0–14 years of age, after accidents. Leukemia is the most common cancer in children, representing approximately one-third of pediatric cancers. Approximately 3800 children are diagnosed annually with acute lymphoblastic leukemia (ALL) or acute myeloblastic leukemia (AML) in the United States (U.S.).[1] A small but steady annual increase from 1975 and 2012 in the age-adjusted incidence rate of childhood leukemia in the U.S. has resulted in an overall rise of 55% in the annual number of cases during the past three and a half decades. Modern treatment protocols cure 80–90% of children with leukemia with fewer sequelae than

Childhood leukemia has been trending upward in California in recent decades

It has risen especially among Latinos, reflecting a national trend and raising concerns about early environmental exposures to harmful chemicals.

Legend: Latinos, All Races Combined, Non-Latino Whites

Y-axis: CHILDHOOD LEUKEMIA RATE PER 1,000,000

X-axis: YEAR, '88–'12
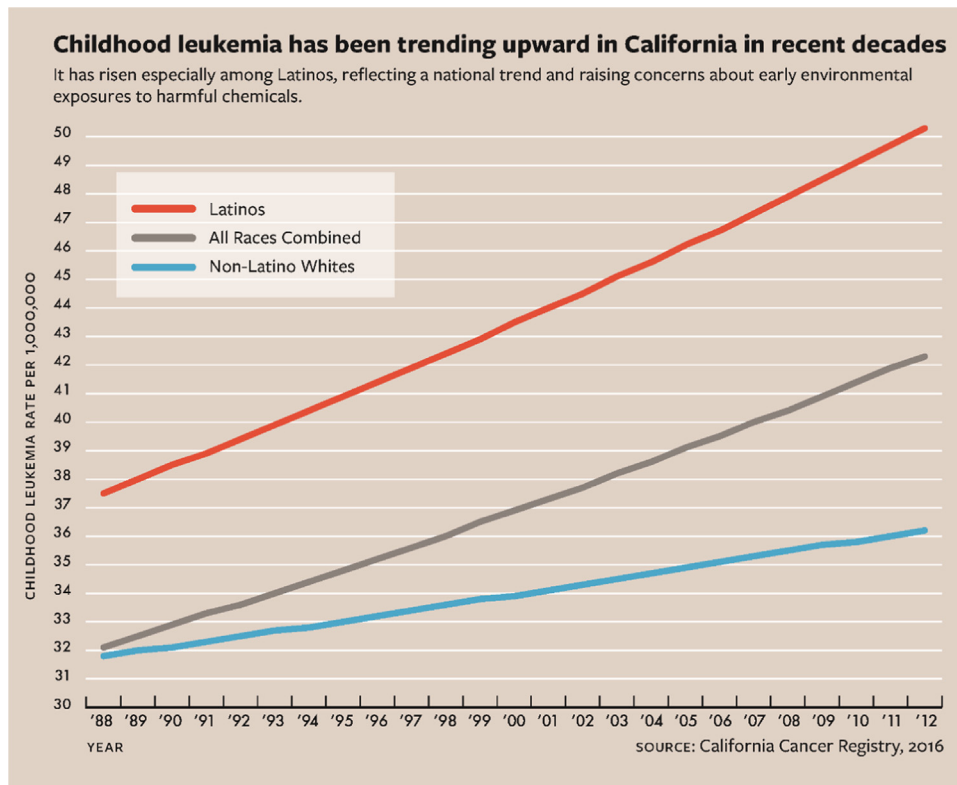
SOURCE: California Cancer Registry, 2016

FIG. Incidence of childhood leukemia in California by race-ethnicity, 1988–2012. Adapted with permission from Giddings et al.[7]

previous regimens. Still, even with improved treatments, the immediate and long-term consequences of childhood leukemia continue to exact a heavy toll.[2,3] The impacts and costs of childhood leukemia extend beyond the care of the sick child; affecting family, friends, and the community. Long-term and late-appearing secondary effects include detriments to neurocognitive development, mental health, endocrine system function, and general health.[4] To avoid these risks completely, it would be beneficial to prevent the disease altogether.

Though new genetic risk factors are likely still to be discovered, to date only a small fraction (less than 10%) of childhood leukemia cases can be attributed to the influence of genetics, including to genetic syndromes such as Down's.[5,6] Moreover, the aforementioned increase in childhood leukemia incidence—which is not fully explained by diagnostic trends—indicates that causal factors for childhood leukemia have become more prevalent in the last few decades. Since genetic factors do not change on this time scale, it is probable that environmental factors play a significant role in the etiology of childhood leukemias and their recent upward trends.[6] These facts underscore the importance

of developing an approach to primary prevention of childhood leukemia focused on reducing exposure to environmental risk factors for the disease.

Children of Latino (also referred to as Hispanic) descent have a higher incidence of leukemia than whites, African-Americans or Asian-Americans nationally and in California, a highly-populated and ethnically diverse State. Moreover, over the past 25 years, childhood leukemia incidence has been rising in California at a faster pace in Latino children, compared to white children (Fig),[7] suggesting that Latino children (or parents) are even more vulnerable to and/or more exposed to harmful environmental factors than others.

Exposure to carcinogens has generally been considered a non-threshold event and modeled in a linear fashion. However, there are chemicals for which a supra-linear dose–response curve has been observed, indicating that the risk from low-dose exposure may actually be proportionally greater than would be expected with a linear dose–response curve.[8] One such example is the known leukemogen, benzene, which is metabolized to active intermediary compounds. This finding is consistent with other exposures of concern to pediatric environmental health, such as lead, where a

non-linear dose–response relationship has resulted in worse-than-anticipated health effects from low-dose environmental exposures that were presumed to be safe.[9] As such, findings from observational studies—where participants are exposed to chemicals at environmental levels as opposed to higher dose occupational levels—are critical to avoid underestimating risk.

Research into environmental, infectious, and dietary causes of childhood leukemia has been limited, amounting to only a small fraction of the total Federal funding for childhood leukemia research (e.g., 3–7% of National Institutes of Health and 1% of National Cancer Institute total funding in 2010–2011).[10] Funding for treatment/outcome-related studies has been far greater than for those studies examining etiology. The dramatic increases in children cured clearly justifies the expenditures made to improve treatment, but research on etiologic factors that may lead to prevention is also important. Despite limited funding, evidence demonstrating associations between environmental, infectious, and dietary exposures and the risk of developing childhood leukemia is accumulating.

This issue provides an overview of key biological concepts in childhood leukemia research and summarizes the environmental, infectious, and dietary risk factors for childhood leukemia that have been identified in epidemiologic studies from around the world. Our purpose is not to conduct a systematic review of the field of childhood leukemia epidemiology—an endeavor which could fill an entire book—but rather to provide a concise perspective of the subject for the benefit of clinicians and policy makers. The literature cited in this issue spans a wide gamut. Whenever possible, the authors emphasize relevant findings from well-designed meta-analyses of published data and from large international collaborations that have pooled and analyzed individual-level data from multiple studies. In some instances, both pooled analyses and meta-analyses (including unpublished data) were conducted in parallel. Because most of these comprehensive studies fulfill criteria for systematic reviews, they provide the strongest evidence of associations between childhood leukemia and its risk factors. However, when warranted by the novelty of the research, the authors also discuss "one-off" findings of particular interest. The authors are associated with the California Childhood Leukemia Study (CCLS) and the Center for Integrative Research on Childhood Leukemia and the Environment (CIRCLE) at the University of California, Berkeley. This research group, begun by Patricia Buffler, PhD, has studied environmental causes of childhood leukemia for

25 years. In this article, we identify many of the major epidemiologic investigations of childhood leukemia worldwide and we rely on our collective expertise to highlight the literature that we believe will be most instructive to clinicians and policy makers. However, we acknowledge that particular emphasis has been paid to the work of our research group and its collaborators in the Childhood Leukemia International Consortium (CLIC).

Natural History of Leukemia as a Disease

Development of Blood Cells and the Formation of Leukemia

Hematopoiesis is a process involving extreme cellular blast growth, which produces 10^{11} blood cells per day throughout life. The activity of certain cell differentiation stages (defined by cell surface markers and the potential of the progeny) varies throughout life due to different needs of the organism. These changes in the activity of blood cell types over the course of development are reflected in the distinct types of blood cells with the propensity for cancer in childhood and adulthood.

Although the maternal immune system protects the child before and shortly after birth (with maternal antibodies), the child's immune system must begin its education immediately after birth. This education of the adaptive immune system requires exposures to immune stimuli (e.g., infections) leading to the formation of billions of naïve pre-B and pre-T cells. Leukemias in children arise from these naïve, pre-antigen stages, typically leading to primitive precursor blast cell leukemic populations. That is, the majority of childhood leukemias are of the pre-B cell or, to a lesser extent, pre-T-cell phenotype (exhibiting cell surface markers of normal pre-B or pre-T cells) and appear as clonal outgrowths of normal pre-B or pre-T cells "frozen" at a particular stage of differentiation.

Through the adaptive formation of antibodies and T-cell receptors that respond to specific antigens, a stable long-lived repertoire of cells is developed by the time a child reaches young adulthood. The pre-B and pre-T stages decrease in frequency after adolescence, exemplified by the involution of the thymus and the reduction in size of the pre-B cell population in the bone marrow. As a result, adults typically contract hematopoietic cancers (lymphomas and leukemias) in post-antigen-stimulated B and T-cells and the myeloid

lineage predominates in adult tumors. Distinct from adult leukemias, the unique properties of childhood leukemia cells are likely to be important for understanding the environmental sensitivities for leukemogenesis in this age group.

Childhood leukemia, like all cancers, is a product of two or more molecular changes in a stem-like cell that has the ability to divide while maintaining an immature state. Because they are formed from blood cells, leukemias have an inherent capacity for mobilization in the bloodstream and extravasation. Precursor blood cells also have an enormous capacity for "blast-like" growth, and an ability to travel throughout the body without restriction. These attributes are among the six "hallmarks of cancer,"[11] and the fact that hematopoietic precursors harbor these "cancer-like" attributes may explain why leukemias seem to need far fewer genetic aberrations for tumor progression compared to solid tumors, which need to evolve additional metastatic capacities via genetic mutations. This simplicity may also help explain the short latency of childhood cancers.

The genetic simplicity of leukemia combined with the young age of onset has allowed researchers to delineate—within the lifetime of the child—the timing of the formation of characteristic genetic aberrations.[12] These changes appear to occur within two time frames —prenatal initiating events that induce some cellular changes, and postnatal genetic and epigenetic events that allow the emergence of acute disease. This research was made possible by the availability of archived newborn blood spots that are routinely collected at birth by heel prick from neonates (e.g., by the State of California Newborn Screening Program), including from children with leukemia. Several translocations commonly found in leukemias that were assessed using archived newborn blood spots, including t(12;21) *ETV6-RUNX1*, t(8;21)*RUNX1-MTG8*, inv (16)*CBFB-MYH11*, have indicated a clear presence of the mutations in neonatal blood at birth in children who contract leukemia later in life.[13–16] Several other mutations, including t(1;19)*TCF3-PBX1*, *FLT3*, and *RAS* mutations clearly occur postnatally.[17–19] The mutations associated with leukemia are generally insufficient to cause disease by themselves. This is the case for *ETV6-RUNX1* and *RUNX1-MTG8*, the most

common translocations for ALL and AML, respectively. Studies using cord blood from healthy children without cancer indicate that these translocations may occur at a rate of 1% or more in the general population,[20,21] while the disease is much more rare.

Mutational Mechanisms in Leukemia

Recent investigations into the precise molecular attributes of leukemia point largely to three pathways: (1) aberrations in a small number of lineage-specific transcription factors such as *ETV6*, *RUNX1*, *IKZF1*, and *PAX5* (2) defects in receptor protein tyrosine kinases and their downstream pathways (i.e., *RAS/MEK/ERK*), and (3) epigenetic modifiers. Mutations may involve translocations that comprise fusion genes, copy number alterations (most common are deletions), single nucleotide mutations, and broad changes in epigenetic features such as DNA methylation aberrations. The molecular formation of the initiating translocations may provide some clues as to their causes. In the past several years, many translocation breakpoints were shown to be induced by enzymatic mutagenic processes—normally utilized by the immune system to diversify antibody and T-cell repertoire—which were aberrantly targeted to oncogenes and genomic enhancers.[22] These types of translocations are common in hematopoietic cancers that form after birth in response to antigenic stimulation. Interestingly, leukemia translocations including the most common in children such as *ETV6-RUNX1* do not show signs of such activity and their origin remains a mystery. The lack of a clear endogenous path toward translocation formation points to exogenous causes such as *in utero* environmental exposures, and points again to the oncologic immaturity of childhood leukemia blasts. Environmental causes may also interact with endogenous mutagenic mechanisms in children after birth. Many of these postnatal secondary rearrangements show the clear involvement of the activity of the enzymes that create antibody diversity, that is, recombinase activating gene (RAG) and adenosine deaminase (AID) in the formation of secondary deletions and mutations.[23] Illegitimate targeting of these endogenous enzymes has long been known to be stimulated by exposures as diverse as pesticides and smoking. As

> *The development of childhood leukemia is a multi-step process; initiation occurs in utero for most leukemias, whereas progression into acute disease usually takes place after birth.*

such, there is evidence that postnatal environmental exposures may initiate childhood leukemia via the stimulation of endogenous mutagenic mechanisms including recombinase activating gene activity.[24,25]

Apart from the chromosome breakage events mentioned above, additional mutations include point mutations and epigenetic modifications. Point mutations are caused by electrophilic chemicals that are either exposed to bone marrow cells directly or else they are metabolically activated, and their metabolites are exposed to bone marrow cells. Many oxidized reactive metabolites are produced from chemicals circulating in the bone marrow due to the presence of highly metabolically active cells such as neutrophils (containing myeloperoxidase, for instance) and the high levels of heme iron. Metabolites that adduct to DNA can directly cause miscoding mutations if unrepaired, or can result in repair-induced strand breaks. There is little current evidence that point mutations such as those found in *RAS* are caused by environmental chemicals[26]; however, the most common translocation in ALL, *ETV6-RUNX1*, appears to be strongly and specifically associated with parental smoking[27] and home paint use,[28,29] which provides some credence to viability of this pathway.

Epigenetic modifications are a normal part of a blood cell's development from a stem cell to a mature cell. Changes to the usual epigenetic programming can occur, however, as cells adapt to new environments. This type of adaptation is the essence of the "developmental origins of health and disease" initiatives that seek to understand when such adaptations early in life can lead to later disease risk, such as the demonstration that starvation *in utero* can lead to obesity and cardiac disease risk later in life.[30] Adaptations can occur as the result of exposures to specific environmental factors—for instance the specific demethylation of CpG loci in the gene *AHRR* has been exquisitely related to cigarette smoke.[31] Likewise, methylation changes have also been observed in response to folic acid exposures.[32] Our understanding of the specific effects of environmental exposures on epigenetic features is just in its infancy, and it is unknown whether these perturbations could impact leukemogenesis.

The Role of Immune Factors in a Cancer of the Immune System

Infection is a direct cause of viral-induced cancers, such as human papillomavirus-induced cervical cancer and Merkel cell virus-induced skin cancer. Inflammation from infection is also a risk factor for many cancers, resulting from the collateral damage of tissue disorganization, tissue remodeling, and chronic exposure to reactive oxygen species following inflammatory processes. Childhood ALL is also a disease of the immune system, which begs the question can infection directly stimulate leukemia or stimulate leukemia via inflammatory processes?

Viruses that directly integrate into the genome have not been reported in childhood ALL. Epidemiological studies have, however, demonstrated clear effects of immune factors on leukemogenesis, most overtly in the form of a consistently observed reduced risk of childhood ALL associated with more childhood contacts in daycare [odds ratio (OR) = 0.77; 95% confidence interval (95% CI): 0.71−0.84; N = 7399 cases] and other markers of early exposure to immune stimulus such as breastfeeding for at least 6 months (OR = 0.86, 95% CI: 0.79−0.94), having an older sibling (OR = 0.94, 95% CI: 0.88−1.00), or a history of four or more common infections in the first year of life (OR = 0.88, 95% CI: 0.79−0.98).[33] Just as regular immune stimulation appears to reduce risk for allergies and asthma, the same immune exercise can reduce the risk of leukemia. In the absence of these priming exposures, children may respond too strongly to the myriad of infections subsequently encountered in school, resulting in a cytokine "storm" and excess cell stimulation, secondary mutations, and in some cases, leukemia. This putative pathology is referred to as the "Greaves hypotheses" after its first proponent.[34] Other ancillary data on immune education seem to fit this pattern as well—normal childhood vaccines, the presence of older siblings, and breastfeeding were all associated with reduced risks of childhood leukemia. Population mixing, in which large numbers of a "new" population are mixed into a standing community, seems to transiently increase the risk of leukemia and also fit with the notion of an infectious stimulation for childhood ALL.[35] A corollary hypothesis to Greaves' was suggested by Kinlen who noticed that leukemia space–time clusters often followed recent population mixing events, such as the creation of new towns or population movements during warfare. He proposed that such mixing facilitated the transmission of a specific leukemia-initiating virus which, while plausible, was not followed up with biological validation as noted above. More likely, population mixing permits the transmission of common viruses to populations

without herd immunity rather than spreading specific leukemia-initiating viruses.

Recent studies have noted that the child's medical records confuse the infection issue somewhat—ALL patients visit their general practitioner for infections in the first year of life much *more commonly* than children who do not grow up to get leukemia.[36,37] This suggests that the damage wrought by fulminant infections may occur much earlier than previously thought, and also that children who get leukemia may respond to infection differently, that is, more strongly to typical childhood infections. Part of this sensitivity may be a lack of immunomodulation from suppressive cytokines like IL-10 that tend to be present at lower levels in newborns who go on to develop leukemia.[38]

Chemicals as Leukemogens

The ability of a chemical to act as carcinogen was originally thought to hinge on its capacity as mutagen, but it is likely that many other more biologically relevant activities are important in leukemogenesis as well. Some chemicals exhibit properties that allow them to target the bone marrow specifically, due to its metabolic activity (benzene for an example). Other chemicals may impact the immune system indirectly, setting up the individual for aberrant responses to infection. The role of exogenous factors such as chemicals, many of which are immunosuppressive, in this process is unknown and likely to be a major research field in the future. Other activities of chemicals are summarized in a recent review of chemicals as carcinogens.[39] Below, we discuss chemical exposures that may cause leukemia and weigh the evidence for causal relationships.

Environmental Risk Factors for Childhood Leukemia

Exposure Science in Studies of Childhood Leukemia Risk

As mentioned earlier, childhood leukemia is the most common form of pediatric cancer; but, for the purposes of epidemiological study, it is a rare disease. As such, the vast majority of epidemiological investigations into the causes of childhood leukemia are forced to employ a case–control study design. In many instances, case–control studies of childhood leukemia are designed to assess children's exposure to disease risk factors retrospectively. That is, a child is first diagnosed with leukemia, then s/he is enrolled in the case–control study, and only afterwards can investigators begin to assess the agents to which s/he has been exposed. This design imposes limitations on the epidemiologist, as etiologically relevant specimens—biological and environmental—are not necessarily available for collection by the time the child is under study. As discussed above, childhood leukemia can be initiated during the prenatal period, but most cases are not diagnosed until the child is between 2 and 4 years old. This leaves a long time interval between the first windows of susceptibility to leukemogenic agents and the time period when investigators can start measuring a child's exposure to those agents. To overcome these challenges, childhood leukemia investigators have employed a variety of strategies to assess children's exposures to potentially carcinogenic agents.

Using Parent Interviews to Assess Children's Exposures to Chemicals

One simple way to circumvent the need for the collection of biological or environmental samples during etiologically relevant time periods is to interview participating parents to obtain information about their child's history of exposure to specific agents. Such interviews can be used to pinpoint historical exposures during critical windows of a child's development (e.g., the second trimester of pregnancy), they can be wide-ranging in scope, and they can be especially effective in assessing parents' conscious behaviors (e.g., smoking habits, residential pesticide use, occupational histories). On the other hand, interview-based exposure assessments have inherent limitations; they are imprecise measures of chemical exposure, they provide little information about any of a child's exposures that go unrecognized by the parents, and they are potentially subject to recall and reporting biases if parents of case and control children remember or report their children's exposures in different ways. In practice, though, reproducibility studies have suggested that, for some of the environmental exposures that are of interest in childhood leukemia research—ionizing radiation,[40–42] pesticides,[43] and smoking[27]—there is minimal evidence of differential recall between cases and controls.

Measuring Chemicals in Settled Dust

Another strategy to obtain information about a child's exposure to chemicals during etiologically relevant time periods is to measure levels of chemicals in stable environmental matrices. For example, persistent chemicals accumulate on settled dust particles, which can become trapped deep within a carpet, and this settled dust acts as a long-term reservoir for these chemicals.[44] With limited exposure to direct sunlight and microbial action, persistent chemicals, like polychlorinated biphenyls (PCBs), are extremely slow to degrade on dust particles that settle indoors. As a result, collecting samples of settled dust from carpets or other household surfaces and measuring levels of persistent chemicals in these samples provides an integrated measure of chemical contamination over a long period of time.

As part of the California Childhood Leukemia Study, we have collected multiple dust samples from a large group of homes at time intervals of several years between sampling rounds. We found that while there was substantial variability in chemical levels between sampling rounds, there was also moderate correlation in the relative ranking of exposures (i.e., rankings from highest to lowest exposures) among homes over time.[45–47] These findings support the hypothesis that chemical levels in dust samples collected after diagnosis may be informative surrogates for chemical contamination that was present in the home during important developmental periods of a child's life.

Accidental ingestion of settled dust is an important route of human exposure to chemicals along with the consumption of contaminated food and the inhalation of contaminated air. For example, it has been suggested that dust ingestion is the major route of exposure to the flame retardant chemicals, polybrominated diphenyl ethers (PBDEs) in North America[48] and positive relationships have been observed between PBDE levels in matched samples of dust and serum among U.S. adults.[49,50] Due to their tendency to make hand-to-mouth contact and their proximity to the floor, young children are expected to receive a relatively large proportion of their total chemical intake via settled dust compared to adults,[51] and a positive relationship has been observed between PBDE levels in matched samples of dust and serum in one investigation of toddlers from North Carolina.[52] Likewise,

Chemicals measured in samples of settled dust collected from a child's home after diagnosis are useful surrogates for the chemical exposures s/he received during etiologically-relevant periods before and after birth.

research from the Center for Integrative Research on Childhood Leukemia and the Environment also indicates a relationship between levels of persistent chemicals in matched samples of settled dust and biospecimens.[53,54] Taken together, the observation that chemical levels can be correlated in matched samples of settled dust and human serum as well as the observation that chemical levels in settled dust are relatively stable over time support the use of chemical levels measured in dust collected after diagnosis as surrogates for chemical exposures that children received during etiologically relevant time periods (before diagnosis).

Estimating Ambient Environmental Exposures Using Geographic Information Systems

An alternative strategy for assessing a child's history of environmental exposures is to estimate ambient pollution using Geographic Information Systems (GIS) and geospatial modeling and to use these estimates of ambient conditions as surrogates for the child's total exposure to chemicals. Many governing bodies record a child's home address on the birth certificate and this information can be obtained for research purposes contingent on appropriate ethical review and approval. Exposure models based on GIS data and geocoded birth addresses could provide useful information about children's exposure to chemicals at the time of birth and, potentially, throughout the prenatal period as well (if participating mothers did not change residence during pregnancy). Moreover, complete residential histories can be obtained from parents via interview, which allows for a more comprehensive model of a child's historic exposures to ambient chemicals. Agricultural pesticide application,[55,56] traffic-related air pollution,[57] and electromagnetic fields[58] have been estimated using GIS in the context of epidemiological studies of childhood leukemia. One limitation of using estimates of ambient pollution as surrogates for total exposures is the inability to account for chemical exposures that occur indoors. This is a substantial drawback, because children tend to spend the vast majority of their time indoors, there are distinct chemical sources indoors, and chemical exposures tend to be higher indoors than outdoors.[59,60]

Measuring Chemicals in Archived Pre-diagnostic Biospecimens

Perhaps the most straightforward way to obtain pre-diagnostic biospecimens would be to establish a prospective birth cohort and follow leukemia incidence in the participating children into adulthood. However, as discussed above, this study design is generally not feasible for childhood leukemia and will generally be limited by a small number of available cases. The International Childhood Cancer Cohort Consortium seeks to combine a number of large infant/child prospective studies (on the order of 100,000 participants per study)—which were originally designed to examine environmental and genetic determinants of common childhood diseases—for pooled analyses of childhood leukemia and other childhood cancers.[61]

Alternatively, it may be possible to utilize archived biospecimens—collected before diagnosis as part of routine medical testing—to measure prenatal chemical exposures.[62] For example, in many countries, blood spots are collected from each newborn infant by heel-stick for the purposes of genetic screening. In the State of California, blood spots left over from genetic screening are archived in a State laboratory and made available for research contingent upon appropriate ethical review and approval. These archived neonatal blood spots provide a useful resource for childhood leukemia research, offering insight into the chemicals to which the developing fetus was exposed during the prenatal period, including folate,[63] cotinine,[64] and PBDEs.[65] Using current technology for exposure biology, investigators can characterize prenatal exposure to thousands of different chemicals with as little as a few drops of archived neonatal blood. Some important technical considerations include the potential instability of chemical analytes during long-term storage, the possibility of chemical contamination during storage, and the complex dynamics of newborn metabolite levels immediately after birth.[66] Despite these limitations, the use of archived pre-diagnostic biospecimens for exposure assessment in epidemiological studies of childhood leukemia is very promising.

> *Epidemiological studies have identified several environmental risk factors for childhood leukemia and those findings have been confirmed with large meta-analyses and pooled analyses that combined data from thousands of children with leukemia and healthy controls.*

Using these strategies for assessing children's exposure to environmental agents, epidemiologists have identified several suspected environmental risk factors for childhood leukemia, including pesticides, parental smoking, paint, petroleum solvents, traffic emissions, persistent organic pollutants, and radiation, as summarized in Table 1.

Pesticides

Several studies have suggested that home pesticide exposure before birth and during a child's early years may increase the risk of childhood leukemia. Indeed, exposure to pesticides is one of the most frequently investigated chemical risk factors for childhood leukemia. A causal link between exposure to pesticides and childhood leukemia is supported by many studies, including the California Childhood Leukemia Study, which demonstrated a relationship between exposure to insecticides—as a general class—and childhood leukemia.[67] Existing studies have generally used interviews with parents to assess children's exposure to pesticides; as such, no specific pesticide, or class of pesticides, has been implicated as the causal agent underlying these observations.

Pooled Analyses of Home Pesticide Use and Childhood Leukemia

Investigators from the Childhood Leukemia International Consortium pooled individual parents' responses to interview questions about children's exposure to pesticides from 12 case–control studies.[29] Each contributing study used a unique set of questions, often written in different languages, so exposure data were harmonized into compatible formats before pooled analyses could be conducted using multivariable logistic regression. ALL was associated with any pesticide exposure shortly before conception (OR = 1.39; 95% CI: 1.25–1.55; $N = 2785$ cases and 3635 controls), during pregnancy (OR = 1.43; 95% CI: 1.32–1.54; $N = 5055$ cases and 7370 controls), and after birth (OR = 1.36; 95% CI: 1.23–1.51; $N = 4162$ cases and 5179 controls). Corresponding odds ratios for risk of AML were 1.49 (95% CI: 1.02−2.16, $N = 173$ cases and 1789 controls), 1.55 (95% CI: 1.21–1.99; $N = 344$

TABLE 1. Environmental risk factors for childhood leukemia

Childhood leukemia risk factor	Exposure measure	Level of consensus	Subtype specificity	Exposure details	Odds ratio (95% CI)
Home pesticide use	Parental interview	Pooled analysis of 12 studies from CLIC.[29]	ALL	Before conception	1.39 (1.25, 1.55)
			ALL	During pregnancy	1.43 (1.32, 1.54)
			ALL	After birth	1.36 (1.23, 1.51)
			AML	Before conception	1.49 (1.02, 2.16)
			AML	During pregnancy	1.55 (1.21, 1.99)
			AML	After birth	1.08 (0.76, 1.53)
Parental occupational exposure to pesticides	Parental interview	Pooled analysis of 13 studies from CLIC & meta-analysis of CLIC + non-CLIC studies.[74]	ALL	Maternal during pregnancy	1.01 (0.78, 1.30)
			ALL	Paternal at conception	1.20 (1.06, 1.38)
			T-cell ALL	Paternal at conception	1.42 (1.04, 1.94)
			ALL after 5y	Paternal at conception	1.38 (1.13, 1.67)
			AML	Maternal during pregnancy	1.94 (1.19, 3.18)
			AML	Paternal at conception	0.91 (0.66, 1.24)
Proximity to agricultural pesticide application	GIS Model	Novel finding.[55]	ALL	Insecticides, moderate, lifetime	1.5 (0.9, 2.4)
			ALL	Fumigants, moderate, lifetime	1.7 (1.0, 3.1)
			ALL	Organophosphates, moderate, lifetime	1.6 (1.0, 2.7)
			ALL	Chlorinated phenols, moderate, lifetime	2.0 (1.0, 3.8)
			ALL	Triazines, moderate, lifetime	1.9 (1.0, 3.7)
Chlorthal, an herbicide	Settled dust levels	Novel finding.[80]	ALL	Detected, 1st Tertile vs. Not Detected	1.49 (0.82, 2.72)
			ALL	Detected, 2nd Tertile vs. Not Detected	1.49 (0.83, 2.67)
			ALL	Detected, 3rd Tertile vs. Not Detected	1.57 (0.90, 2.73)
Parental smoking	Parental interview	Pooled analysis of 14 studies from CLIC & meta-analysis of CLIC + non-CLIC studies.[83]	AML	Paternal at any time	1.34 (1.11, 1.62)
			AML	Maternal during pregnancy, Latinas	2.08 (1.20, 3.61)
			AMMoL	Paternal at any time	1.87 (1.08, 3.25)
Home paint use	Parental interview	Pooled analysis of 8 studies from CLIC.[86]	ALL	1–3 months before conception	1.54 (1.28, 1.85)
			ALL	During pregnancy	1.14 (1.04, 1.25)
			ALL	After birth	1.22 (1.07, 1.39)
			ALL	Professional painter, during pregnancy	1.66 (1.21, 2.28)
			ALL—t(12;21)	During pregnancy	1.51 (1.08, 2.11)
Parental occupational exposure to paint	Parental interview	Pooled analysis of 13 studies from CLIC.[89]	ALL	Paternal at conception	0.93 (0.76, 1.14)
			ALL	Maternal during pregnancy	0.81 (0.39, 1.68)
			AML	Paternal at conception	0.96 (0.65, 1.41)
			AML	Maternal during pregnancy	1.31 (0.38, 4.47)
		Meta-analysis.[88]	ALL	Maternal during pregnancy	1.23 (1.02, 1.47)
Parental occupational exposure to solvents	Parental interview	Meta-analysis.[88,90]	ALL	All solvents, maternal during pregnancy	1.25 (1.09, 1.45)
			ALL	Petroleum, maternal during pregnancy	1.42 (1.10, 1.84)
			ALL		1.71 (0.91, 3.24)[a]

TABLE 1. (*Continued*)

Childhood leukemia risk factor	Exposure measure	Level of consensus	Subtype specificity	Exposure details	Odds ratio (95% CI)
				Benzene, maternal during pregnancy	
		Replicated.[91]	ALL	Org. solvents, paternal at conception	1.48 (1.01, 2.16)
			ALL	Cl-hydrocarbon, paternal at conception	2.28 (0.97, 5.37)
Traffic-related air pollution	GIS model	Two independent meta-analyses.[92,93]	ALL	Traffic density	1.25 (0.92, 1.69)
			Any	Traffic density	1.53 (1.12, 2.10)
			ALL	Nitrogen dioxide estimates	1.21 (1.04, 1.41)
			AML	Benzene estimates	2.28 (1.09, 4.75)
PAHs	Settled dust levels, vacuum cleaners	Novel finding.[94]	ALL	Benzo[*a*]pyrene	1.42 (0.95, 2.12)
			ALL	Dibenzo[*a,h*]anthracene	1.98 (1.11, 3.55)
			ALL	Benzo[*k*]fluoranthene	1.71 (0.91, 3.22)
			ALL	Indeno[*1,2,3-c,d*]pyrene	1.81 (1.04, 3.16)
			ALL	PAH toxic equivalence	2.35 (1.18, 4.69)
PCBs	Settled dust levels	Novel finding.[81]	ALL	Any PCB detected vs. none detected	1.97 (1.22, 3.17)
			ALL	Top quartile Σ_6PCB vs. bottom quartile	2.78 (1.41, 5.48)
PBDEs	Settled dust levels	Novel finding.[95]	ALL	Top quartile ΣPenta-BDEs vs. bottom	0.7 (0.4, 1.3)
			ALL	Top quartile ΣOcta-BDEs vs. bottom	1.3 (0.7, 2.3)
			ALL	Top quartile ΣDeca-BDEs vs. bottom	1.0 (0.6, 1.8)
			ALL	BDE-196 concentrations	2.1 (1.1, 3.8)
			ALL	BDE-203 concentrations	2.0 (1.1, 3.6)
			ALL	BDE-206 concentrations	2.1 (1.1, 3.9)
			ALL	BDE-207 concentrations	2.0 (1.03, 3.8)

ALL = acute lymphoblastic leukemia; AML = acute myeloblastic leukemia; AMMoL = acute myelomonocytic leukemia; CI = confidence interval; CLIC = Childhood Leukemia International Consortium; GIS = geographic information systems; PAHs = polycyclic aromatic hydrocarbons; PCBs = polychlorinated biphenyls; PBDEs = polybrominated diphenyl ethers.
[a]Relative risk reported.

cases and 4666 controls) and 1.08 (95% CI: 0.76–1.53, $N = 198$ cases and 2655 controls), respectively.

The Childhood Leukemia International Consortium investigators[29] confirmed the observed association between home pesticide exposure during pregnancy and childhood leukemia using meta-analyses as well. Other investigators have reported similar findings in independent meta-analyses,[68–70] generally observing the strongest associations for indoor insecticide use.

Pooled Analyses of Parental Occupational Exposure to Pesticides and Childhood Leukemia

Given the consistently observed association between home pesticide use during early childhood and leukemia risk, a logical extension of this line of research has been to examine the effect of parental occupational exposure to pesticides on childhood leukemia risk. There is evidence that adults exposed to pesticides at work can track these chemicals back to their homes on their shoes, clothing, and skin, potentially exposing their families.[71,72] Moreover, paternal exposure to pesticides before conception could result in germ cell damage, whereas maternal exposure to pesticides during pregnancy could also expose the fetus to these chemicals.[73] The Childhood Leukemia International Consortium investigators pooled individual parents' responses to interview questions about job histories and the data were harmonized to a compatible format that characterized parents' pesticide exposures at work.[74] ALL was associated with paternal exposure

to pesticides at work around the time of conception (OR = 1.20; 95% CI: 1.06−1.38; N = 8169 fathers of cases and 14,201 fathers of controls), but was not associated with maternal exposure during pregnancy (OR = 1.01; 95% CI: 0.78−1.30; N = 8236 case and 14,850 control mothers). In contrast, AML was associated with maternal exposure to pesticides at work during pregnancy (OR = 1.94; 95% CI: 1.19−3.18; N = 1329 case and 12,141 control mothers), but was not associated with paternal exposure around the time of conception (OR = 0.91; 95% CI: 0.66−1.24; N = 1231 case and 11,383 control fathers). The modest association between paternal exposure to pesticides around the time of conception and ALL risk in the offspring was more evident in children diagnosed at an older age (5+ years old) and in children with the T-cell ALL subtype. The Childhood Leukemia International Consortium's findings of a significant association between maternal exposure to pesticides during pregnancy and AML risk in the offspring is consistent with previous reports.[75–77]

In a meta-analysis that accompanied the above-referenced pooled analysis, the Childhood Leukemia International Consortium investigators[74] found a positive association between maternal occupational exposures to pesticides during pregnancy and AML as well as between paternal occupational exposures around conception and T-cell ALL. This meta-analysis followed a systematic review and it included studies participating in the Childhood Leukemia International Consortium as well as non-participating, independent studies. Other investigators[78,79] have reported similar findings in independent meta-analyses, observing an association between prenatal maternal exposure to pesticides at work and childhood leukemia.

GIS-Estimated Ambient Pesticide Levels and Childhood Leukemia

Investigators from the California Childhood Leukemia Study have also evaluated the association between residential proximity to agricultural pesticide applications and childhood ALL.[55] For the families of 213 ALL cases and 268 matched controls, the authors linked residential histories together with agricultural pesticide use reports from the California Department of Pesticide Regulation, to assess whether living within a half-mile (0.8 km) of pesticide applications was associated with childhood leukemia risk. Elevated ALL

risk was associated with lifetime moderate exposure, but not high exposure, to certain physicochemical categories of pesticides, including organophosphates, chlorinated phenols, and triazines, and with pesticides classified as insecticides or fumigants.

Exposure to Herbicides and Childhood Leukemia

Epidemiological studies of childhood leukemia that use environmental or biological samples are relatively scarce. In one such study, investigators from the California Childhood Leukemia Study evaluated the relationship between childhood ALL and herbicide concentrations in settled dust as surrogates of herbicide exposures.[80] The herbicide analysis included 269 ALL cases 0–7 years of age and 333 healthy controls matched on date of birth, sex, and race/ethnicity. Dust samples were collected from carpets using a high-volume small-surface sampler or from participant vacuum cleaners. Concentrations of agricultural or professional herbicides (alachlor, metolachlor, bromoxynil, bromoxynil octanoate, pebulate, butylate, prometryn, simazine, ethalfluralin, and pendimethalin) and residential herbicides (cyanazine, trifluralin, 2-methyl-4-chlorophenoxyacetic acid, mecoprop, 2,4-dichlorophenoxyacetic acid, chlorthal, and dicamba) were used in logistic regression adjusting for age, sex, race/ethnicity, household income, year and season of dust sampling, neighborhood type, and residence type. The risk of childhood ALL was associated with dust levels of chlorthal; compared to homes with a measurement below the analytical limit of detection, odds ratios for the first, second, and third tertiles were 1.49 (95% CI: 0.82−2.72), 1.49 (95% CI: 0.83−2.67), and 1.57 (95% CI: 0.90−2.73), respectively (p value for linear trend = 0.05). No other herbicides were identified as risk factors of childhood ALL. Metayer et al.[80] postulated that 2,3,7,8-tetrachlorodibenzo-p-dioxin —a potent carcinogen and an impurity found in chlorthal—might be the causal agent underlying the observed association.

Limitations of Existing Research on Pesticides and Childhood Leukemia

Previous studies of the relationship between pesticide exposure and childhood leukemia, including pooled analyses conducted by the Childhood Leukemia International Consortium have utilized interviews to assess pesticide exposures to children and their parents.

Unfortunately, this study design has precluded investigators from identifying specific chemicals that may be causal agents underlying the observed associations. Findings from the California Childhood Leukemia Study seem to rule out organochlorine pesticides, such as DDT and chlordane, as the culpable pesticides underlying the observed association with childhood leukemia.[81]

Summary of Existing Research on Pesticides and Childhood Leukemia

Pooled analyses of data from studies around the world show a relationship between home pesticide use—especially of insecticides indoors—and the risk of childhood leukemia, which is confirmed by independent systematic reviews and meta-analyses. Pooled analyses of data from the Childhood Leukemia International Consortium demonstrate a relationship between prenatal maternal exposure to pesticides at work and the risk of childhood AML. Likewise, these findings were supported by independent systematic reviews and meta-analyses. Future studies will continue to exam relationships between pesticide exposures and the risk of specific leukemia subtypes and will also identify the specific pesticides which act as causal agents.

Parental Smoking

Parental tobacco use is another suspected risk factor for childhood leukemia that has received a lot of attention from researchers. Cigarettes contain numerous harmful constituents and tobacco use is well known to cause a variety of cancers in adults, including leukemia, via both direct and secondhand means of exposure. Likewise, there is evidence that parental cigarette smoking may also be associated with childhood cancer risk.

Investigators from the California Childhood Leukemia Study, for example, examined the association between parental smoking and childhood leukemia among 281 ALL cases, 46 AML cases, and 416 controls matched on age, sex, maternal race, and Latino ethnicity.[82] Maternal smoking was not associated with an increased risk of either ALL or AML. Paternal preconception smoking was significantly associated with an increased risk of AML (OR = 3.84, 95% CI: 1.04−14.17) and marginally associated with an increased risk of ALL (OR = 1.32, 95% CI: 0.86−2.04).

Pooled Analyses of Parental Cigarette Smoking and Childhood AML

The Childhood Leukemia International Consortium pooled individual parents' responses to interview questions about tobacco use from 14 case–control studies, representing 1300 AML and 15,000 controls.[83] Individual studies ascertained information about parental cigarette smoking at a number of stages of the child's development with varying degrees of specificity, including maternal smoking during pregnancy and paternal smoking during the three months before conception. The findings from the pooled analyses strengthened the existing evidence of modest associations between paternal cigarette smoking at any time and childhood AML, with dose–response relationships ($p < 0.05$). Maternal smoking during pregnancy was associated with an increased risk of AML for Latino children only.

Meta-analyses of Parental Cigarette Smoking and Childhood ALL

In 2009, a review of studies which evaluated the association between parental smoking and childhood leukemia revealed that 6 of 13 studies which had examined the relationship between paternal smoking and childhood leukemia reported significant positive associations.[84] Subsequently, Liu et al.[85] conducted a meta-analysis, which suggested that childhood ALL was associated with paternal smoking during preconception (OR = 1.25, 95% CI: 1.08−1.46) during pregnancy (OR = 1.24, 95% CI: 1.07−1.43), and after birth (OR = 1.24, 95% CI: 0.96−1.60), with a dose–response relationships observed between childhood ALL and paternal smoking before conception or after birth.

Parental Cigarette Smoking and Childhood Leukemia Subtypes

There is some evidence that the strength of the association between parental cigarette smoking and childhood leukemia varies by the cytogenetic subtype of the tumor. For example, Metayer and colleagues[27] reported that children with a history of paternal prenatal smoking combined with postnatal passive smoking had a 1.5-fold increased risk of ALL (95% CI: 1.01−2.23), compared to those without smoking history; but this joint effect was seen for B-cell precursor ALL with t (12;21) only (OR = 2.08, 95% CI: 1.04−4.16), not for high hyperdiploid B-cell ALL. Similarly, the

aforementioned pooled AML analysis conducted by the Childhood Leukemia International Consortium found that the highest smoking-related risk was seen for the myelomonocytic leukemia, a subtype common in treatment-related AML. Childhood leukemia comprises many subtypes and these findings demonstrate that each subtype may have a distinct set of characteristic risk factors corresponding to its unique etiology. As such, studies that evaluate subtype-specific chemical risk factors are the most likely to identify true relationships. Tellingly, when risk factors for each leukemia subtype are considered separately, higher odds ratios tend to be revealed.

Limitations of Existing Research on Tobacco Use and Childhood Leukemia

As was the case for pesticides above, previous studies of the relationship between parental tobacco use and childhood leukemia, including pooled analyses conducted by the Childhood Leukemia International Consortium, have utilized interviews to characterize parental smoking histories. This method of exposure assessment is useful, because it allows investigators to examine the effect of parental smoking at critical windows of a child's development and because it enables investigators to untangle the separate effects of cigarette smoking done by the mother, father, or other family members. Moreover, in contrast to other environmental exposures that are of interest to leukemia researchers, parents are conscious of the number of cigarettes they tend to smoke each day and they can help quantify their own exposures to tobacco. However, recall and reporting biases are still concerns, as parents (especially parents of children with leukemia) may not accurately remember or may not feel comfortable discussing their past tobacco use history during the interview. The lack of an observed association between maternal smoking during pregnancy and childhood leukemia may be related to this potential for bias when using interview data to assess exposure. Alternatively, the lack of an observed association may also be the result of smoking-induced adverse birth outcomes (e.g., fetal loss, still birth) that preclude the subsequent development of childhood leukemia, thereby biasing epidemiological findings.

Summary of Existing Research on Tobacco Use and Childhood Leukemia

Pooled analyses of data from studies around the world show a relationship between paternal smoking before conception and AML risk. Likewise, these findings were supported by an independent systematic review and meta-analysis. Future studies will provide an increased focus on the role of prenatal maternal smoking on leukemia risk in Latino children and will pool data from the Childhood Leukemia International Consortium for an analysis of smoking-related ALL risk.

Chemicals Found in Paints, Petroleum Solvents, and Traffic Emissions

A collection of studies have investigated the associations between childhood leukemia and a loosely-related group of environmental exposures including paint, petroleum solvents, and vehicle traffic. These general exposure categories share characteristic chemical signatures, including the leukemogenic agent, benzene.

Investigators from the California Childhood Leukemia Study examined the association between childhood leukemia and the use of paint or petroleum solvents in the home before birth and in early childhood. The analysis included 550 ALL cases, 100 AML cases, and one or two controls per case individually matched for sex, age, Latino ethnicity, and race. Conditional logistic regression techniques were used to adjust for income. Home paint exposure was associated with ALL risk (OR=1.65; 95% CI: 1.26−2.15). The association was restricted to ALL with t(12;21) (OR = 4.16, 95% CI: 1.66−10.4). Home use of petroleum solvents was associated with an increased risk for AML (OR = 2.54, 95% CI: 1.19−5.42) but not ALL.

Pooled Analyses of Home Exposure to Paint and Childhood Leukemia

The Childhood Leukemia International Consortium pooled individual responses to questions about home paint exposures from eight case–control studies.[86] Data were harmonized to account for inter-study differences in reported paint types, time periods of exposure, and leukemia subtypes and a compatible format was used in logistic regression. ALL risk was associated with home paint exposure in the 1–3 months before conception (OR = 1.54; 95% CI: 1.28−1.85; $N = 3002$ cases and 3836 controls), during pregnancy (OR = 1.14; 95% CI: 1.04−1.25; $N = 4382$ cases and 5747 controls), and after birth (OR = 1.22; 95% CI: 1.07−1.39; $N = 1962$ cases and 2973 controls). The

risk was greater if someone other than the parents did the painting, for example, a professional painter, which is indirect evidence of a dose–response relationship. The paint–leukemia association was stronger for ALL with t(12;21) than for other cytogenetic subtypes of leukemia.

Meta-analyses of Parental Occupational Exposures to Paint, Solvents, Vehicle Exhaust, and Childhood Leukemia

As an extension of the research that has identified an association between exposure to paint in the home and childhood leukemia, meta-analyses have demonstrated associations between childhood leukemia risk and parental exposures in related occupational settings.

For example, a meta-analysis summarizing the existing literature on parental occupational exposures and childhood cancer found that relationships between childhood leukemia and paternal exposure to paints, solvents (e.g., benzene and trichloroethylene), and employment in motor vehicle-related occupations were among the strongest of the more than 1000 occupation–childhood cancer combinations that were evaluated.[87] The studies that comprised this meta-analysis had several limitations related to the quality of the exposure assessment including the small numbers of exposed cases studied, the likelihood of false positives due to multiple comparisons, and possibility of publication bias. Despite these limitations, this meta-analysis provides evidence that when parents are exposed to certain chemicals at work, the effects are harmful to their offspring.

Another meta-analysis summarized findings from 28 case–control studies and one cohort study that investigated the relationship between maternal occupational exposures and childhood leukemia in the offspring using 16,695 participating cases and 1,472,786 controls.[88] ALL risk was associated with maternal paint exposures at work during pregnancy (OR = 1.23, 95% CI: 1.02−1.47), with maternal solvent exposures at work during pregnancy (OR = 1.25, 95% CI: 1.09−1.45), and with maternal petroleum exposure at work during pregnancy (OR = 1.42, 95% CI: 1.10−1.84). No publication bias was found in this meta-analysis and consistent results were observed for subgroup and sensitivity analyses. However, an analysis of parental occupational paint exposures pooled from 13 case–controls studies revealed no increased risk for childhood ALL or AML.[89]

Carlos-Wallace et al.[90] conducted meta-analyses to evaluate the risk of childhood leukemia associated with parental occupational exposure to benzene and solvents, as well as household use of products containing benzene and solvents. Maternal occupational exposure to benzene was associated with increased risk of childhood leukemia, yielding a summary relative risk of 1.71 (95% CI: 0.91−3.24). Use of household products containing benzene, aromatic hydrocarbons, solvents, or petroleum, was also associated with childhood leukemia risk, with a summary relative risk of 1.67 (95% CI: 1.01−2.78). The above associations were stronger for AML than for ALL and strongest for women who were exposed during pregnancy.

The California Childhood Leukemia Study examined the relationship between occupational exposure to organic solvents and the risk of childhood leukemia.[91] Occupational histories were obtained via interview using 19 task-based job modules from parents of children with ALL ($N = 670$), children with AML ($N = 104$), and healthy control children ($N = 1021$). Logistic regressions were used to estimate odds ratios adjusted for socio-demographic factors. Among children with non-Latino fathers, none of the exposures evaluated were associated with risks of ALL and AML. In contrast, exposure to any organic solvents in Latino fathers was associated with an increased risk of childhood ALL (OR = 1.48, 95% CI: 1.01−2.16); in multivariable analyses and the odds ratio for exposure to chlorinated hydrocarbons, in particular, was elevated (OR = 2.28, 95% CI: 0.97−5.37), whereas risk estimates for other exposures—aromatic hydrocarbons, glycol ethers, and other hydrocarbon mixtures—were close to one. One common industrial chlorinated hydrocarbon, which might be the causal agent underlying the observed association, is trichloroethylene (TCE). As with other analyses that rely on interview-derived exposure data, the specific chlorinated hydrocarbon or mixture of chlorinated hydrocarbons responsible for the associations observed in these studies is not known. A large majority of mothers were not exposed to chemicals at work, and no associations were reported for risk of childhood ALL and AML.

Traffic-Related Air Pollution and Childhood Leukemia

Three recent meta-analyses independently demonstrated an association between childhood leukemia and postnatal traffic exposure.[90,92,93] Boothe et al.[92]

combined findings from seven studies to estimate that childhood leukemia was positively associated with postnatal traffic density near the residence (OR = 1.53, 95% CI: 1.12−2.10). There was no association between childhood leukemia and prenatal traffic exposures.

Filippini et al.[93] combined 6 ecologic and 20 case–control studies that had assessed home exposure to traffic-related pollution by estimating traffic density in the neighboring roads, by estimating the vicinity to gas stations, or by modeling ambient nitrogen dioxide and benzene concentrations with GIS. Among high-quality studies that used traffic density to assign exposure, no significant increase in childhood leukemia risk was observed, even in the highest exposure category (OR = 1.07, 95% CI: 0.93−1.24). Among studies that used NO_2 estimates as the measure of exposure, there was a marginally significant association with childhood leukemia (OR = 1.21, 95% CI: 0.97−1.52), which was stronger for ALL (OR = 1.21, 95% CI: 1.04−1.41) than for AML (OR = 1.06, 95% CI: 0.51−2.21). Among studies that used benzene estimates as the measure of exposure, there was a stronger association with AML (OR = 2.28, 95% CI: 1.09−4.75) than ALL (OR = 1.09, 95% CI: 0.67−1.77). Observed associations between childhood leukemia and exposure to traffic pollution were generally stronger for exposures in the postnatal period compared to the prenatal period.

Carlos-Wallace et al.[90] conducted meta-analyses to evaluate the risk of childhood leukemia associated with traffic density and traffic-related air pollution. Both measures of traffic were associated with childhood leukemia; the summary relative risk was 1.48 (95% CI: 1.10−1.99). The relationship was stronger for AML than for ALL and stronger in studies that involved detailed models of traffic pollution than in those that estimated traffic density.

The findings from these three meta-analyses support a link between ambient exposure to traffic pollution and childhood leukemia risk, particularly due to benzene.

Benzene as the Potential Causal Agent

Once again, most of the studies that have evaluated the risk of childhood leukemia associated with paint, petroleum solvents, or traffic density are based on parent interviews. As such, it is challenging to identify the specific causal agent underlying the observed associations in these existing studies. Benzene is one potential culprit as it is a well-known leukemogen that is present in oil-based paints, petroleum solvents used in occupational and residential settings (e.g., in paint thinner), and vehicle exhaust. However, given that childhood leukemia subtype analyses have yielded disparate results depending on the specific exposure measure that was used in the meta/pooled analysis, it is also possible that this loose grouping of chemical exposures actually comprises several distinct chemical risk factors for leukemia. For example, in addition to benzene, other chemicals, such as 1,3-butadiene, styrene, xylene, and polycyclic aromatic hydrocarbons (PAHs) might also play a role in some of these observed relationships. The recent development of a mouse model for childhood leukemia will enable investigators to evaluate the role of specific chemical risk factors in the etiology of childhood leukemia.

Summary of Existing Research on Paint, Solvents, Traffic and Childhood Leukemia

Pooled analyses of data from studies around the world show a relationship between home exposure to paint and ALL risk. These findings were indirectly supported by a variety of systematic reviews and meta-analyses, which showed evidence of relationships between childhood leukemia and exposure to petroleum solvents (at home and at the mother's work) and traffic (as measured by surrounding traffic density and modeled concentrations of traffic-related air pollutants). Several possible chemical risk factors may explain the observed association, including the well-known leukemogen, benzene.

Persistent Organic Pollutants

Epidemiological studies of childhood leukemia that use environmental or biological samples are relatively scarce. A series of analyses conducted as part of the California Childhood Leukemia Study have evaluated the relationship between childhood ALL and chemical concentrations in settled dust collected from participating homes as surrogates for chemical exposures.

Polycyclic Aromatic Hydrocarbons (PAHs) and Childhood Leukemia

The California Childhood Leukemia Study evaluated the relationship between childhood ALL and PAH concentrations in settled dust.[94] As part of this population-based case–control study, dust samples were collected from 251 ALL cases and 306 birth-certificate controls using a high-volume small-surface

sampler (N = 185 cases, 212 controls) or directly from participants' household vacuum cleaner bags (N = 66 cases, 94 controls). Logistic regression was used to evaluate the relationship between ALL risk and log-transformed concentrations of 9 individual PAHs, the summed PAHs, and the summed PAHs weighted by their carcinogenic potency (the toxic equivalence) while adjusting for demographic characteristics and duration between diagnosis/reference date and dust collection. Among participants with dust samples collected by high-volume small-surface sampler, risk of ALL was not associated with increasing concentration of any PAHs. However, among participants with dust samples collected by participants' vacuum cleaners, a positive association was observed between ALL risk and increasing concentrations of benzo[a] pyrene (OR = 1.42, 95% CI: 0.95−2.12), dibenzo[a,h] anthracene (OR = 1.98, 95% CI: 1.11−3.55), benzo[k] fluoranthene (OR = 1.71, 95% CI: 0.91−3.22), indeno [1,2,3-cd]pyrene (OR = 1.81, 95% CI: 1.04−3.16), and the toxic equivalents (OR = 2.35, 95% CI: 1.18−4.69). The observed association between ALL risk and PAH concentrations among participants with dust collected by vacuum suggests that PAH exposure may increase the risk of childhood ALL; however, understanding the reasons for the different results by sample type requires further scrutiny.

PAHs are byproducts of incomplete combustion that are found at high concentrations in cigarette smoke and vehicle exhaust. PAHs, especially dibenzo[a,h]anthracene, are potent human carcinogens. As such, it is possible that one PAH or a combination of PAHs may be the causal agent(s) responsible for the observed associations between parental smoking and childhood leukemia or between traffic density and childhood leukemia.

Polychlorinated Biphenyls (PCBs) and Childhood Leukemia

The California Childhood Leukemia Study has also evaluated the relationship between childhood ALL and levels of six PCBs—industrial chemicals that are probable human carcinogens and immune system disruptors—in settled dust.[81] The PCB analysis included 184 ALL cases 0–7 years of age and 212 birth certificate controls matched to cases by birth date, sex, race, and Latino ethnicity. Dust samples were collected from the room where the child spent the most time using the high-volume small-surface sampler. In

homes where any PCB was detected in the dust, there was a 2-fold increased risk of ALL (OR = 1.97, 95% CI: 1.22−3.17). When considering the sum of the six PCBs analytes, compared to those in the lowest quartile of Σ_6PCBs, the highest quartile was associated with about a 3-fold risk of ALL (OR = 2.78, 95% CI: 1.41−5.48). The risk of ALL was positively associated with increasing concentrations of PCB congeners 118, 138, and 153 in dust. The associations with PCBs were stronger among non-Latino whites than among Latinos despite the presence of a similar distribution of PCB levels among controls in each racial/ethnic groups.

Polybrominated Diphenyl Ethers (PBDEs) and Childhood Leukemia

Along the same lines, the California Childhood Leukemia Study evaluated the relationship between childhood ALL and levels of PBDEs—chemical flame retardants—in settled dust.[95] PBDEs are structural analogs to PCBs that also cause immune system perturbations. The PBDE analysis included 167 ALL cases 0–7 years of age and 214 birth certificate controls matched on date of birth, sex, and race/ethnicity. Dust samples were collected from carpets in the room where the child spent the most time while awake using a high-volume small-surface sampler or by sampling from participants' household vacuum cleaners. Concentrations of 14 PBDE congeners were measured including constituents of the Penta- (28, 47, 99, 100, 153, 154), Octa- (183, 196, 197, 203), and Deca-BDEs commercial mixtures (206–209). Odds ratios were calculated using logistic regression, adjusting for demographics, income, year of dust collection, and sampling method. Comparing the highest to lowest quartile showed no association with ALL for summed Penta- (OR = 0.7, 95% CI: 0.4−1.3), Octa- (OR = 1.3, 95% CI: 0.7−2.3), or Deca-BDEs (OR = 1.0, 95% CI: 0.6−1.8). Comparing homes in the highest tertile to those below the analytical limit of detection, revealed a significant positive association with ALL risk for BDE-196 (OR = 2.1, 95% CI: 1.1−3.8), BDE-203 (OR = 2.0, 95% CI: 1.1−3.6), BDE-206 (OR = 2.1; 95% CI: 1.1−3.9), and BDE-207 (OR = 2.0, 95% CI: 1.03−3.8).

Interestingly, the significant associations with ALL risk observed in this analysis were for minor PBDE congeners that are found in dust at relatively low concentrations; whereas the most abundant PBDE congeners (e.g., BDEs 47, 99, and 209) were not associated with ALL risk. These low-concentration

PBDE congeners were measured with less analytical precision than their more common analogs, because the measured values were relatively close to the analytical limit of detection. In other words, the low-level PBDE congeners that were associated with ALL risk in this analysis were the ones measured with the least precision and, therefore, the ones with the greatest potential for a spurious finding. Still, there may be a plausible biological mechanism to explain the inconsistency of the risk estimates between PBDE congeners, as toxic and carcinogenic effects are expected to differ by congener.[48,96] The fact that PCBs and PBDEs have a similar chemical structure lends credence to the hypothesis that these chemicals may be acting via the same mechanism of action, for example, immune dysregulation.

Strengths of Existing Research on Persistent Organic Pollutants and Childhood Leukemia

Unlike much of the research described in this section, one strength of the existing research on persistent organic pollutants and childhood leukemia is the use of objective environmental measurements to assess chemical exposures, rather than interviews. Not only does this reduce the likelihood of recall bias, but it also allows investigators to identify specific chemicals as causal agents in the etiology of leukemia. Recognizing causal agents can be the first step in planning a successful intervention that will reduce future incidence of leukemia.

Limitations of Existing Research on Persistent Organic Pollutants and Childhood Leukemia

The relative stability of persistent organic pollutants in settled dust allows for exposure measurements that have limited temporal variability. This stability is a benefit of the sampling technique, because the resulting measurements represent long-term average levels of chemical contamination, which can be useful when trying to estimate past chemical exposures. However, this stability also obscures short-term fluctuations in chemical levels that might be important to investigators who want to identify critical windows of a child's development when chemical exposures are especially harmful. That is, measuring chemical levels in settled dust will not enable a researcher to distinguish the leukemogenic effect of prenatal vs. postnatal chemical exposures, for example.

Moreover, children are exposed to chemicals through several other pathways in addition to the ingestion of contaminated settled dust. In particular, the ingestion of settled dust plays a relatively minor role in children's exposure to PCBs compared to the ingestion of PCB-contaminated food. This is owing to the bioaccumulative nature of PCBs and the fact that they have been banned from production in the U.S. for several decades. Indeed, it is a testament to the persistence of these hazardous chemicals that they can still be so readily measured inside homes. In these analyses, the design of the California Childhood Leukemia Study did not account for chemical exposures received via the inhalation of contaminated air, the ingestion of contaminated food, or any other pathways. As such, the dust measurements are limited surrogates for total chemical exposure.

To date, the California Childhood Leukemia Study has only utilized dust samples to identify risk factors for ALL, the most common leukemia subtype. There is an insufficient number participants with dust samples available to analyze the risk of AML or to stratify by cytogenetic subtype.

Also of some concern is the fact that the subset of California Childhood Leukemia Study participants who were eligible for and consented to dust sampling had higher socioeconomic status than the full California Childhood Leukemia Study population and its underlying source population, the State of California. As such, the findings from these studies may not be representative of the general population. Fortunately, data from the California Childhood Leukemia Study indicates that both the case families and the control families participating in dust sampling had elevated socioeconomic status, which limits the risk of differential selection bias.

Perhaps the most important limitation of these studies is that they have not been substantiated by independent investigators. Whereas many members of Childhood Leukemia International Consortium and other studies have collected interview data about pesticides, smoking, and paint; very few have measured chemicals in environmental samples. As such, there are no meta-analyses or pooled analyses published showing the risk of ALL associated with exposure to persistent organic pollutants, as there have been previously for the other, more well-studied, ALL risk factors that were discussed above.

Summary of Existing Research on Persistent Organic Pollutants and Childhood Leukemia

Three novel findings from the California Childhood Leukemia Study suggest that home exposures to persistent organic pollutants, such as PAHs, PCBs, and PBDEs, are associated with an increased risk of ALL. Future studies should attempt to interrogate these associations to replicate or refute their veracity.

Radiation

In utero exposure to low-dose radiation delivered from medical x-rays is one of the few widely-recognized risk factors for childhood leukemia.[97] While the prevalence of fetal exposure to x-rays *in utero* has decreased markedly following radiation protection standards, the use of medical imaging procedures, including computerized tomography (CT) scans,[98] has increased drastically during the past 30 years. In fact, CT scans are now the largest medical sources of radiation in economically developed countries.[99] In addition, CT scans deliver an effective dose of radiation that is up to several hundred times stronger than conventional x-rays (depending on the target organ), which has led to major increases in the per capita radiation dose from medical sources (up 600% in the US since 1980).[99] The carcinogenic effects of CT scans have not been established, but exposures to children are especially concerning because they are more sensitive to radiation-induced cell damage.[97]

Findings on children's postnatal exposure to low-dose medical radiation and the risk of childhood leukemia are inconsistent, with modest positive associations reported in some studies, but not all.[97,99] Risk prediction models have anticipated increased risks of childhood leukemia following CT scans, but these models were criticized for extrapolating from the effects of much higher levels of radiation that were observed in the Life Span Study of atomic-bomb survivors.[100–102] Only one case–control study to date has published results on self-reported history of CT scans showing no increased risk of childhood ALL, based on small numbers of exposed children.[103] Recent cohort studies with access to medical data in Europe,[101,104–106] Australia,[107] and the US,[102] have reported small to moderate increases in the risk of leukemia in children exposed to CT scans; findings, however, were based on small number of excess cases ranging from 6 to 74. Pearce et al.[106] conducted a retrospective cohort study of 178,604 UK children

and young adults with CT scans from 1985 to 2002. Patients were followed up through 2008 and linked with 74 leukemia diagnoses and 135 brain cancer diagnoses. A cumulative dose of 50 milligray was estimated to triple the risk of childhood leukemia within 10 years of the first CT scan; likewise, a cumulative dose of 60 milligray tripled the risk of brain cancer.[106] The main criticism of the study was the lack of an unexposed control group. Other cohort studies are underway[108] including a pooled European study (EPI-CT)[104] of about one million subjects (age 0–21 years). Although the number of excess childhood leukemia cases is still likely to be low (estimated to be approximately 60–100), this study will obtain more precise exposure information than previously possible, including individual doses of radiation for each organ.

Confounding by indication (reverse causation) is also a concern in studies of the relationship between medical radiation and childhood leukemia. In a French cohort study, the analyses accounting for child's cancer-predisposing factors (mostly rare genetic conditions in less than 2% of children) showed a modest impact on the risk of childhood leukemia associated with CT scans.[109] This was consistent with a case–control study of prenatal x-rays showing an overall 13% reduction in relative risk of childhood cancers, after adjusting for maternal illnesses during pregnancy.[110] Others have argued that cancer-predisposing conditions may instead act as effect modifiers.[111–113] Overall, despite methodological challenges, epidemiologic studies so far mostly support an association between postnatal exposure to CT scans and childhood leukemia, while results for lower dose x-rays are less consistent.

Pooled analyses reported that exposure to high levels of extremely low-frequency-electromagnetic fields over 0.3 or 0.4 μT is associated with an increased risk of childhood leukemia,[114,115] which was the basis to classify extremely low-frequency-electromagnetic fields as possibly carcinogenic to humans (Group 2B).[116] Methodological issues including possible confounding, selection bias, and measurement errors have been put forward as an alternate explanation for the observed association, and animal studies are ongoing to identify possible biological mechanisms.[117,118] If the association between extremely low-frequency-electromagnetic fields and childhood leukemia is causal, the overall population attributable risk has been estimated to be 1.9% (1–4% depending on the countries).[117,118]

Future Steps in Identifying Environmental Causes of Childhood Leukemia

A multitude of studies on the environmental causes of childhood leukemia, including those conducted by our research team and others that are described above, have led to progress in identifying the etiological roles of environmental exposures in childhood leukemia. However, much work remains to be done. As discussed, several of the observed associations between chemical exposures and childhood leukemia are derived from interview data, an approach which can limit an investigator's ability to identify specific chemical risk factors for childhood leukemia. As such one goal of future research will be to understand which specific causal agents underlie previously observed associations. For example, in collaboration with the National Cancer Institute, the California Childhood Leukemia Study is conducting a study to measure glyophosate in participating homes. This study will follow-up on a previously observed association between reported residential herbicide use and childhood ALL. The California Childhood Leukemia Study has observed associations between childhood leukemia risk and levels of certain PCBs, PBDEs, PAHs, and herbicides in settled dust. These unique findings need to be confirmed in independent studies, preferably in ones that use a distinct method for assessing children's exposure to chemicals.

As an alternative approach for identifying the causal agents in childhood leukemia, the Center for Integrative Research on Childhood Leukemia and the Environment will employ a mouse model of ALL with t(12;21) to test the carcinogenic potential of a variety of chemicals, including, for example, compounds that comprise the broadly-defined groups of pesticides, solvents, or traffic pollutants. The mouse model will also be helpful in identifying mechanisms of action for the chemical risk factors of childhood leukemia. In fact, this is a central goal of the Center, as immunological factors and epigenetics will both be interrogated as possible cancer mechanisms. Moreover, state-of-the-science untargeted analytical approaches will allow investigators to identify novel chemical risk factors for childhood leukemia, by examining relationships between exposure and disease that have not been considered, to date.

Dietary Risk Factors for Childhood Leukemia

Introduction

Diet has been linked to several cancers in adults and children.[119] These observations may be explained by various biological mechanisms such as exposure to dietary mutagens, mutagenesis due to nutrient deficiencies, and intake of micronutrients and other dietary components that may protect against the development of cancer by supporting cellular integrity, reducing inflammation and improving immune response.[120–122] A growing body of research also suggests that the influence of particular nutrients on epigenetic processes may contribute to carcinogenesis.[123]

The role of the intrauterine environment is crucial in determining risk of disease later in life, and the "developmental origins of health and disease" hypothesis posits that nutritional and environmental exposures *in utero* permanently alter gene expression and the physical development of the fetus through a process called "programming."[124,125] This hypothesis is likely central to the development of childhood leukemia, as well. Indeed, maternal nutrition during pregnancy may be related to both the occurrence of primary and secondary oncogenic events that lead to leukemia in the offspring. Subsequently, a child's diet during the early years of life is likely to also play an important role in leukemogenesis. Breastfeeding has been consistently found to reduce leukemia risk in children, via intake of essential nutrients not readily available in newborns and due to the resulting beneficial effects of immune system priming. In contrast, the impact of diet —both the mother's and the child's—on childhood leukemia has been less studied.

Here we provide an overview of the current knowledge about the associations between diet and childhood leukemia.

> *Diet quality is a comprehensive measure of nutritional status, and healthy maternal diet at the time of conception and during pregnancy is linked to a reduced risk of leukemia in the offspring.*

Maternal Diet

Epidemiologic studies examining the relationship between maternal diet during pregnancy and the risk of childhood leukemia, have been mostly conducted in developed countries. Exposures of interest varied to include food groups (e.g., fruits, vegetables, proteins), micronutrients from dietary and supplement sources (e.g., folate and vitamins), food sources of topoisomerase II inhibitors (known risk factors for treatment-related leukemia), consumption of coffee, tea, and alcohol, and holistic measures of a healthy diet.

Food Groups

Fruits and vegetables contain a variety of vitamins and minerals that have anti-cancer, anti-proliferative, and anti-inflammatory effects,[123] and the consumption of fruits and vegetables has been associated with a reduced risk of various types of cancer.[119] Some food groups, in particular fruits and vegetables, have been associated with childhood leukemia risk in several studies. Research has found statistically significant negative associations between maternal consumption of fruits and vegetables and risk of childhood ALL,[126–128] and one study found significant or near-significant inverse linear trends between the risk of infant leukemia and maternal consumption of fresh fruits and vegetables, especially for specific ALL subtypes.[129] Negative associations have also been observed for childhood leukemia and maternal consumption of other food groups, specifically protein sources such as fish and seafood[128] as well as beans and beef.[126,127] One study demonstrated an increased risk of ALL with increased maternal consumption of meat or meat products and sugars or sirups.[128]

Folate and Other One-Carbon Metabolism Nutrients

The one-carbon metabolism cycle is critical for the synthesis of DNA and RNA, the conversion of homocysteine to methionine, and the formation of s-adenosylmethionine (SAM), the primary methyl donor for DNA, RNA, proteins, and lipids.[130] Folate and other B vitamins are important cofactors in the one-carbon metabolism cycle,[130] and maternal folic acid supplementation during pregnancy has been

> *Reduced risks of childhood leukemia are associated with adequate folate before conception and early in pregnancy, breastfeeding, and early exposure to routine childhood infections.*

demonstrated to influence DNA methylation in children.[131] Maternal folic acid supplementation also protects against some childhood diseases, such as neural tube defects.[132] High folate intake has been associated with reduced risk of breast[133] and colorectal[134] cancer and increased risk of prostate cancer[135] among adults, whereas meta-analyses have indicated no effect of folic acid supplementation on adult cancer incidence.[135–137] Maternal intake of folate and other nutrients involved in one-carbon metabolism may influence childhood leukemia risk due to the importance of these nutrients for DNA synthesis and repair, chromosomal integrity, and epigenetic processes that determine gene expression and influence cancer risk, including histone modification, levels of non-coding RNAs, and DNA methylation.[123,130]

Practices of prenatal folic acid supplementation have varied substantially across countries and over time, and individual epidemiologic studies that have evaluated the relationship between maternal folate intake through supplements and the risk of childhood ALL have yielded mixed findings. However, a recent Childhood Leukemia International Consortium analysis, the largest to date, pooled original interview data from 12 studies (representing 6963 ALL, 585 AML, and 11,635 healthy controls) to observe that folic acid supplementation was protective against childhood leukemia.[138] Folic acid taken before conception or during pregnancy—with or without intake of other vitamins—was associated with a reduced risk of childhood ALL (OR = 0.80, 95% CI: 0.71−0.89) and AML (OR = 0.68, 95% CI: 0.48−0.96), after adjustment for study center.[138] Interestingly, the reduced risks were seen only among women with low and medium education levels—a surrogate marker for low socio-demographic status and possibly for a low-quality (low-folate) diets—suggesting that women who enter the peri-conception period with inadequate folate/vitamin levels would benefit the most from prenatal folate and vitamin supplementation.

Only a small number of studies, however, have examined the role of folate intake from food or the role of any other nutrients involved in the one-carbon metabolism cycle in the development of childhood leukemia. In addition, there has been only limited

consideration of the role of maternal diet on risk of AML. A case–control study in Australia found some evidence that higher dietary intakes of folate and B_{12} from food in the last 6 months of pregnancy were associated with a decreased risk of ALL, whereas higher dietary intakes of vitamin B_6 were unexpectedly associated with an increased risk of ALL.[139] Previous analyses from a subset of the California Childhood Leukemia Study population examined the total intake of folate, vitamin B_6 or vitamin B_{12} from both diet and supplements, and found no associations with ALL.[126,127,140] However, in a recent and expanded California Childhood Leukemia Study analysis (681 ALL cases, 103 AML cases, and 1076 controls) that employed principal components analysis to account for the high correlations between nutrients, higher maternal intake of one-carbon metabolism nutrients from food and supplements was associated with a reduced risk of ALL (OR = 0.91, 95% CI: 0.84−0.99) and possibly AML (OR = 0.83, 95% CI: 0.66−1.04).[141] The association of ALL with nutrient intake exclusively from food (excluding supplements) was similar to the association of total nutrient intake from food and supplements, both in the study population overall and within racial/ethnic groups. However, high intake of B vitamins from supplements (versus none) was associated with a statistically significant reduced risk of ALL in children of Latinas (OR = 0.36 95% CI: 0.17−0.74), but not in children of non-Latina white women (OR = 0.76, 95% CI: 0.50−1.16) or Asian women (OR = 1.51, 95% CI: 0.47−4.89).[141] Racial/ethnic differences in nutrient intake and in genetic polymorphisms in the one-carbon (folate) pathway may partly explain the observed difference in leukemia risk.

In a biomarker analysis conducted as part of the California Childhood Leukemia Study, folate concentration measured in neonatal blood samples were similar between children with leukemia (313 ALL cases and 44 AML cases) and 405 controls, suggesting that folate levels at the end of pregnancy did not affect leukemia risk.[63] The study was conducted in California where most pregnant women used prenatal vitamin supplementation, therefore limiting the ability to detect an association. Moreover, late pregnancy may not be the period of a child's development during which a beneficial effect of folic acid and multivitamins, is critical to leukemia risk. However, this explanation would not be consistent with observations from the large pooled analyses of the Childhood Leukemia International Consortium that showed reduced risks

of ALL and AML associated with self-reported supplementation during each trimester of the pregnancy.[138]

Newborn and child serum-nutrient levels are influenced by many factors, including maternal and child genetic polymorphisms.[142] Many studies have found significant associations between single nucleotide polymorphisms (SNPs) in folate-related genes, such as *MTHFR* variants, and childhood leukemia; but, there are inconsistencies in the specific SNPs that have been identified across studies.[140,143–147] A study examining the largest number of genes and SNPs in the folate pathway found statistically significant associations between SNPs in genes *CBS*, *MTRR*, and *TYMS/ENOFS* (but not *MTHFR*) and childhood ALL.[140] Levels of maternal folate intake during pregnancy, and child's Latino ethnicity were found to modify some of these associations.[140] Other studies, however, did not report such interactions.[144,148,149] Key findings regarding folate intake and other vitamins are summarized in Table 2.

Topoisomerase II Inhibitors

The use of topoisomerase II inhibitors (a nuclear enzyme involved in DNA replication) in cancer chemotherapy has long been known to be associated with common *MLL* gene translocations that are characteristic of therapy-related AML.[150] Consequently, it was hypothesized that topoisomerase inhibitors may be involved in the etiology of infant leukemia, because this subtype commonly involves the same *MLL* gene translocation that has been identified in these therapy-related leukemias.[151] Aside from chemotherapeutic agents, topoisomerase inhibitors are found in diverse sources, including herbal medicines, quinolone antibiotics, certain types of laxatives, and pesticides.[152] Certain dietary sources also contain topoisomerase inhibitors including, but not limited to, tea, coffee, wine, and certain fruits and vegetables.[152] Recent laboratory studies, however, suggest that tea, wine, and cocoa do not inhibit topoisomerase activity *in vitro* and thus are unlikely to increase the risk of *MLL* translocations.[153]

A small exploratory study examining maternal exposure to topoisomerase inhibitors during pregnancy and the risk of childhood leukemia found an increased risk of AML with increasing topoisomerase II inhibitor exposure (OR = 10.2; 95% CI: 1.1−96.4; N = 29 cases for high exposure), but no increased risk for ALL

TABLE 2. Association between folate and other vitamins and risk of childhood leukemia: selected case–control studies

Population	No. of cases	Source of vitamins	Period of interest	OR (95% CI)

Childhood Leukemia International Consortium.[138]	6963 ALL 585 AML	Maternal supplement	Prenatal	Folate only
				  ALL: OR = 0.80 (0.78, 0.92)
				  AML: OR = 0.68 (0.48–0.96)
				Any vitamins
				  ALL: OR = 0.85 (0.80, 0.94)
				  AML: OR = 0.92 (0.75–1.14)

Australia.[139]	333 ALL	Maternal diet	Pregnancy	Folate
				  OR_{Q2} = 0.68 (0.44, 1.06)
				  OR_{Q3} = 0.58 (0.37, 0.91)
				  OR_{Q4} = 0.44 (0.27, 0.71)
				  OR_{Q5} = 0.70 (0.44, 1.12)
				  p-trend = 0.05
				B_{12} vitamin
				  OR_{Q2} = 0.72 (0.47, 1.10)
				  OR_{Q3} = 0.79 (0.71, 1.21)
				  OR_{Q4} = 0.85 (0.71, 1.31)
				  OR_{Q5} = 0.49 (0.71, 0.77)
				  p-trend = 0.02
				B_6 vitamin
				  OR_{Q2} = 1.04 (0.67, 1.62)
				  OR_{Q3} = 1.15 (0.74, 1.81)
				  OR_{Q4} = 1.28 (0.82, 2.00)
				  OR_{Q5} = 1.60 (1.02, 2.51)
				  p-trend = 0.03

California.[141]	681 ALL 103 AML	Maternal diet & supplements	Peri-conception	One-carbon metabolism nutrients (i.e., folate, B vitamins) ALL: OR_{PC} = 0.91 (0.84, 0.99) AML: OR_{PC} = 0.91 (0.66, 1.04)
California.[63]	317 ALL 44 AML	Blood levels	Neonatal	Hemoglobin concentration of folate at birth No difference in between ALL, AML, and controls

ALL = acute lymphoblastic leukemia; AML = acute myeloblastic leukemia; Q = quintile; PC = principal component for one-carbon metabolism nutrients.

(OR = 1.1; 95% CI: 0.5–2.3; N = 82).[151] Subsequent studies confirmed a positive relationship between maternal dietary intake of topoisomerase II inhibitors and risk of infant AML with a MLL gene translocation, but have found no association between dietary intake of topoisomerase II inhibitors and risk of other subtypes of infant AML or any type of ALL.[126,129]

Coffee, Cola, and Tea

An early case–control study of 280 cases and 288 hospitalized controls found an increased risk of ALL among children of mothers reporting coffee consumption more than four cups a day during pregnancy (OR = 2.4; 95% CI: 1.3–4.7 for 4–8 cups; and OR = 3.1, 95% CI: 1.0–9.5 for >8 cups), with similar ORs observed for acute non-lymphoblastic leukemia that did not reach statistical significance.[154] Subsequent case–control studies have found maternal

consumption of coffee during pregnancy to be associated with an increased risk of ALL, AML, and possibly infant leukemia, while others have failed to find an association, as summarized in a recent meta-analysis.[155] There is some evidence from these studies that the increased risk of leukemia with maternal coffee consumption may be more pronounced among children born to non-smoking mothers.[156,157] Similarly, cola-based drinks have been associated with increased risk of childhood ALL (summary OR = 1.31, 95% CI: 1.09–2.47), while reduced risks have been reported with maternal tea consumption during pregnancy (summary OR = 0.85, 95% CI: 0.75–0.97).[155] A general limitation of those studies is the lack of information on the type of drinks (e.g., caffeinated or not, green or black tea), which contain different nutrients and other compounds with either anti- or pro-carcinogenetic properties.

Alcohol

Maternal alcohol intake before or during pregnancy has been hypothesized to influence childhood leukemia risk by altering immune function or by teratogenic effects on cell differentiation.[158] Alcohol is also an antagonist to folate metabolism and methionine synthase and may modify DNA methylation status in interaction with folate levels.[159] A systematic review and meta-analysis of 21 case–control studies found that alcohol intake during pregnancy was associated with AML (summary OR = 1.56, 95% CI: 1.13−2.15 produced from 9 studies comprising 731 cases) but not with ALL (summary OR = 1.10, 95% CI: 0.93−1.29 produced from 11 studies comprising 5108 cases).[159] Heterogeneity between studies was explained in part by some studies[160,161] that demonstrated a negative association of childhood leukemia with maternal alcohol consumption during pregnancy. Repeating the meta-analysis by subgroup of alcohol indicated an increased risk of AML associated with reported consumption of wine but not beer or spirits, providing some additional support for the topoisomerase II hypothesis.[159] For ALL, there was an association between maternal consumption of spirits during pregnancy, but not beer or wine.[159] One subsequent study supported the finding of an increased risk of AML with maternal alcohol consumption during pregnancy[162] while another did not find an association[156]; neither found a relationship between maternal alcohol consumption and ALL. In contrast, two other recent studies found that maternal consumption of alcohol during pregnancy was associated with a decreased risk of ALL[163] and of infant leukemia.[164]

Healthy Diet Index

In contrast to studies that have evaluated the role of a limited number of specific nutrients or food components, measures of overall diet quality may better represent nutritional status and the complex biological interaction of multiple nutrients.[165] Diet quality indices are often positively correlated with biological markers of micronutrient intake and have been associated with reduced risk of all-cause mortality, including cancer risk.[166,167] Maternal dietary patterns and quality have

also been associated with birth outcomes, such as neural tube and congenital heart defects.[168]

In a recent study[169] overall maternal diet quality, as summarized by a diet quality index using a modified version of the 2010 Healthy Eating Index, was associated with a reduced risk of childhood ALL (OR for each five point increase on the index = 0.88, 95% CI: 0.78−0.98). A more pronounced reduction in risk was observed among younger children and children of women who did not use vitamin supplements before pregnancy. There was a similar reduced risk of AML with increasing maternal diet quality score, although this association was not statistically significant (OR = 0.76, 95% CI: 0.52−1.11). No single diet quality index component (i.e., food group or nutrient) appeared to account for the results, suggesting that the quality of the whole diet and the cumulative effects of many dietary components may be important in influencing childhood leukemia risk.[169]

Breastfeeding for six months or longer, is associated with a reduced risk of childhood leukemia, whereas early introduction to milk formula may increase leukemia risk.

Paternal Diet

In contrast to maternal diet, very few studies have examined the relationship between paternal diet before conception and childhood leukemia. One study suggested that the risk of childhood leukemia increased with increasing paternal consumption of hot dogs (sources of carcinogenic compounds from N-nitroso precursors).[170] Also, there is no strong indication that paternal intake of folate and other vitamins from diet and supplements before the child's conception reduced the risk of leukemia in the offspring.[171,172]

Child's Diet

As mentioned earlier, breastfeeding and duration of breastfeeding (6 months of more) have been associated with the risk of childhood ALL, as summarized in recent pooled[173] and meta-analyses[174] conducted by the Childhood Leukemia International Consortium. Besides breastfeeding, little is known about the influence of child's early diet. Feeding with formula as early as 14 days after birth,[175] alone or in combination with breast milk, was associated with an increased risk of childhood ALL and dose–response relationships were reported for the duration of formula

feeding.[175,176] These studies contrasted previous null findings.[177] Infants and children fed with milk formula have been found to have higher serum levels of IGF-1 than those breastfed, and fetal growth pathway has been hypothesized to play a role in leukemogenesis.[176] Associations between a child's consumption of various food groups and the risk for childhood ALL or for all leukemias combined are inconsistent, especially regarding the consumption of fruits and fruit juice, as well as the consumption of meat.[170,175,177–179] Older age at introduction to solid food in general,[176] and possibly older age at introduction to vegetables in particular,[175] was associated with an increased risk of childhood ALL, while a reduced risk was reported for late introduction to eggs.[175] Child's consumption of cola-based drinks does not appear to be associated with leukemia, in contrast to maternal consumption during pregnancy.[155]

Increased risks of childhood leukemia have been consistently associated with exposures to pesticides, tobacco smoke, solvents, and traffic-related pollution.

Conclusions

Most of the evidence to date supports the role of prenatal folate supplementation, alone or with other vitamins, in reducing childhood leukemia risk. Apart from the possible beneficial intake of fruits and vegetables both during pregnancy and in the early years of life, studies have led to mixed or isolated findings regarding the potential leukemogenic effect of other food groups, likely due to small sample sizes and challenges of collecting accurate descriptions of participants' diets. In addition, there has been relatively limited consideration of the role of maternal diet on risk of AML, a less common subtype than ALL. Finally, measures of overall diet quality may represent nutritional status and the complex biological interaction of multiple nutrients better than single-nutrient assessment, and should be used in future studies.

A Clinical Perspective on Environmental Health Literacy

Nurses, doctors, and other health care providers are highly respected as sources for health information; as such they play an important role in translating new scientific findings to the public.[180] It has long been recognized that health care providers should act as resources for information on environmental health for their patients; unfortunately, U.S. medical education is largely void of training in Environmental Medicine.[181] Pediatricians and other providers report low self-efficacy in basic skills of Environmental Medicine such as taking a history of environmental exposures.[10,182,183] A survey of members of the American College of Obstetrics and Gynecology reported that although three quarters of those surveyed agreed that counseling patients could reduce exposure to environmental hazards, fewer than 20% routinely discussed environmental exposures—even known developmental toxicants—with their patients. Despite a lack of training in environmental health, clinicians report a high interest in learning more about current environmental health research as it may apply to their practice.[10,182]

Environmental Health Literacy is an evolving discipline that "combines key principles and procedural elements from the fields of risk communication, health literacy, environmental health sciences, communications' research and safety culture."[184] A basic level of environmental health literacy will help clinicians to have a sense of self-efficacy about environmental health and to fulfill roles as alert clinicians, educators, and advocates for children's health.

The key studies on environmental risk factors for childhood leukemia are rarely published in clinical journals and presentations on new environmental epidemiologic research are rare at clinical meetings. These circumstances require clinicians to make a special effort to stay informed about the impact of the environment on health. Fortunately, many online resources are becoming available to make this easier (Text Box 1).

Childhood Leukemia: Is it Time for Primary Prevention?

As presented in the preceding sections of this article, there is a large and growing body of literature that demonstrates the role of environmental agents in determining the risk for childhood leukemias. This is in contrast to other pediatric cancers that are more rare and for which there have been far fewer environmental

epidemiologic studies conducted. The evidence implicating environmental causes of childhood leukemia comes from a variety of individual studies worldwide and includes meta- and pooled analyses from the Childhood Leukemia International Consortium, as discussed in the *Environmental Risk Factors for Childhood Leukemia* section. Exposures to agents such as pesticides, tobacco smoke, solvents, and traffic-related pollution have been consistently linked to an increased risk of developing childhood leukemia. On the other hand, intake of vitamins and folate supplementation during the preconception period or pregnancy has been associated with a reduced risk of childhood leukemia as have breastfeeding and early exposure to infection, as characterized by attendance at large daycare and pre-school settings. Despite the fact that many studies have identified modifiable risk factors (increased or decreased risk) for childhood leukemia we are aware of no current prevention program that specifically addresses childhood leukemia, anywhere in the world. The American Cancer Society does support programs that discourage tobacco use and promote healthy nutrition and exercise for children, with the understanding that addressing these factors early in life will reduce future cancer burden.[1] Why is it that activities to reduce childhood leukemia have not been incorporated into cancer prevention programs when potentially modifiable risk factors have

been identified? Recently, our research group has suggested that the time is right to develop activities focused on primary prevention of childhood leukemia.[185,186]

What Evidence Is Needed Before We Take Action?

Historically, there have been many chemicals for which early warning signs of serious health impacts have been ignored due to a lack of scientific consensus. In some cases, protective efforts and corrective actions were not undertaken until many years or even decades after the first trouble was spotted.[187] For example, long after initial concerns were raised about DDT, PCBs, and lead, these chemicals continued to be used in large quantities. While these chemicals were eventually banned or restricted in use, in the interim they continued accumulating in the environment, and left a long-term legacy of detrimental exposures that were unnecessary and avoidable.

The European Community recognizes the precautionary principle, which provides justification for public policy actions in situations of scientific uncertainly in order to reduce health threats. In contrast, in the U.S., the regulatory framework generally requires scientific consensus of proof of harm before policy actions are carried out. The lack of public health campaigns specifically focused on primary prevention of childhood leukemia may, in part, result from this tendency to avoid taking precautionary actions. In clinical medicine, our mandate to "do no harm" often dictates that we are wary of false positives, for example, when interpreting results from a clinical trial. However, in the context of environmental epidemiology, it is also important to avoid making interpretations that will yield false negatives, because a failure to identify a hazard and take preventive actions poses a threat to the public health.

At this time, despite steadily accumulating evidence that environmental exposures increase the risk of childhood leukemia, authoritative bodies, including the International Agency for Research on Cancer (IARC), consider only radiation and parents' active smoking as "causative" factors in the development of childhood leukemia. The Agency reviews individual chemicals only periodically and many of the suspected environmental risk factors for childhood leukemia have not been reviewed in the last decade; a period

of time during which the environmental epidemiology of childhood leukemia has developed substantially.

Clinical medicine has embraced an evidence-based approach and uses systematic reviews (e.g., Cochrane, GRADE) as the gold standard for determining the quality of evidence. The highest quality of evidence (within the evidence-based paradigm) is obtained from double blinded, randomized trials, but this study design would be impossible and unethical in the context of childhood leukemia research on environmental exposures. Prospective cohort studies, which generally are thought to provide high quality of evidence, are prohibitively expensive for a disease like childhood leukemia with an incidence of less than 100 per million population. Even an international effort to combine existing mother–child cohorts leads to small numbers of children diagnosed with leukemia and other cancers. Studies assessing the role of environmental exposures in childhood leukemia would almost exclusively be given a lower quality of evidence rating, given that they are usually, by necessity, observational studies with case–control-designs. Adaptations of the systematic review methodology have been developed to respond to the needs of environmental health and may allow for more precautionary assessments in the future.[188,189]

Primary prevention of cancer includes reducing exposures to risk factors or changing the underlying conditions which result in disease. While the CDC has been exploring opportunities for early life prevention of child and adult cancers, there are diverse opinions about whether there is an adequate evidence base for primary prevention of cancer.[185] In a summary of expert opinion on what evidence should be necessary

to support taking action, suggestions range from animal studies and toxicologic profiles to high-quality systematic reviews (Text Box 2).[185]

Addressing Specific Evidence Needs for Action

Many of the requirements suggested as a rationale for undertaking primary prevention programs listed in Text Box 2 have already been satisfied in the context of childhood leukemia research. For example, many of the risk factors identified in recent research are common, resulting in widespread exposure to the general population. Moreover, childhood leukemia could certainly be considered "a severe and dreaded outcome." Though childhood leukemia treatment results in an 80–90% cure rate, the treatment has long-term health implications for those treated, as well as profound impacts on the families and the communities who endure it. While most items on the checklist for taking preventive action (Text Box 2) have been completed, one notable exception is that, to date, animal studies of leukemia have been limited, since it is only recently that animal models of human childhood leukemia have been developed.[190]

Structured systematic reviews and meta-analyses are viewed as key elements that support the validity of findings from individual studies. Multiple meta-analyses have been conducted on the most highly-studied risk factors for childhood leukemia: pesticide use, tobacco smoke, and traffic-related air pollution. As noted in the *Environmental Risk Factors for Childhood Leukemia* section, the Childhood Leukemia International Consortium has investigated many of these key risk factors for childhood leukemia using meta-analyses and pooled analysis of original data from case–control studies. These studies have been carefully conducted and can be considered systematic reviews of the epidemiologic literature.

Each factor in this issue that has been associated with altered risk of childhood leukemia is also associated with altering the risk of other health outcomes in children as well as adults. In fact, these same exposures that are implicated in the risk for childhood leukemia have substantial documentation of their non-cancer health impacts, including neurobehavioral deficits and respiratory disorders. Thus, acting to prevent childhood leukemia would also reduce the incidence of other diseases, and *vice versa*. These potential co-benefits should lessen any concerns that an error in attribution

TABLE 3. Examples of exposures associated with altered risk (increased or decreased) for developing childhood leukemia and. co-benefits of improved health outcomes by clinical and public health actions

Exposure	Health impacts other than childhood leukemia	Clinical recommendations	Public health activities
Pesticides	Neurobehavioral disorders, asthma, adverse birth outcomes, adult cancer, reproductive toxicity	American Academy of Pediatrics recommends Integrated Pest Management, exposure reductions. Advocates clinicians become familiar with acute and chronic/subclinical effects and provide anticipatory guidance	Integrated Pest Management recommended by U.S. EPA and cooperative extension services
Tobacco	Respiratory disease and asthma, adverse birth outcomes, cardiovascular disease, adult cancers, neurocognitive disorders, sudden infant death syndrome	Smoking cessation, avoidance of secondhand smoke universally recommended	National and local tobacco control programs, cessation hotlines
Air Pollution (including traffic related)	Includes preterm birth, decreased birth wt., asthma and respiratory development, cardiovascular dis., neurobehavioral disorders	Less amenable to individual action. Recommendations to restrict outdoor activities during high air pollution days (AirNow.gov). Avoid wood fires.	Many programs for air pollution reduction. Local programs to encourage walking and biking. No idle zones, replacement of old diesel vehicles. School siting regulations.
Folate (risk reduction) supplementa- tion/healthy diet	Inadequate folate early in pregnancy associated with neural tube defects, increase in autism risk, other birth defects	Preconception or prenatal folate supplementation recommended by American College of Obstetrics and Gynecology and American Academy of Family Physicians and others	Fortification of supplementation recommended by U.S. Preventive Services Task Force
Breastfeeding (risk reduction)	Sudden infant death syndrome, diarrhea, bacteremia, otitis media, childhood obesity, respiratory infection.[204]	Promote breastfeeding as the norm, develop skills to assess and collaborate with obstetrical community and certified counselors, serve as advocates for breastfeeding	2011 Surgeon General's Call to Action to Support Breastfeeding: Actions for non-governmental organizations, government, employers, etc. All states have breastfeeding coalitions, programs to promote and support breastfeeding in minority communities.[205]

would result in unwarranted actions with potential negative impacts on health or increased financial burdens without benefit to society. Moreover, some high-risk behaviors—such as parental smoking—already have clinical and/or public health recommendations that attempt to alter exposure patterns. Although these efforts are to be applauded, including an additional focus on the potential of reducing childhood leukemia in these existing public health campaigns may improve effectiveness. With the exception of tobacco control and lead poisoning prevention, efforts at wide-scale promotion of children's environmental health activities have received limited funding and attention. When evaluating the costs and benefits of reducing exposure to an environmental hazard, one must consider the total social and economic impacts for risk reduction associated with all relevant health outcomes (such as cancer, neurobehavioral deficits, and respiratory disorders). Examples of risk factors and protective factors associated with childhood leukemia, other co-morbidities associated with these exposures, and current clinical or public health recommendations relevant to these exposures are presented in Table 3.

Moving Toward Prevention

There have been rare instances when the conventional American wisdom—that a determination of causation is required before any action can be taken to protect the public health—has been bypassed to great benefit. For example, in 1964, the U.S. Surgeon General supported action to reduce tobacco use stating

> Although the causative role of cigarette smoking in deaths from coronary disease is not proven, the Committee considers it more prudent from the public health viewpoint to assume that the established association has causative meaning than to suspend judgment until no uncertainty remains.[191]

Similarly, the "Back to Sleep" campaign sponsored by the U.S. National Institute of Child Health and Human Development to reduce sudden infant death syndrome (SIDS) is another example of a highly successful public health measure that has saved many lives despite being adopted with less-than-uniform agreement on causation.[192] In 1992, the American Academy of Pediatrics issued its policy statement suggesting that infants be placed to sleep on their backs or sides rather than prone.[193] At that time there were several case–control studies, but no prospective

randomized clinical trials, to support the American Academy of Pediatrics recommendation. Indeed, the American Academy of Pediatrics statement acknowledged many limitations in the epidemiological literature that was available for SIDS at that time. As highlighted in the policy statement abstract

> This recommendation is made with the full recognition that the existing studies have methodologic limitations and were conducted in countries with infant care practices and other SIDS risk factors that differ from those in the United States (eg, maternal smoking, types of bedding, central heating, etc).

In fact, the recommendation was in part informed by ecologic studies, which is the study design that generally provides the least convincing support for causality. These ecologic studies reported on SIDS incidence following large-scale changes in regional sleep positioning practice; observing that when parents started putting children to sleep in a prone position the incidence of SIDS increased.[194] Subsequently, in 1994, the "Back to Sleep" campaign was launched to discourage prone sleeping for infants. By 2000, the U.S. mortality rate for SIDS had dropped to one-half of the rate in 1990. A set of additional recommendations aimed at decreasing SIDS was included in the 2011 American Academy of Pediatrics policy statement based on findings of varying scientific rigor.[192]

In making these policy statements, American Academy of Pediatrics adapted a strength of evidence scheme from the U.S. Preventive Services Task Force with a highest level of recommendation that requires

> …good and consistent scientific evidence (i.e., there are consistent findings from at least 2 well-designed, well-conducted case–control studies, a systematic review, or a meta-analysis). There is high certainty that the net benefit is substantial, and the conclusion is unlikely to be strongly affected by the results of future studies.

Many of the childhood leukemia risk factors listed in Table 1 have multiple studies demonstrating their effect and at least one meta-analysis if not a systematic review. Moreover, at least for the environmental agents that have been assessed via the comprehensive, pooled analyses conducted by the Childhood Leukemia International Consortium, it is unlikely that future studies will contradict the current findings. Finally, when one takes into account the multiple other diseases that are also associated with these exposures, the benefit of

taking public health action to reduce human exposure should be considered substantial. Under the American Academy of Pediatrics rubric noted above many of the risk factors in Table 3 should receive the highest rating for evidence quality.

Examples of Primary Prevention in Clinical and Public Health Practice

Folate

As noted in the *Dietary Risk Factors for Childhood Leukemia* section, adequate folate during the preconception and very early pregnancy periods is not only associated with reductions in the incidence of childhood leukemia but it also protects against neural tube and other birth defects and possibly autism.[195,196] In 1992, the U.S. Public Health Service recommended that all women capable of becoming pregnant take 400 µg of folic acid daily. In 1998, the United States introduced fortification of enriched cereal grain products with folate. It has been estimated that folate fortification has resulted in approximately 1300 fewer children being born with neural tube defects, annually.[197] Despite these dramatic results, nearly one quarter of women of childbearing age in the National Health and Nutrition Examination Survey (2007–2012) were found to have suboptimal folate-blood levels.[198] In addition, Latinas were noted to have significantly lower blood folate levels than white women. Given that Latino children—those living in Central or South American as well as those living in California—are recognized to be at greater risk of childhood leukemia than white children, a public health campaign targeting folate supplementation in Latinas of childbearing age could be a particularly important opportunity for childhood leukemia prevention.

A caution would be a concern about the possibility of some women exceeding the tolerable upper intake level for folic acid. The National Health and Nutrition Examination Survey estimated that 2.7% of participants (primarily women) exceed these recommended folate values.[199] Nonetheless, a careful emphasis on improving nutritional status by ensuring fresh foods and folic acid supplementation for women of pregnancy age seems warranted.

> *Risk factors for childhood leukemia are also associated with the risk of developing other cancers, neurobehavioral deficits, and respiratory disorders.*

Tobacco

Although tobacco control programs and policies have significantly reduced smoking, there are still between 15% and 23% of young adult men and women who smoke in the U.S.[200] It is likely that most are not aware of the link between paternal smoking around the time of conception and a child's subsequent risk of developing leukemia. To prevent soon-to-be-dads from smoking before conception, fuller implementation of proven tobacco control strategies aimed at preventing smoking initiation and reducing smoking in teenagers and young adults is needed.

Pesticides

Pesticide exposure, both prenatal and postnatal, has been associated with leukemia risk. This supports introduction of programs focused on the use of safe pesticide practices during the preconception period. An example of materials that target an audience of people who are considering becoming, or currently are, pregnant is available from the Program for Reproductive Health and the Environment at the University of California, San Francisco. These include Pesticides Matter: Steps to Reduce Exposure and Protect Your Health (http://prhe.ucsf.edu/prhe/pesticidesmatter.html).

Preconception Care

Recently, reproductive health professionals involved in the care and support of women of childbearing age have begun to emphasize preconception care. These professionals are interested in including environmental factors as part of their message to their patients about health promotion before conception and during pregnancy.[201] Including both men and women in health promotion provides an ideal opportunity to address environmental exposures prior to early critical windows of development, even before conception. Initial studies on the effectiveness of strategies to promote behavior change to reduce chemical hazard exposures preconception and during pregnancy indicate that perceived normative pressure (perception of what is common among peers and important to family, friends and doctors) is a key element.[202] The U.S. Centers for Disease Control and Prevention and the American College of Obstetrics and Gynecology have begun programs to address preconception health (http://www.cdc.gov/preconception/index.html, see Preconception Health and Health Care). An effort should be made to ensure that environmental health literacy and childhood cancer prevention activities are addressed within the context of these evolving programs and included in a new standard of care.

The cancer prevention activities suggested by our research on childhood leukemia and others[203] largely reinforce programs already in existence by different public health entities (e.g., tobacco cessation, healthy diet during pregnancy and folate supplementation, avoidance of exposure to volatile organic compounds, pesticides, and paint). Public health agencies and health care systems can partner to extend current programs with similar goals. Innovative cross-agency, multidisciplinary program opportunities include

- Enhance the use of news media and add risk reduction for childhood leukemia to environmental health literacy education activities for the general public, as appropriate.
- Include environmental health messaging in preconception, prenatal, and child preventive health care and as part of programs such as "Text 4 Baby" and "Bright Futures."
- Assure that preconception health programs include environmental health components and additional emphasis on healthy diet.
- Use emerging systematic review methodologies to evaluate environmental health risks with the goal of having environmental health programs recognized as evidence-based medicine.
- Improve health care provider counseling for women and couples to integrate concepts of environmental health—specifically the risk factors associated with childhood leukemia—into medical education at all levels (during schooling and post-graduate education) for nurses, physicians, and allied health professionals.
- Develop policy initiatives to reduce exposures to chemicals associated with childhood leukemia (and other negative health outcomes) during pre-pregnancy, pregnancy, and early childhood.

The currently available toxicologic and observational epidemiologic studies (including meta and pooled analyses) provide a strong evidentiary basis for the presence of casual associations (of small to moderate sizes) between several environmental exposures and childhood leukemia. Awaiting a more complete evidentiary basis for decision-making, though ideal, will

result in significant delays in safeguarding children's health. Education of clinicians and the public on primary prevention—actions that an individual can take to reduce their own family's exposures to chemical risk factors for childhood leukemia as well as other disorders—is something that can occur now. Ultimately, regulatory actions based on the evolving science are needed to shift the burden from the individual to producers.

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