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Childhood Leukemia: Electric and Magnetic Fields as Possible Risk Factors

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Numerous epidemiologic studies have reported associations between measures of power-line electric or magnetic fields (EMFs) and childhood leukemia. The basis for such associations remains unexplained. In children, acute lymphoblastic leukemia represents approximately three-quarters of all U.S. leukemia types. Some risk factors for childhood leukemia have been established, and others are suspected. Pathogenesis, as investigated in animal models, is consistent with the multistep model of acute leukemia development. Studies of carcinogenicity in animals, however, are overwhelmingly negative and do not support the hypothesis that EMF exposure is a significant risk factor for hematopoietic neoplasia. We may fail to observe effects from EMFs because, from a mechanistic perspective, the effects of EMFs on biology are very weak. Cells and organs function despite many sources of chemical "noise" (e.g., stochastic, temperature, concentration, mechanical, and electrical noise), which exceed the induced EMF "signal" by a large factor. However, the inability to detect EMF effects in bioassay systems may be caused by the choice made for "EMF exposure." "Contact currents" or "contact voltages" have been proposed as a novel exposure metric, because their magnitude is related to measured power-line magnetic fields. A contact current occurs when a person touches two conductive surfaces at different voltages. Modeled analyses support contact currents as a plausible metric because of correlations with residential magnetic fields and opportunity for exposure. The possible role of contact currents as an explanatory variable in the reported associations between EMFs and childhood leukemia will need to be clarified by further measurements, biophysical analyses, bioassay studies, and epidemiology. *Key words:* childhood leukemia, contact currents, contact voltages, electric and magnetic fields, EMF, review. *Environ Health Perspect* 111:962–970 (2003). doi:10.1289/ehp.6020 available via *http://dx.doi.org/* [Online 25 February 2003]

Whether health risks result from exposure to power-line electric or magnetic fields (EMFs) remains unclear. Epidemiologic studies have repeatedly shown small associations between measures of residential power-line magnetic fields and childhood leukemia. The possibility that these associations are caused by bias or confounders, however, cannot be ruled out (Savitz 2003). In addition, extensive investigations in animals at much higher levels of EMFs have not demonstrated adverse effects (Boorman et al. 2000). Recently, the International Agency for Research on Cancer (IARC 2002) designated EMFs as a class 2B carcinogen ("possibly carcinogenic"), based on "consistent statistical associations of high-level residential magnetic fields with a doubling of the risk of childhood leukemia." The California Department of Health Services (CADHS 2002) recently issued a report concluding that "EMFs can cause some degree of increased risk of childhood leukemia, adult brain cancer, Lou Gehrig's disease, and miscarriage." Hence, the question of whether electric-power use has a possible role in childhood leukemia risk remains in the forefront of concern.

To assess past research and suggest future directions in the area of childhood leukemia and EMFs, the Electric Power Research Institute and the Harvard School of Public Health sponsored a workshop titled "Childhood Leukemia: Added Risk from the Use of Electricity?" on 8 November 2001, in Lexington, Massachusetts. This workshop brought together a number of experts.

The epidemiologic associations reported between EMFs and childhood leukemia remain unexplained. Integrating all the lines of evidence presents a challenge to accurately evaluating potential health effects from EMFs. Epidemiologic results, when available, often predominate over rodent bioassay and other laboratory data in hazard identification and risk assessment. However, the epidemiology studies of EMFs and childhood leukemia, all of case–control design, pose several issues, and the link between EMFs and leukemia has not been supported by laboratory data. In many of the epidemiology studies, the small proportion of the study population classified as receiving high exposure levels limits the precision of the effect estimate. In addition, confounding and differential selection and participation of controls by attributes associated with exposure can lead to biased effect estimates (Ahlbom et al. 2000; Hatch et al. 2000). Finally, the relevant exposure metric is not known; thus, it has not been possible for epidemiologists to quantify EMF exposure appropriately in the study populations. Experimental approaches also have limitations, such as *a*) requiring high-dose to low-dose extrapolation, *b*) requiring interspecies extrapolation, *c*) using "pure" EMF signals of specific frequency and field strength that may not mimic real human exposures, and *d*) being subject to practical and logistic bounds on study size (statistical power). Epidemiologists have been hampered because experimental studies of EMFs have not identified biologic mechanism(s) that could serve as the basis for designing new studies. The goal of the workshop described here was to review the science and consider new directions for EMF research in the areas of epidemiology, exposure metrics, animal studies, and biophysics.

Childhood Leukemia and EMFs

A major focus of EMF research during the past 20 years has been to determine whether, and how, EMFs might increase the risk of cancer, particularly childhood leukemia. The rationale for investigating EMFs stems from the original observation that childhood leukemia correlated with the proximity of overhead utility lines (Wertheimer and Leeper 1979). Early research focused on quantifying EMF exposure by electrical wiring configurations ("wire codes") and determining whether wire codes were accurate surrogates for magnetic-field exposure. More recently, however, magnetic-field exposure itself ("spot" and 24-hr average) has become the focus of investigation (Ahlbom et al. 2001; Greenland et al. 2000).

If typical residential magnetic fields are used as the exposure metric, then adverse EMF effects are not expected to occur. In a review of the EMF literature, the National Institute of Environmental Health Sciences (NIEHS 1999) identified 1 mV/m as a tissue electric field that could plausibly be associated

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with a biologic effect. At 5 μT (equivalent to 50 mG), which is roughly five times higher than the highest average field recorded in the "1,000-home study" (Zaffanella 1993), the induced-electric-field level in human tissues, including bone marrow, remains below this 1 mV/m "benchmark" dose (Kavet et al. 2001). Nonetheless, when Greenland et al. (2000) pooled the epidemiology studies of childhood leukemia, they found evidence of increased risk at the upper-end magnetic field levels to which a small proportion of U.S. residents are exposed. The authors estimated a relative risk (RR) of 1.7 [95% confidence interval (CI), 1.2–2.3] for exposures above 0.3 μT (3 mG), and a population attributable fraction of 3% (95% CI, –2% to > 8%) for exposures above 0.05 μT. Another pooled analysis by Ahlbom et al. (2000) produced similar results for a 0.4-μT cut point. The data from the 1,000-home study (Zaffanella 1993) show that 4.7% of residences in the United States have average spot measurements (point-in-time measurements averaged across available rooms) ≥ 0.3 μT, and 2.6% have fields ≥ 0.4 μT.

Interpretation of the associations between childhood leukemia and EMFs rests on understanding several lines of evidence: *a*) clinical data on etiology and pathogenesis of childhood leukemia; *b*) results from EMF-exposed laboratory animals; *c*) survey data on EMF levels present in households and whether the intensity is sufficient to induce biologic effects; and *d*) consideration of alternative EMF exposure metrics.

Biology of Childhood Leukemia

Leukemia is a cancer of blood progenitor cells that arises in the bone marrow, where stem cells normally differentiate into lymphoid and myeloid progenitor cells. Lymphoid progenitor cells form mature B cells or T cells. Myeloid progenitor cells yield neutrophils, monocytes, or eosinophils. Marrow precursor cells also produce red blood cells and platelets. Leukemia can be classified according to the presumed cell of origin (myeloid or lymphoid) as well as its clinical course (chronic or acute). Chronic lymphocytic leukemia and chronic myelogenous leukemia, which likely originate in primitive stem cells, are characterized by protracted, subacute disease. Acute lymphoblastic leukemia (ALL) and acute myelogenous leukemia (AML) refer to cancer of lymphoid or myeloid progenitor cells, with rapid onset and deterioration without aggressive therapy. Most childhood leukemia is either ALL or AML. Leukemia can be further subclassified according to morphology, genetic alterations, cell surface markers, and other characteristics (Table 1).

Childhood leukemogenesis is likely a multistep process. For ALL, specific oncogene-associated translocations and other abnormalities have been identified in 45% of cases, and random translocations in an additional 25%; but in 30% of the children with ALL, specific genetic alterations have not been identified (Look 1997). Factors predisposing to the development of leukemia in children include underlying genetic disorders, family history, ionizing radiation, chemotherapeutic agents, and possibly infection or environmental chemicals. The underlying genetic disorders associated with an increased risk of developing childhood leukemia include Down syndrome (overall 15-fold increase in risk), defects in DNA repair (Bloom syndrome, Fanconi anemia), congenital marrow failure (Kostmann syndrome, Diamond-Blackfan anemia, and Schwachman-Diamond syndrome), neurofibromatosis type I, and Li-Fraumeni syndrome (Miller 1967; Robison and Neglia 1987).

Family history is a risk factor for the development of childhood leukemia. In identical twins, there is a 25% concordance rate, which is highest in infancy. However, if the diagnosis is made in one sibling after 7 years of age, leukemia risk does not appear to be increased in the other sibling (Miller 1967).

Few environmental or exogenous agents are known to cause the development of childhood leukemia. Postnatal ionizing radiation is a contributing factor. Survivors living within 1,000 meters of the atomic bomb blast in Japan showed a 20-fold increase in leukemia rates; however, children exposed to these bombs *in utero* did not exhibit an increased risk of leukemia (Miller 1967). Pediatric patients given therapeutic irradiation exhibit higher leukemia rates. Similarly, after certain kinds of chemotherapy, there is an increased risk of developing AML (Pui et al. 1989; Tucker et al. 1987).

In contrast to these few known agents, the number of suspected risk factors is much greater. Sources of radiation from prenatal exposure, nearby nuclear plants, or natural background have all been considered as risk factors, as well as radon from groundwater or indoor sources. Investigation into causal factors has included chemical exposures from maternal or child medications, pesticides, parental smoking, or parental occupation. Factors associated with pregnancy and early development, such as maternal pregnancy history, maternal age, birth weight, birth order, and breast-feeding, have also been considered as potential risk factors. A role for infections in childhood leukemogenesis has been proposed from two perspectives. Greaves and colleagues (Greaves 1997; Greaves and Alexander 1993) suggest that unusual timing of postnatal infections could provoke recruitment and proliferation of undifferentiated B cells or T cells with preleukemic translocations. Kinlen (1995, 1997) has proposed that common infections can occasionally trigger a leukemic response, and that an increased leukemia risk is evident when comparing leukemia rates of populations with unusually large influxes of new residents,

Table 1. Childhood leukemia types, subtypes, and features.

Type (%)	Subtype (%)	Morphology	Common genetic abnormalities (%)	Characteristics
ALL (74)	B progenitor (80–85)	L1, L2	t(12;21) (20) t(9;22) (4) 11q23 translocations (6) t(1;19) (5)	Precursor B-cell markers on cell surface, no surface immunoglobulin, ploidy abnormal in 35% of cells
	T cell (10–15)		7q35/TCRβ (3) 14q11/TCRαg (4) 9p deletions	T-cell markers on cell surface, higher median age of patients, higher white blood cell count, bulky disease, male predominance
	Mature B cell (1–2)	L3	t(8;14), t(2;8), or t(8;22) (2)	Surface immunoglobulin, same as Burkitt's lymphoma
AML (19)	Undifferentiated (2)	M0	Monosomy 5/7	
	Myeloblastic (45)	M1, M2	t(8;21)	
	Promyelocytic (10)	M3	t(15;17)	DIC (bleeding)
	Myelomonocytic (20)	M4	11q23/MILL	Infants, chloromas, secondary AML
	Myelomonocytic with eosinophilia[a]	M4Eo	Inversion 16	
	Monocytic (17)	M5	11q23 translocations	Infants, chloromas, secondary AML
	Erythroleukemia (1)	M6		Exceedingly rare in children
	Megakaryocytic (5)	M7	t(1;22)	Down syndrome, infants, myelofibrosis

DIC, disseminated intravascular coagulation.
[a]Percent not available.

potentially bringing in pathogens, to rates among stable populations.

Epidemiology of Childhood Leukemia

Although cancer in childhood (younger than 20 years) is rare, childhood leukemia is the most common form of childhood cancer and represents about one-third of the total childhood cancers in the United States (Linet et al. 1999). For children 0–20 years old, leukemia rates average around 2–3 per 100,000 person-years, but the rate peaks at two or three times this level in 0–4-year-olds. ALL constitutes about three-fourths of U.S. cases of childhood leukemia. Each year, about 2,400 new cases of childhood ALL are reported, with an incidence of approximately 3 per 100,000. Age-specific incidence rates are slightly higher in whites than in blacks at most ages, but between 3–4 years of age, white children show a dramatic peak in rates not seen in black children. Male:female ratios show slightly higher risk for males (1.2:1.0 for all ages), except between 15 and 19 years of age, when the male:female ratio is 2:1. AML constitutes about one-fifth of U.S. cases of childhood leukemia. In contrast to ALL, AML rates do not show a peak at younger ages, and marked gender differences are not apparent at any age.

Childhood leukemia rates vary by geographic locale and ethnicity. In general, ALL rates are the highest in the United States (whites only) and Europe, intermediate in India and China, and the lowest in North Africa and the Middle East. Great Britain reports similar rates and patterns as the United States (Draper 1991). Internationally, however, ALL leukemia rates exhibit a 4-fold range, from about 2 cases per 100,00 person-years in Bangalore, India, to about 8 cases per 100,000 person-years in Costa Rica, in 0–4-year-olds (Parkin et al. 1998). In Africa, T-cell and mature B-cell leukemias are more frequent than is the B-cell progenitor subtype, which may be due to the high incidence of Burkitt's lymphoma associated with AIDS. For AML, the higher incidences are reported in Asia, with lower rates in North America and India.

In the United States, childhood leukemia incidence rates differ by race within geographic areas, but they are similar for the same race among different geographic areas (NCI 2003). In general, leukemia rates are the highest for white children from higher social classes. For black children, the 0–4-year-old ALL case rates per 100,000 person-years are 2.4 (Greater Delaware Valley), 2.5 (Los Angeles), 2.8 [SEER (Surveillance, Epidemiology and End Results) areas], and 2.9 (New York State); for white children, the rates are 5.9 (Greater Delaware Valley), 6.9 (Los Angeles), 6.2 (SEER areas), and 6.2 (New York State) for the same age group.

In the United States, the overall incidence for childhood leukemia has been declining over the past several decades (NCI 2003). Data from 1973 through 1994 show 10.5–13.3% decreases in leukemia incidence, depending on age group. Advances in treatment have led to even more dramatic declines in leukemia mortality, with corresponding increases in 5-year survival rates.

Some have suggested that investigations of childhood leukemia "clusters" might provide clues to the association between childhood leukemia and environmental agents, such as EMFs. Apparent clustering may arise for etiologic, statistical, or sociologic reasons. One U.S. childhood leukemia cluster was reported in Woburn, Massachusetts. Local residents from the east side of Woburn identified a transient, approximate doubling, of the childhood leukemia incidence rate. This area had been highly industrialized since the 1700s, and polluted well water was detected in the 1970s. In an extensive follow-up analysis, the Massachusetts Department of Public Health (1997) confirmed 19 cases of childhood leukemia but found little or no association with children drinking the polluted water (RR = 1.2; 95% CI, 0.3–5.0). An exceedingly imprecise result was reported for pregnant mothers drinking the polluted water, with a 95% CI covering a 100-fold range (RR = 8.3; 95% CI, 0.7–94.7). The extreme imprecision is attributed to the small sample size, which is a problem in most cluster investigations. For comparison, in EMF studies (Greenland et al. 2000) even the smallest leukemia case group was twice as large as the case group in the Woburn study. Although clusters are often the focus of media attention, the examination of cluster studies has not been particularly informative in elucidating additional factors in the development of childhood leukemia or other diseases (Gawande 1999).

Pathogenesis of Acute Leukemia

The multistage process in the development of acute leukemias includes an initial event, a survival or proliferation advantage that causes clonal expansion, additional genetic or epigenetic events that promote escape from programmed cell death or block cell differentiation, and finally, functional bone marrow failure with clinical disease. As discussed above, some of the initiating events are chromosomal translocations. For example, treatment of patients having solid tumors with inhibitors of topoisomerase II, such as etoposide, can induce translocations involving the *Mll* gene on chromosome 11q23, leading to AML or ALL.

In cases where genetic alterations constitute a critical component of the disease process, use of transgenic mice can provide valuable information on pathogenesis. The mutations induced by chromosomal translocations in human leukemias can be introduced into laboratory mice, and leukemogenicity can be assessed in distinct target cells. In one model, altered DNA is introduced *in vitro* to a fertilized mouse egg. The genetically altered egg is implanted into a foster mother. One of her progeny will then carry the altered genes and can be bred to generate additional mice for experimental studies. A major disadvantage of this system is that the transgene is present in all tissues, not just the bone marrow. Alternatively, bone marrow can be harvested from donor mice, altered genetic material introduced *in vitro*, and the transduced bone marrow transplanted into irradiated syngeneic (genetically identical) recipient mice. However, this model system is labor intensive, and experimental variability does occur.

Using these model systems, several aspects of acute leukemia pathogenesis have been elucidated:

- Translocation-induced leukemia oncogenes often confer disease specificity (see Table 1).
- Leukemia-specific oncogenes are insufficient as single agents to induce an acute leukemia phenotype in mice (Higuchi et al. 2002).
- In contrast to acute leukemias, chronic myelogenous leukemia is likely the consequence of a single genetic event (Philadelphia chromosome translocation) (Li et al. 1999).
- Cellular context determines the response of the hematopoietic system to leukemia oncogenes (Li et al. 1999).
- Continued expression of some leukemia translocation oncogenes is required for maintenance of the leukemia phenotype (Huettner et al. 2000).
- Disruption of the ARF/p53 tumor suppressor pathway is a major step in the progression of acute leukemia (Eischen et al. 1999; Unnikrishnan et al. 1999).

Further studies of EMF effects on hematopoietic cell lines should be based on B-lymphoid development and could be useful for identifying pathways that might be complemented in a mouse model. Mouse models, however, may be insensitive to weak EMF effects. For example, in p53 knockout mice, inactivation of both alleles for p53 greatly increases the percentage of lymphomas and decreases the survival time of affected animals, but residential EMF exposure may not be strong enough to inactivate the second allele (Jacks et al. 1994).

Animal Carcinogenicity Studies with EMFs

Epidemiologic studies are often inconclusive and may report associations in the absence of a causative link. In such situations, well-designed and controlled studies using experimental model systems can provide critical data for

human hazard assessments. Three approaches have been used to evaluate the cancer risk from exposure to 60-Hz magnetic fields: *a*) chronic oncogenicity bioassays, *b*) oncogenicity bioassays in genetically engineered (transgenic or knockout) mice, and *c*) multistage (co-carcinogenesis or tumor promotion) studies.

Chronic oncogenicity evaluations. The advantages of chronic oncogenicity bioassays include their use of standardized models and study designs that are widely accepted by regulatory agencies. Two-year oncogenicity studies in rodents are supported by a large historical database assembled for numerous chemical and physical agents. These assessments have demonstrated value for predicting human responses. Disadvantages of the animal studies include the need for interspecies extrapolations of organ-specific effects and the common requirement to extrapolate data from high-dose experimental exposures to low-dose human exposures.

Three large-scale, long-term studies of EMF exposure have been conducted in rats (Boorman et al. 1999; Mandeville et al. 1997; Yasui et al. 1997) and two in mice (Babbitt et al. 2000; McCormick et al. 1999). Descriptions and findings from these investigations are summarized in Table 2. Using identical study designs and exposure protocols, McCormick, Boorman, and co-workers examined the tumorigenic effect of EMFs in rats and in mice. The authors evaluated hematopoietic neoplasias and other putative target tissues (breast, brain) for solid tumors. Male rats exposed intermittently to 1,000 μT (10 G) exhibited a statistically significant decrease in leukemia incidence; no significant effects occurred in female rats or in other groups of males. In female mice exposed intermittently to 1,000 μT, a statistically significant decrease in malignant lymphoma was observed; no effects occurred in male mice or in other groups of females. For both rats and mice, the authors reported no significant differences in the incidence of breast or brain tumors in any group. Using different exposure protocols, Yasui et al. (1997) reported no differences in leukemia or lymphoma incidences in rats exposed to either 500 μT or 5,000 μT (5 or 50 G). Likewise, Mandeville et al. (1997) reported no effects on the incidence of leukemia in female rats exposed to 2, 20, 200, or 2,000 μT (0.02, 0.2, 2, or 20 G). Finally, Babbitt et al. (2000) saw no differences in total hematopoietic neoplasms or lymphomas in female mice exposed to 1,400 μT (14 G) (circularly polarized) EMFs.

Evaluations in genetically altered mice. The advantages of using transgenic mice are that weak effects can be magnified and effects occurring only in sensitive subpopulations can be detected. Relevant mechanisms of action may also be identified in sensitive animal models. However, if the historical database is small or nonexistent, there is limited context with which to interpret the data. Also, for many of these sensitive-animal models, their ability to predict human responses is unknown.

Two models have been developed in transgenic mice and applied to the investigation of EMF effects. In the first model, Berns et al. (1994) developed a transgenic mouse carrying the *pim-1* oncogene. After a single dose of *N*-ethyl-*N*-nitrosourea, lymphoma develops within 4–6 months; neoplastic cells show T-cell markers. If no carcinogen is given, spontaneous T-cell and B-cell lymphomas develop within 15–18 months. Animals die shortly after lymphoma is apparent, and therefore, survival is a useful indicator of disease progress. This model has been used in two studies investigating the

Table 2. Oncogenicity studies in animals exposed to EMF over a lifetime.

Species	Group size	Exposure	Percent incidence of hematopoietic neoplasia		Reference
Rats (F344)	100/both sexes/		Leukemia: male	Leukemia: female	Boorman et al. (1999)
	exposure group	Sham control	50	20	
		10 G (continuous)	50	25	
		10 G (intermittent; 1 hr on/off)	36*	22	
		2 G (continuous)	47	24	
		0.02 G (continuous)	44	18	
		60 Hz, 18.5 hr/day			
Rats (F344)	48/both sexes/		Leukemia: male	Leukemia: female	Yasui et al. (1997)
	exposure group	Sham control	10	16	
		50 G	8	14	
		5 G	8	12	
			Lymphoma: male	Lymphoma: female	
		Sham control	0	0	
		50 G	0	2	
		5 G	0	2	
		50 Hz, 22.6 hr/day			
Rats (F344)	50 female/		Leukemia		Mandeville et al. (1997)
	exposure group	Sham control	10		
		20 G	10		
		2 G	6		
		0.2 G	18		
		0.02 G	8		
		60 Hz, 20 hr/day			
Mice	100/both sexes/		Lymphoma: male	Lymphoma: female	McCormick et al. (1999)
(B6C3F1)	exposure group	Sham control	8	32	
		10 G (continuous)	7	26	
		10 G (intermittent)	6	20*	
		2 G (continuous)	4	22	
		0.02 G (continuous)	7	31	
		60 Hz, 18.5 hr/day			
Mice	190 or 380 female/		Total hematopoietic neoplasms		Babbitt et al. (2000)
(C57BL/6)	exposure group	Sham control	56		
		14 G (circularly polarized)	59		
			Lymphoma		
		Sham control	35		
		14 G (circularly polarized)	37		
		60 Hz, 18 hrs/day			

*$p < 0.05$ versus sham control.

effects of EMF exposure (Harris et al. 1998; McCormick et al. 1998). Survival and lymphoma incidence were unaffected in several different EMF exposure formats (Table 3). In the second model (Donehower 1996), one (hemizygous) or both copies of the *p53* gene are deleted from the germ line. McCormick et al. (1998) evaluated lymphoma incidence in TSG-*p53* mice exposed to 1,000 μT (10 G) continuous EMFs (Table 3). EMF exposure had no effect on survival and lymphoma incidence.

Multistage (promotion) studies. Multistage study designs have the potential to identify weak effects and thus have increased sensitivity. They are useful for identifying nongenotoxic effects or effects that occur only in populations exposed to other agents. Their primary disadvantage relates to their unknown accuracy for predicting human responses.

Two promotional studies have investigated the response of mice to EMFs in conjunction with ionizing radiation (Babbitt et al. 2000) or dimethylbenz[*a*]anthracene (Shen et al. 1997). The study design and findings are summarized in Table 4. No increases in lymphoma incidence due to the EMF exposure occurred in these two studies.

EMFs and Interactions with Matter

If power-line EMFs initiate or modulate the onset of disease in humans, then it should be possible to identify a mechanism by which EMFs alter molecules, chemical reactions, cell membranes, or biologic structures in a functionally significant manner. An "electric field" is produced by electrically charged objects, such that the size and direction of the electric field predicts the size and direction of force on electric charges. Likewise, a "magnetic field" is produced by moving charges, and the magnetic field predicts force on moving charges. Therefore, any EMF bioeffects must solely and ultimately be the result of forces; there are no other actions of EMFs. The plausibility of a biologic effect depends on whether EMF forces can significantly modify biologic processes having electrically responsive elements [e.g., ions, charged proteins, neural electric currents, magnetic molecules (free radicals), and magnetic particles].

The measurement units used for EMFs reflect the force exerted. The unit of measure for electric fields is volts per meter (V/m), which is identical to newtons per coulomb (N/C), where the newton is the metric unit for force, and the coulomb is the metric unit for quantity of electric charge; that is, the electric field gives the force per unit charge. The unit of measure for magnetic field is the tesla (T); typical environmental fields are in the microtesla (μT) range, which is one-millionth of a tesla. A metric unit, the tesla is identical to newtons/ampere-meter (N/A-m), and therefore, the magnetic field gives force per unit length (meter) of unit current (ampere).

Next, one can ask how the forces and energies conveyed by EMF exposure compare with forces and energies endogenous to biologic systems. As discussed below, the energies and forces exerted by environmental, 60-Hz EMFs seem well below those present in biologic systems. That is, normal living cells operate under conditions of energy and force "noise" such that 60-Hz EMF effects will be lost in this background. Theoretically, one could postulate that a low-noise, multicellular organ system might respond to feeble EMF influences and separate them from noise, similar to what happens in a manmade electronic circuit that responds to 60-Hz EMFs. However, the construction of a biologic system capable of responding to 60-Hz EMFs imposes severe size, averaging time, temperature stability, and conductivity constraints. Although sharks can respond to extremely weak, slowly changing electric fields in seawater, their sensor organ (*ampulla* of Lorenzini) is complex, containing a large number (~10,000) of receptor cells, in which small interactions are integrated to generate a change that stands out against noise (Adair 2001; Adair et al. 1998). Aside from such specialized sensory systems, fundamental force and energy considerations appear to preclude disruption of biology by weak EMFs. Table 5 lists mechanisms by which EMFs might alter biologic function, but the strengths of EMF interaction energies and forces are found to be small compared with the endogenous energies

Table 3. EMF studies in genetically engineered mice.

Species	Group size	Exposure	Percent incidence of lymphoma		Reference
Mice (*pim-1*)	30/both sexes/ exposure group		Male	Female	McCormick et al. (1998)
		Sham control	49	47	
		10 G (continuous)	23*	47	
		10 G (intermittent)	57	53	
		2 G (continuous)	43	45	
		0.02 G (continuous)	47	45	
		60 Hz, 18.5 hr/day, for 26 weeks			
Mice (*pim-1*)	100 female/ exposure group		T-cell	B-cell	Harris et al. (1998)
		Sham control	5	23	
		10 G (continuous)	8	22	
		10 G (intermittent)	7	28	
		1 G (continuous)	8	18	
		0.01 G (continuous)	4	25	
		50 Hz, 20 hr/day, up to 18 months			
Mice (TSG-*p53*)	30/both sexes/ exposure group		Male	Female	McCormick et al. (1998)
		Sham control	3	3	
		10 G (continuous)	0	7	
		60 Hz, 18.5 hr/day, for 26 weeks			

*$p < 0.05$ versus sham control.

Table 4. Multistage oncogenicity studies with EMF.

Species	Group size	Exposure	Percent incidence of lymphoma			Reference
Mice (C57BL/6)	380 female/ exposure group	X-ray:	3.0 Gy	4.0 Gy	5.1 Gy	Babbitt et al. (2000)
		Sham control	41	38	53	
		14 G	34	41	47	
		(circular) 60 Hz, 18 hr/day, lifetime				
Mice (Swiss Webster)	155–165/ exposure group	Dimethylbenz[*a*]anthracene:				Shen et al. (1997)
		Sham control		24		
		10 G		22		
		50 Hz, 3 hr/day, 5 days/week, for 16 weeks				

and forces characteristic of the living system (Valberg et al. 1997).

Table 5 shows that, in terms of energy or force at the whole-body scale or at the molecular scale, the effect of "large" EMFs is many orders of magnitude below the typical forces and energies that accompany life processes. For example, x-rays can produce significant molecular damage even when the total energy deposited in the body is small. However, the energy of a 60-Hz EMF photon is vastly less than that of x-rays and is too weak to alter molecular structures. The intensity of the electric field per se could be increased to levels where it accelerates individual free electrons to electron-volt energies, exceeding those needed to break a chemical bond (e.g., in corona discharge). However, the level of electric-field intensity required for this type of molecular damage is far above what a person is exposed to in environmental, power-line EMFs.

Likewise, EMF forces on biologic structures can be calculated easily, but the force required to distort the shape of complex biologic molecules—for example, DNA or enzymes—is far larger than what the electric component of EMFs can provide. However, the magnetic component of EMFs will act on magnetic particles or with single-molecule magnetic dipole (e.g., free radicals). Although magnetite particles are plausible geomagnetic field sensors (Kirschvink et al. 1992, 2001), functional biogenic ferromagnetic material has been established only in a limited number of organisms (e.g., magnetotactic bacteria). In these organisms, the magnetic interaction provides sensory guidance and is not likely to lead to internal malfunctions. Although magnetic forces may be adequate to twist ferromagnetic particles, the response of the particles to EMFs is limited by the reversal of the power-line magnetic field direction 120 times every second. That is, the net twist over any 1/60th of a second will be zero, and because of the viscosity of biologic materials, only a tiny amount of twist will take place during the 1/120th of a second that the magnetic field points in a given direction.

Coupling of EMFs to biologic effects. Most theoretical analyses of EMF actions have emphasized physical parameters and have analyzed models of individual cells or subsystems of single cells (mainly membranes and magnetosomes) (Adair 1991, 1994; Kirschvink et al. 2001; Polk 1992, 1994; Weaver and Astumian 1990). The shark provides an example of how a multicellular system can detect weak electric fields (described above), and the possibility that some multicellular structures may amplify electric fields has been considered (Fear and Stuchly 1998; Gowrishankar and Weaver 2003). The importance of biologic system size also has been emphasized in a model for the biologic detection of small magnetic field differences (Weaver et al. 2000). Multicellular system models begin with the recognition that EMFs are physical, not chemical, agents, as illustrated in the following causal chain (Weaver 2002):

EMFs → Physics → Chemistry → Biology

A necessary condition for biologic activity is that EMF-induced changes must exceed chemical changes from natural or background influences. Changes in biology are coupled to EMFs through changes in biochemistry, which in turn must have an ongoing, metabolically driven chemical process (reaction or transport rate) that is sensitive to EMFs. The assumption behind predicting the "weakest" detectable field is that this limit is determined by the ability of weak fields to alter the biochemistry, but it is not limited by the ability of a small number of molecules to alter the biologic system.

A key consideration is the size of the EMF-induced chemical change relative to naturally occurring changes in the same chemical process, which can be thought of as a chemistry-based signal-to-noise (S/N) ratio. For example, the signal (S) can be the EMF-induced, accumulated change in an ionic or molecular flux (Astumian et al. 1995), or the change in the average number of receptor-bound ligands (Weaver et al. 2000). But the accumulated change in flux or receptor-bound number also varies because of other natural processes, which constitute a generalized chemical noise (N), including the sources listed in Table 6. The totality of the sources of competing chemical change on Table 6, ($N_{\Delta N} + N_{\Delta T} + N_{\Delta C} + N_{\Delta M} + N_{\Delta E}$), can be expected to be much larger for humans *in vivo* than for cellular preparations studied *in vitro* (Weaver et al. 1999). Therefore, for the intact organism, the overall chemistry-based signal-to-noise ratio can be written symbolically as

$$\left(S_{\mathrm{EMF}}/N_{\mathrm{overall}}\right) = \frac{S_{\mathrm{EMF}}}{N_{\Delta N} + N_{\Delta T} + N_{\Delta C} + N_{\Delta M} + N_{\Delta E}}$$

The question of how to add the various competing chemical changes has not been fully addressed. If the competing changes can be regarded as random (and independent), then each of the competing changes can be added as the sum of their magnitudes squared (Weaver et al. 1999). In summary, the *in vivo* human biochemical environment exhibits considerable noise. This inherent, background noise must be quantitatively reconciled with the relatively small levels of 60-Hz EMF "signal" if one is to predict alteration of ongoing biochemical processes by EMFs. The effect threshold for voltage-gated channels in single, long cells is predicted to be about 50 V/m, which in a human-sized organism corresponds to the electric field induced by a magnetic field of about 1 T (10,000 G) (Weaver et al. 1999). If temperature noise is ignored, the threshold electric field is about 0.1 V/m, which corresponds to a magnetic field of 6,000 μT (60 G) (Weaver et al. 1999). As system size increases, fundamental noise tends to increase at a slower rate than does the induced EMF signal. Hence, the constraint that signal should exceed noise ($S/N > 1$) is more likely to be met in a large, multicellular system rather than in individual, isolated cells (Weaver et al. 2000).

Another difficulty in coupling EMFs to biologic effects has been assessing perturbations in membrane transport systems. An improved approach for evaluating molecular transport has been developed that might have application to predicting EMF effects on cell function (Gowrishankar and Weaver 2003), which uses a multicellular model based on elementary transport models that can be assembled into both membranes and bulk electrolyte. The model can predict voltages, currents, dissipated power density, and chemical changes throughout the system. Simulation of the bone marrow by the lattice transport model may be particularly appropriate in testing the hypothesis that contact currents are a potential causal link between EMFs and childhood leukemia. Marrow within bone is mechanically protected from

Table 5. Biologic process strength compared with EMF interaction strength.

Interaction process	Interaction strength in living system	Interaction strength for typical "large" EMF levels[a]
Heating	Basal metabolism ~100 W	Absorbed 60-Hz EMF energy = ~0.00001 W (i.e., 10 μW is 10,000,000-fold below basal metabolism)
Photon absorption	Chemical bond energies of ~0.1–5 eV	60-Hz EMF photons = ~0.000001 eV (i.e., EMF ~1 μeV, vs. x-rays ~500–5,000 eV)
Force (electrical)	Biologic forces ~1–100 pN	Molecule with electric charge of ±100 = ~0.0002 pN (pN = 10^{-12} N = 0.000000000001 N)
Force (magnetic)	Biologic forces ~1–100 pN	Twisting force on microscopic ferromagnetic particles (acting like compass needles), ~2 pN, but EMF force alternates direction every 1/120th sec, and averages to zero
Biochemistry	Free-radical recombination lifetimes ~2 nsec	Free-radical chemistry requires larger fields, and any effects occur over nanoseconds, so 60-Hz field with period of 17 msec appears same as static field

[a]e.g., E = 1,000 V/m and M = 100 μT (or 1,000 mG).

motion [a source of generalized noise, ($N_{\Delta M}$) (Vaughan and Weaver 1998)], and should also partially attenuate biologically generated electric fields, potentially decreasing background field noise, ($N_{\Delta E}$).

Contact Currents as a Possible Explanatory Exposure

A "contact current" occurs at home or in the workplace when a person touches two conductive surfaces that are at different electrical voltages. Typically, these currents may flow from hand to hand or from a hand through the feet, depending on how the contact with the conductive surfaces is made. Sensory reactions to contact current depend on the level of current, the physical dimensions and anatomical features of the exposed individual, the size of the contact area (e.g., touch or grip), and unspecified sensitivity factors unique to that individual (reviewed in Reilly 1998). For example, adult men experience sensory thresholds at electric currents between 100 and 500 μA, with progressively lower thresholds for women and children due to their smaller size; a child's lower perception threshold is about 50 μA.

Associations between residential magnetic fields and the risk of childhood leukemia have been observed, but the magnetic fields per se appear to be too weak to cause biologic effects, and leukemia bioassays in rodents are uniformly negative. It is conceivable that the magnetic field measurements are acting as a surrogate for some other exposure. An exposure, such as contact currents, could be an explanatory factor for the observed epidemiologic associations if three conditions are satisfied: *a*) an association is present between contact current exposure and the measured power-line magnetic field level, *b*) levels of contact current expected in a home are sufficient to deliver an adequate dose to the bone marrow, and *c*) a target population (i.e., small children) has the opportunity to encounter contact currents.

Association between magnetic fields and contact voltages. In a computer model, two sources of contact voltage were considered, which appear either between the electrical panel (*P*) and the water line entering the house (*W*), or between the water line (*W*) and the earth ground (*E*) (Kavet et al. 2000). The first source, V_{P-W}, occurs in the grounding conductor that connects the neutral wire at the electrical service panel (fuse or breaker box) to the water line entering the house (as required by the National Electrical Code). The grounding conductor carries a fraction of a home's net load current producing an ohmic voltage across the conductor's length. Because appliance frames also are connected via the third or "green" wire in the power cord to the service panel neutral, an individual can be exposed to V_{P-W} when simultaneously touching an appliance frame and a water fixture.

The second source arises from the voltage between the water pipes and the earth, V_{W-E}. This voltage results from ground currents in the primary and secondary electrical distribution circuits that flow from the water pipes into the earth. V_{W-E} also can result from induction caused by magnetic fields from heavily loaded power lines that may be nearby. V_{W-E} produces a voltage between water pipes and the drainpipe (V_{W-D}), because the drainpipe is sunk into the soil and therefore becomes a component in the earth return pathway. Exposure to a contact voltage could occur to a person bathing while contacting a water fixture or the water stream. If any segment of the water supply or drainpipe is nonconductive, exposure does not occur. Basic engineering principles suggest that, across large populations, V_{W-E} and the residential magnetic field should be associated with each other (Kavet and Zaffanella 2002).

In a computer-modeled neighborhood, Kavet et al. (2000) observed that V_{P-W} is highly correlated to the magnetic field attributable to the ground current within a particular residence. In a pilot study of 36 residences (Kavet and Zaffanella 2002), the degree of correlation between contact voltages and magnetic field measurements varied. V_{P-W} was poorly correlated to spot-measured magnetic fields (B_{avg}) (both log-transformed). This discrepancy is due most likely to the effects of magnetic fields from nearby lines, which may have "swamped" the fields from the ground path. On the other hand, V_{W-E} was significantly ($p < 0.001$) correlated to B_{avg} (both log-transformed) with the highest levels of V_{W-E} (> 400 mV) associated with proximity to high voltage transmission lines (i.e., probably due to magnetic field induction). V_{W-D}, however, was not significantly correlated with B_{avg} (22 valid data points). The results suggest a positive association between magnetic field exposure and contact voltage due to V_{W-E}, but a more precise description of the relation between V_{W-D} and B_{avg} will require a larger sample. V_{W-E} is the source voltage for V_{W-D}, and V_{W-D} is some fraction of V_{W-E}, but the fraction varies from house to house. Kaune et al. (2002) failed to find an association between ground currents and case versus control status for childhood cancer, but because of large variations in the conductivity of water pipes, ground currents may not correlate with contact voltages.

Sufficient dose to tissue. Biologic response to an environmental exposure requires sufficient dose as a necessary but not sole condition. A key difficulty with attributing a causal interpretation to the association between childhood leukemia and magnetic fields has been the low dose to target tissue associated with ambient magnetic fields. For example, residential fields away from appliances rarely exceed 1 μT, and studies using anatomically representative computer models report that a 5-μT 60-Hz magnetic field fails to induce even 1 mV/m (the minimum "benchmark" dose for biologic effects; NIEHS 1999) in an adult's bone marrow, with lower values expected for children because of their smaller size (Kavet et al. 2001).

Studies examining contact current dosimetry report that the bone marrow of a child-sized model's lower arm experiences an average of 5 mV/m per μA of contact current into the hand, and 5% of the tissue achieves 13 mV/m per μA (Dawson et al. 2001). Modeled adults experience roughly 40% of the values of the modeled child. Because exposure in the bathtub scenario (summarized above) can reach 30 μA or more, electric fields in a child's marrow of up to 500 mV/m (0.5 V/m) are conceivable, exceeding by several-fold the above 1 mV/m "benchmark dose."

Opportunity for exposure. Although V_{P-W} can technically cause contact current to flow, it is most likely a minor source of exposure, especially to children. Simultaneous contact with an appliance and a water fixture is probably not common and the reach may be beyond a child's physical dimensions. In addition, most appliance contact is with a dry hand, which means the contact resistance can exceed 100 K ohms, resulting in a relatively low current. In contrast, contact with the water fixture in a bathtub involves a wet hand that essentially short-circuits the insulating outer layer of the skin. Moreover, if children bathe several hundred times per year, then ample opportunity exists for some level of contact, although such behaviors have not been studied.

Table 6. Noise processes that compete with EMF interaction strength.

Noise process	Symbol	Source of competing chemical changes
Stochastic chemical noise	$N_{\Delta N}$	Randomizing collisions and fluctuations inherent to an aqueous biological environment
Temperature variations	$N_{\Delta T}$	Environmental and metabolic temperature fluctuations coupling to significant biochemical temperature dependence
Concentration variations	$N_{\Delta C}$	Physiological processes leading to variations in concentrations of ions and molecules
Mechanical noise	$N_{\Delta M}$	Motion of tissues leading to possible mechanical interference with ongoing processes
Background electric fields	$N_{\Delta E}$	Neuromuscular electrical activity and motion-created streaming potentials that lead to background electric fields

Summary of the contact–current metric. Because the three conditions, association between exposures, sufficient dose, and exposure opportunity, have not been refuted in modeled analyses, the contact-voltage explanation remains viable. However, the key exposure parameters have not yet been characterized in a large-sample study. Furthermore, no bioassay or *in vitro* model of childhood leukemogenesis has been studied with controlled applications of contact current, but molecular models of childhood leukemia in molecular engineered mice can provide insight on the possible role of 60-Hz bone marrow electrical fields. The use of transgenic mice allows characterization of the initial genetic alteration that can be applied to the investigation of subsequent epigenetic factors such as 60-Hz currents through the bone marrow. Thus, although some theoretical models support additional inquiry, the lack of definitive data showing magnetic fields to be a surrogate for exposure to contact voltages adds uncertainty as to the direction of future research.

Summary

In children, ALL represents approximately 75% of the total leukemia types. In acute leukemia, initiating events tend to be genetic in origin and commonly are represented by chromosomal translocations. There are known and suspected risk factors, and epidemiologic associations between EMFs and childhood leukemia have made EMFs a suspected risk factor. Animal data on the effects of EMF exposure, however, are overwhelmingly negative regarding EMF exposure per se being a significant risk for hematopoietic neoplasia. We may fail to observe laboratory effects from EMF exposure because typical power-line EMFs do not give a "dose" detectable above the many sources of "noise" in biologic systems. We may fail to detect EMF effects in bioassay systems because EMFs themselves are not the causal exposure in the epidemiologic associations. "Contact voltages" have been proposed as a novel exposure metric, and they meet three plausibility conditions: association with residential EMF levels, biologic effective dose, and opportunities for exposure. If replicable laboratory findings indicate that contact voltages are important in leukemia risk, then epidemiology studies might be designed to explore this proposal further.

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