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Hypothesis: The Risk of Childhood Leukemia Is Related to Combinations of Power-Frequency and Static Magnetic Fields

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We present a hypothesis that the risk of childhood leukemia is related to exposure to specific combinations of static and extremely-low-frequency (ELF) magnetic fields. Laboratory data from calcium efflux and diatom mobility experiments were used with the gyromagnetic equation to predict combinations of 60 Hz and static magnetic fields hypothesized to enhance leukemia risk. The laboratory data predicted 19 bands of the static field magnitude with a bandwidth of 9.1 μT that, together with 60 Hz magnetic fields, are expected to have biological activity. We then assessed the association between this exposure metric and childhood leukemia using data from a case-control study in Los Angeles County. ELF and static magnetic fields were measured in the bedrooms of 124 cases determined from a tumor registry and 99 controls drawn from friends and random digit dialing. Among these subjects, 26 cases and 20 controls were exposed to static magnetic fields lying in the predicted bands of biological activity centered at 38.0 μT and 50.6 μT. Although no association was found for childhood leukemia in relation to measured ELF or static magnetic fields alone, an increasing trend of leukemia risk with measured ELF fields was found for subjects within these static field bands (P for trend = 0.041). The odds ratio (OR) was 3.3 [95% confidence interval (CI) = 0.4–30.5] for subjects exposed to static fields within the derived bands and to ELF magnetic field above 0.30 μT (compared to subjects exposed to static fields outside the bands and ELF magnetic fields below 0.07 μT). When the 60 Hz magnetic fields were assessed according to the Wertheimer-Leeper code for wiring configurations, leukemia risks were again greater with the hypothesized exposure conditions (OR = 9.2 for very high current configurations within the static field bands; 95% CI = 1.3–64.6). Although the risk estimates are based on limited magnetic field measurements for a small number of subjects, these findings suggest that the risk of childhood leukemia may be related to the combined effects of the static and ELF magnetic fields. Further tests of the hypothesis are proposed.

Key words: electromagnetic fields, extremely low frequency, case-control study, static magnetic field, magnetic resonance

INTRODUCTION

Wertheimer and Leeper's [1979] hypothesis that magnetic fields from power lines are a risk factor for childhood cancer has been difficult to evaluate conclusively in epidemiological studies. Several case-control studies have not found a significant risk of childhood leukemia associated with direct measurements of extremely-low-frequency (ELF; 30–300 Hz) magnetic fields in subjects' homes [Savitz et al., 1988; London et al., 1991; Feychting and Ahlbom, 1993].

The failure to observe an association with direct measurements might reflect either the lack of a true causal link between childhood cancer and magnetic fields or shortcomings in the exposure assessments. In children living near 50 Hz transmission lines, Feychting and

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Ahlbom [1993] observed a significant leukemia risk associated with the 1 year average ELF magnetic fields calculated from historic load data. Therefore, short-term direct measurement of the magnetic field may be a poor estimate of exposure over time, resulting in measurement error sufficient to obscure a true association.

Alternatively, magnetic field characteristics other than the average ELF field's magnitude may be biologically important. Although exposure metrics relevant to childhood cancer are not known, biologic effects attributed to the ELF magnetic fields in several laboratory experiments depend on the frequency and orientation of the oscillating field in relation to the static magnetic field [Blackman, 1990; Liboff et al., 1990].

Based on these experimental results, we propose that childhood leukemia might also be due to particular combinations of the static and ELF magnetic fields. To test this hypothesis, we analyzed magnetic field measurements from bedrooms of children enrolled in a case-control study in Los Angeles County [London et al., 1991; Peters et al., 1991].

HYPOTHESIS

The combinations of the static and oscillating magnetic field in this hypothesis are based on experimental data from four biologic systems—calcium efflux from chick embryo brain tissue [Blackman et al., 1982, 1985, 1988, 1990], mobility of calcium-starved diatoms [Smith et al., 1987], calcium efflux from lymphocytes [Liboff et al., 1987], and operant conditioning of rat behavior [Thomas et al., 1986]. The relevant results from these studies are given in Table 1.

In each of these studies, biologic effects were observed from ELF magnetic fields that had specific frequencies and directions in relation to the static magnetic field. In particular, biological effects peaked at frequencies f that were related to the magnitudes B_o of the static magnetic field by the gyromagnetic equation:

$$2\pi f = n\gamma B_o, \qquad (1)$$

where γ is a constant gyromagnetic ratio, and n is an integer that creates a harmonic series of peaks in the biological activity. This relationship was first proposed by Blackman et al. [1985] to explain the calcium efflux observations (Fig. 1). Values for n and γ in Table 1 were determined empirically by fitting equation 1 to laboratory values for f and B_o at which the biological effect in each study achieves a maximum. Conversely, magnetic field combinations that are more than a bandwidth away from the gyromagnetic relationship (Eq. 1) do not produce the biologic effect, as in the calcium efflux results shown in Figure 1.

To develop an exposure metric for combinations of static and oscillating magnetic fields, the exposures that were biologically active in laboratory studies were extrapolated to the 50/60 Hz power frequency found in homes (see Fig. 1). The complete exposure metric is based on the following assumptions.

1. Frequency spectrum: Because we did not measure the frequency spectrum of the magnetic field in the Los Angeles study, we assumed that the ELF spectrum in the child's bedroom was dominated by 60 Hz, the power frequency in North America. This assumption is supported by measurements of the harmonic distortion in bedrooms, which averages 24.5% and is lowest in the early morning hours [Dietrich et al., 1992]. In other environments, our hypothesis would use the appropriate power frequency, e.g., 50 Hz for homes in the rest of the world.

2. Static magnetic field: The gyromagnetic equation (Eq. 1) with the power frequency and the parameters from Table 1 gives a series of 19 static magnetic fields at which biological effects are predicted (Table 1, Fig. 2). As is shown in Figure 2, some of the derived static fields fall within the 24–68 μT [1 microtesla (μT) = 10 milligauss] range of the geomagnetic "reference" fields on the earth's surface [Skiles, 1985]. The 38.0 and 50.6 μT values predicted to be biologically active are in the range of static fields measured in the homes of the Los Angeles County study population (Fig. 3).

3. Exposure-response function: Although the studies summarized in Table 1 report a variety of frequency dependencies, they all showed that the significant response was limited to a band of frequencies about the value fitting the gyromagnetic equation. Without clear guidance from experiments or physical theories, we chose to create dichotomous exposure categories for the epidemiologic analysis. We define an "exposed" subject as one who slept in a bedroom where the measured static magnetic field lies within a bandwidth ΔB_o of a static field value from Table 1; otherwise, the subject is "not exposed."

4. Bandwidth: Plots of biological activity vs. frequency have a full-width, half-maximum bandwidth Δf [Liboff et al., 1990]. In Table 1, we estimate Δf from the few experiments done at closely spaced ELF frequencies [Liboff et al., 1987; Smith et al., 1987]. According to the gyromagnetic equation (Eq. 1), there should also be a static field bandwidth ΔB_o around the B_o values in Table 1. ΔB_o can be estimated from laboratory values of the frequency bandwidth Δf by expressing them as differentials of equation 1:

$$\Delta B_o = \frac{2\pi\Delta f}{n\gamma}. \qquad (2)$$

TABLE 1. Static Magnetic Fields Predicted to Be Biologically Active in Combination With 60 Hz Magnetic Fields, Using Equation 1 and Parameters Derived From Laboratory Studies

Static magnetic fields (μT) predicted to be biologically active at 60 Hz

Harmonic (n)	Calcium efflux[a]		Diatom mobility[b]	$^{45}Ca^{2+}$ influx of lymphocytes[c]	Rat behavior[d]
	Strong*	Weak**			
1	152.0	76.0[e]	78.4	87.9	26.0
2	[f]	38.0			
3	50.6	25.3	26.1		
5	30.4	—	15.7		
6	–	12.7			
7	21.7				
9	16.9				
13	11.7				
15	10.1	—	5.2		
17	8.9				
19	8.0				
γ(Hz/μT)	2.48	4.96	4.81	4.29	14.44
Bandwidth					
Δf (Hz)	<5.5[g]	ND[h]	7.0	1.7	ND
ΔB_o(μT)	<14	ND	9.1[g]	2.9[g]	ND
Spatial orientation	Perpendicular		Parallel	Parallel	ND

†Empirical parameters are the gyromagnetic ratio γ, harmonic parameter n, frequency bandwidth ΔF, and static field bandwidth ΔB_o.
*$P < .01$ in calcium efflux significance test [Blackman et al., 1988].
**$0.01 < P < 0.05$ in calcium efflux significance test.
[a]Blackman et al., 1982, 1985, 1988, 1990.
[b]Smith et al., 1987.
[c]Liboff et al., 1987.
[d]Thomas et al., 1986.
[e]The first harmonic in this series is not significant ($P = 0.12$) but is included in order to obtain integral harmonics.
[f]No significant biological effect is reported at harmonics that are blank.
[g]Bandwidths estimated from equation 2.
[h]ND, not determined in the study.

In Table 1, ΔB_o is estimated with n = 1, because the bandwidth has been studied only at the first harmonic. From the three bandwidths given in Table 1, we selected ΔB_o = 9.1 μT derived from the diatom mobility study [Smith et al., 1987], because this value alone gave us enough subjects "exposed" and "not exposed" to the bands that an epidemiological analysis could be performed.

5. Spatial orientation: In Table 1, the biological effects were found when the static and ELF magnetic fields had either a perpendicular orientation [Blackman et al., 1990] or parallel orientation [Smith et al., 1987; Liboff et al., 1987]. Because the Los Angeles study did not measure the spatial orientation of the magnetic fields, this aspect of the hypothesis cannot be tested with these data.

6. ELF magnetic field: A variety of biological responses to the magnitude of the ELF magnetic field are also reported. For example, the calcium influx of lymphocytes [Liboff et al., 1987] increases monotonically with the ELF field's magnitude in the range below 21 μT where household fields occur. However, Blackman et al. [1982] reported nonlinear "windows" of biological activity with the ELF field magnitude. Litovitz et al. [1990] showed that such exposure-response windows can result from constant magnetic field exposures for periods of several hours. Since the ELF magnetic fields in homes are constantly varying, the windows seen in laboratory studies are unlikely to occur from household exposures.

To simplify the test of the present hypothesis, we chose the time-weighted average (TWA) of the ELF measurements over 24+ h as the measure of exposure to the 60 Hz magnetic field. Leukemia risks influenced by the temporal variability in the ELF magnetic field are treated in a companion paper [Thomas et al., 1994b].

To summarize, we hypothesize that leukemia risk increases steadily with the time-averaged power-frequency magnetic field for subjects whose static magnetic field exposure falls within a derived band of biological

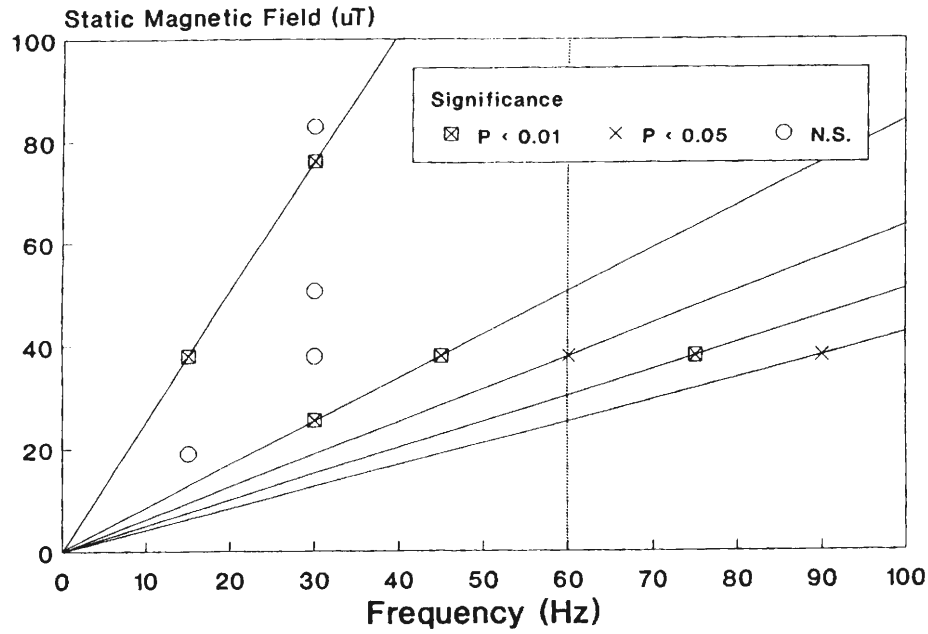

Fig. 1. Studies of calcium efflux [Blackman et al., 1985, 1988]-exposed tissue to the static magnetic field magnitudes and ELF frequencies shown. The gyromagnetic equation (Eq. 1) is fit to data points for significant calcium efflux. Combinations of static and 60 Hz magnetic fields with biological effects are predicted by extrapolation.

activity (Fig. 3). In Los Angeles homes, some subjects are exposed to the derived bands at 38.0 ± 4.6 μT and 50.6 ± 4.6 μT. We also used the Wertheimer-Leeper [1982] code for wiring configuration as a surrogate measure of 60 Hz magnetic field exposure due to its significant association with childhood cancer in past studies [Wertheimer and Leeper, 1979; Savitz et al., 1988; London et al., 1991].

MATERIALS AND METHODS

Subjects were participants in the case-control study of childhood leukemia in Los Angeles County [Peters et al., 1991; London et al., 1991]. Cases were children with leukemia diagnosed in Los Angeles County from birth to age 10 years. Controls were obtained through friends or random digit dialing and were matched to the cases on age, sex, and ethnicity. The current analyses include only the subjects for whom we measured the static magnetic field and at least one indicator of ELF exposure (either 24 h measurements or wiring configuration). In addition, two subjects were excluded, because their static magnetic field measurements were outliers greater than 60 μT. These restrictions left 223 subjects with ELF measurements (124 cases and 99 controls) and 233 subjects with wiring configuration data (132 cases and 101 controls).

An important parameter in the risk analysis is the minimum time subjects had to spend in the home with measurements (expressed as a percentage of the etiologic period). We would expect a clearer association between leukemia risk and the field combinations in subjects with longer exposure durations. However, increasing the duration requirement decreases the number of subjects and the resulting precision of the risk estimates. Since we had no a priori hypothesis on the exposure duration required to see an effect, we examined the effect of the duration parameter on the number of subjects exposed to the static field bands and selected 80% of the etiologic period as the minimum exposure time for the hypothesis test. To test the effect of exposure duration in this hypothesis, we repeated the analysis with durations ≥50% of the etiologic period.

The exposure measurements were taken in the subject's bedroom at the home in Southern California where the subject had lived for the longest portion of the "etiologic" period. The etiologic period was defined as the time between the mother's last menstrual cycle preceding the birth of the cancer case (decided by interview) up to a reference date keyed to the date of the leukemia's diagnosis [London et al., 1991]. For a control, the home for measurements was selected via the same algorithm using the reference date of the matched case.

The static magnetic field was measured in the center of the subject's bedroom with a single-axis flux-gate magnetometer (model MAG-01; Bartington Instruments Ltd., Oxford, United Kingdom). To measure the three

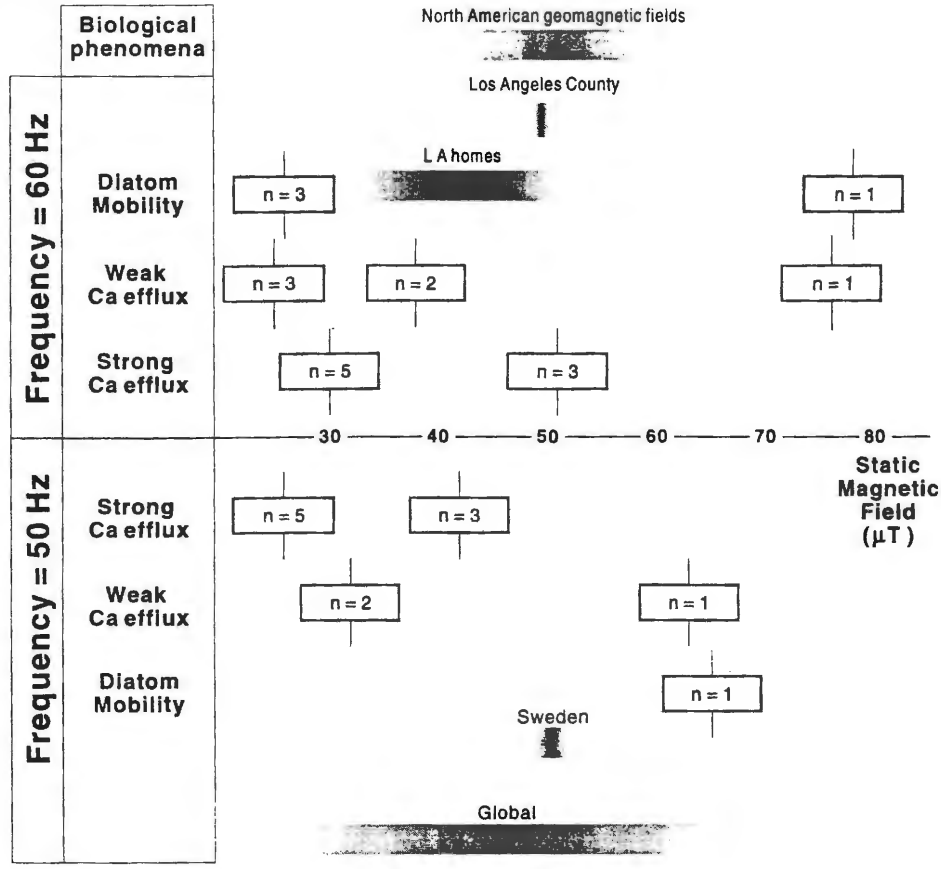

Fig. 2. Static magnetic fields producing biological phenomena are predicted to lie in bands whose center value depends on the power frequency (50 or 60 Hertz) and whose bandwidth is 9.1 μT. The bands are compared to geomagnetic reference fields in various regions [Skiles, 1985] and to the static field measurements in Los Angeles homes.

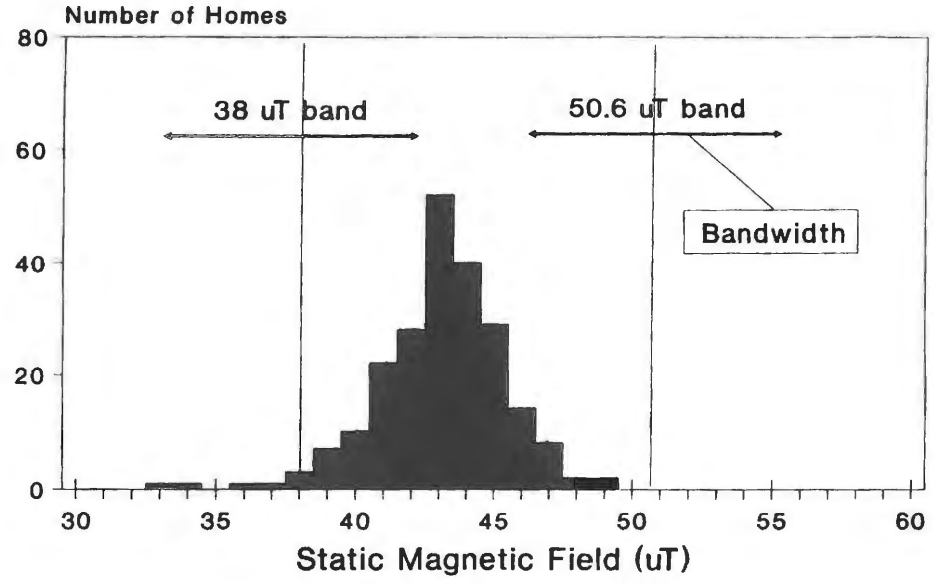

Fig. 3. Distribution of static magnetic fields measured in subject bedrooms in the Los Angeles County study of childhood leukemia. Two outliers at 67.0 and 89.6 μT are not shown.

orthogonal components of the static field, the flux-gate probe was placed into holes in a plastic stand 0.91 m (3 feet) tall. The static field magnitude B_o is calculated by taking the resultant of the three components.

For quality control, the magnetometer was compared annually with a geological magnetometer whose accuracy was ±0.001 μT. In these side-by-side measurements, the geological magnetometer was within the ±0.01 μT fluctuations of our magnetometer. To evaluate precision, the magnetometer measurements were repeated at four homes. The coefficient of variation between repeated measurements was 3.5%. At the study's completion, the magnetometer was calibrated in a Helmholtz coil with a measured DC current, yielding a calculated field of 50.42 μT. The magnetometer's bias was +0.86 μT, which is +1.7% of the absolute static field and 9.5% of the bandwidth. In the analysis, the magnetometer measurements were corrected for this bias.

To measure the ELF magnetic field, an EMDEX or IREQ monitor was placed near the site of the child's bed for 24–72 h [Peters et al., 1991]. The ELF monitors were calibrated throughout the study in Helmholtz coils with measured 60 Hz currents, and their measurements were corrected for the calibration bias. The TWA of the ELF magnetic field resultant was used in the risk analysis.

Configurations of electric distribution and transmission wiring by the homes were classified into the five categories defined by Wertheimer and Leeper [1982] (WL). The WL categories were coded from wiring maps [London et al., 1991]. The wire code computer program from the earlier study was modified to classify homes with "mixed" underground and overhead lines into the appropriate overhead category, consistent with the WL coding rules. Our risk analysis combined subjects whose wiring configurations were Underground or Very Low Current Configuration to form a more stable reference category.

The ELF magnetic field measurements were divided into four categories separated by the 50th, 75th, and 90th percentiles of all 223 ELF measurements (irrespective of the static field exposure). Odds ratios, 95% confidence intervals, and tests for trend [Breslow and Day, 1980] were calculated for the four ELF exposure categories according to whether the subjects were exposed to the putative biologically active bands of the static magnetic field (Table 2). All odds ratios were calculated relative to a reference category with the least a priori risk, which is the lowest ELF magnetic field category with static fields outside the bands. We used unmatched logistic regression to estimate associations with leukemia risk and treated sex, age, and race as confounding variables, as London et al. [1991] did in the original analysis.

RESULTS

Figure 3 shows the distribution of static magnetic field measurements compared to the hypothesized bands of biological activity. The mean and standard deviation of bedroom static fields were 43.6 ± 2.3 μT. (Outliers at 67.0 and 89.6 μT were removed.) Most household static magnetic fields in the Los Angeles County study lay outside the biologically active bands at 38.0 and 50.6 μT, which were derived from the calcium efflux experiments. Among the 223 subjects with static and ELF magnetic field measurements, 26.5% (32 cases and 27 controls) were exposed within the 38.0 μT band, 11.7% (15 cases and 11 controls) were in the 50.6 μT band, 61.4% (76 cases and 61 controls) were between the bands, and one case was below the 38.0 μT band. If exposure durations are required to be at least 80% of the etiologic period, the number of subjects in the two bands is reduced to 26 cases and 20 controls.

To test the hypothesis that the ELF and static field combinations are associated with leukemia risk, odds ratios (OR) for leukemia risk were calculated for subjects exposed to either band for at least 80% of the etiologic period (Table 2). The OR for subjects in the highest ELF field exposure within the bands was 3.3 (95% confidence interval - 0.4–30.5) relative to those in the lowest ELF field category outside the bands. Although none of the individual ORs was statistically significant, a statistically significant trend was observed across the four ELF magnetic field categories for subjects within the bands (P for trend = 0.041). As in the paper of London et al. [1991], the risk estimates are unadjusted for age, sex, or race, because these matching factors did not alter the findings.

In contrast, no association between leukemia risk and ELF magnetic fields was found for children with static magnetic field exposures outside the bands of biological activity (Table 2). Indeed, the ORs were consistently less than one, but the trend was nonmonotonic and far from significant. Such an effect is not predicted by the hypothesis and is probably a chance finding.

A term for multiplicative interaction between exposures to the static field bands and the ELF magnetic field categories (both treated as ordinal variables) was marginally significant (P = 0.075). When the ELF measurements of subjects with exposure durations >80% were considered without regard to the static field bands, the exposure-response profile was essentially flat (OR for the highest ELF exposure category = 1.5, with 95% CI = 0.4–4.9; P for trend = 0.82). When the magnetometer measurements were considered alone, the odds ratios across deciles of the static field displayed no significant pattern (P = 0.88), nor was any OR signifi-

TABLE 2. Risk of Childhood Leukemia From Measured ELF Magnetic Fields, Depending on Whether the Measured Static Magnetic FieldIs Within or Outside the Derived Bands of Biological Activity

Static magnetic field	Minimum exposure duration (percentage of etiologic period)	Leukemia risk for ELF magnetic field measurements (time-weighted averages) 0.00–0.07 μT	0.07–0.14 μT	0.14–0.30 μT	0.30+ μT	*P* (trend)
Within bands	80%	OR[a]: 0.5	0.7	2.3	3.3	0.041
		CI: (0.2–1.4)	(0.2–2.4)	(0.4–12.4)	(0.4–3.5)	
		Ca/Co: 8/11	6/6	7/2	5/1	
Outside bands	80%	1.0[b]	0.1	0.4	0.8	0.300
		—	(0.0–0.4)	(0.1–1.2)	(0.2–3.0)	
		26/17	2/13	5/9	6/5	
Within bands	50%	0.7	0.6	1.7	1.5	0.365
		(0.3–1.7)	(0.2–1.8)	(0.3–4.4)	(0.3–8.4)	
		16/14	8/8	8/4	5/2	
Outside bands	50%	1.0[b]	0.2	0.5	0.9	0.325
		—	(0.1–0.7)	(0.2–1.4)	(0.2–3.0)	
		38/23	6/15	8/10	7/5	

[a]Ca, number of cases; CI, 95% confidence interval; Co, number of controls; OR, odds ratio.
[b]Reference category for all odds ratios with the same minimum for the exposure duration.

cantly different from another (data not shown). Therefore, both the ELF magnitude and the static bands must be considered in order to observe an association with childhood leukemia.

We conducted analyses to examine the sensitivity of these findings to other definitions of exposure. Lowering the exposure duration from 80% to 50% of the etiologic period decreased the association between ELF magnetic field and leukemia risk within the bands. We also examined the associations separately within the 38.0 and 50.6 μT bands predicted to be biologically active. The 38.0 μT band has over twice as many subjects as the 50.6 μT band and contains all of the subjects in the highest ELF exposure category. Not surprisingly, the association was limited to this band (*P* for trend = 0.036).

We examined the change in leukemia risks with variations in the bandwidth from 8.0 to 12.6 μT. When the leukemia risk was calculated for both bands combined and exposure durations >80%, the trend in the exposure-response relationship was significant only for bandwidths ranging from 9.1 to 9.8 μT. We examined the sensitivity of the association to the magnetometer calibration. When the magnetometer measurements were not corrected for the measurement bias, the trend was not significant (*P* = 0.154).

When ELF magnetic field exposures were assessed by wiring configurations (Table 3), the trend in leukemia risk within the static field bands was statistically significant, whether the minimum percentage of the etiological period was 80% (*P* for trend = 0.011) or 50% (*P* for trend = 0.0003). No association was found for subjects whose static field exposure was outside the bands. Within the bands, the odds ratio for the highest wiring category (OR = 9.2 for Very High Current Configurations; 95% CI = 1.3–65.3) was greater than the risk for the highest ELF measurements (OR = 3.3; 95% CI = 0.4–30.5).

Finally, we examined why the static magnetic field measured in the children's bedrooms averaged 43.6 ± 2.3 μT, whereas the geomagnetic reference field ranged from 49.1 to 49.6 μT in Los Angeles County (Fig. 2). This 12% discrepancy between the bedroom fields and the geomagnetic fields was not explained by the +1.7% bias and 3.5% imprecision in our static field measurements. Therefore, we analyzed magnetometer measurements taken inside and outside 103 Los Angeles County homes in a separate study (Sobel, personal communication). Exterior static fields had a mean and standard deviation of 47.8 ± 2.0 μT, which lies between the bedroom fields and the geomagnetic reference fields. In linear regressions, the exterior static field measurement was not a good predictor of interior measurements (*P* = 0.35). Building material (*P* = 0.0005) and type of building (*P* = 0.12) were better predictors. Inside stucco homes, the most common building material in the region, the average static magnetic field was 0.9 μT below the mean exterior field. Therefore, perturbations of the geomagnetic field by building materials, steel objects, and geologic anomalies may explain the deviation between bedroom static fields and the geomagnetic reference fields in Los Angeles County.

DISCUSSION

We found ELF magnetic field measurements to be significantly associated with leukemia risk only within the 38.0 μT and 50.6 μT bands of the static field predicted to be biologically active. These bands were pri-

TABLE 3. Risk of Childhood Leukemia From Wertheimer-Leeper Wiring Configurations, Depending on Whether the Measured Static Magnetic Field Is Within or Outside the Derived Bands of Biological Activity

Static magnetic field	Minimum exposure duration[c]	Leukemia risk for wiring configuration categories: Very low + underground	Ordinary low	Ordinary high	Very high	*P* (trend)
Within bands	80%	OR[a]: 0.6	0.5	2.4	∞	0.011
		CI: (0.1–3.2)	(0.1–1.8)	(0.5–11.7)	Undefined	
		Ca/Co: 4/5	8/13	9/3	6/0	
Outside bands	80%	1.0[b]	0.9	0.8	0.6	0.508
		—	(0.3–2.7)	(0.2–2.4)	(0.1–2.5)	
		10/8	16/15	14/15	5/7	
Within bands	50%	0.5	0.6	4.0	9.2	0.0003
		(0.1–1.7)	(0.2–1.9)	(1.0–16.8)	(1.3–64.6)	
		5/10	10/15	14/3	10/1	
Outside bands	50%	1.0[b]	1.3	1.1	1.1	0.938
		—	(0.5–3.5)	(0.4–2.9)	(0.3–3.5)	
		13/12	22/16	24/20	8/7	

[a]Ca, number of cases; CI, 95% confidence interval; Co, number of controls; OR, odds ratio.
[b]Reference category for all odds ratios with the same minimum for the exposure duration.
[c]Percentage of etiologic period.

marily derived from calcium efflux data. The association was found mostly in the 38.0 μT band, where most of the exposures occurred. No significant association with leukemia risk was observed for ELF or static magnetic fields considered alone nor for the field combinations outside the bands. The association between leukemia risk and ELF magnetic field measurements disappeared when the bandwidth was increased too far beyond the 9.1 μT value derived from the experimental evidence or when subjects with exposure durations less than 80% of the etiological period were included in the risk analysis. If this finding proves correct, leukemia risk may relate to complex combinations of magnetic field properties including the magnitude and frequency of the ELF field and the magnitude of the static field.

The analysis of wiring configurations (Table 3) also supports the hypothesis, because the association with this surrogate for 60 Hz magnetic fields is stronger within the static field bands. As in the previous studies [Savitz et al., 1988; London et al., 1991; Feychting and Ahlbom, 1993], the associations with leukemia in our data were stronger when exposures to 60 Hz magnetic fields were assessed by wiring configuration than by the ELF measurements. These results are consistent with the hypothesis that electrical wiring is a better surrogate for the long-term average of the household ELF magnetic field than short-term measurements due, perhaps, to the wiring's greater stability [Davon et al., 1993; Thomas et al., 1994a].

Our data have several weaknesses for evaluating the proposed hypothesis. Few homes in Los Angeles lie within the static field bands of interest. Thus, the analysis within the bands was based on small numbers of subjects, and the risk estimates have wide confidence intervals. Other geographical locations have geomagnetic fields at the bands of biological activity (Fig. 2) and would be better sites for testing this hypothesis.

The results from these sparse data are sensitive to modifications in parameters for the hypothesis, as reflected by the change in the associations when the exposure duration parameter is modified. According to the hypothesis, leukemia risks should become clearer with greater exposure durations. However, raising the exposure duration limit decreases both the number of subjects and the precision of the risk estimates. For example, increasing the minimum exposure duration from 80% to 100% reduced the number of exposed subjects from 48 to 18, which eliminated the statistical significance of the trend. We cannot determine whether the decreased significance in the risk with increasing exposure duration results from a failure of the hypothesis or the small numbers of subjects. A similar problem was encountered in the sensitivity analysis for the exposure duration with wiring configuration (Table 3).

Our inability to adjust for potential confounders is another potential weakness due to the small number of subjects within the bands. In London et al. [1991], other factors associated with leukemia risk (socioeconomic status and environmental exposures such as incense, pesticides, hair dryer use, and father's chemical exposures) did not materially alter the association between wiring configuration and leukemia, and similar results could be expected here. Although confounding

by a factor not yet known to influence leukemia risk is always possible, this factor would need to be jointly associated with the ELF magnetic field, the static magnetic field bands, and leukemia risk to produce the observed association.

Another weakness is the assessment of static magnetic field exposures by taking a single measurement at the center of the child's bedroom. Since iron in mattress springs and elsewhere can perturb the geomagnetic field, the child's static magnetic field exposure during sleep may be different from the value measured in the room's center [Swanson, 1994]. Accurately testing this hypothesis requires simultaneous measurements of the static and ELF magnetic field, their relative orientation, and the frequency spectrum. Since these sources of exposure misclassification should not have differed between cases and controls, they would not be expected to produce an association between leukemia risk and the magnetic field combinations. However, it would be desirable to monitor personal exposure to the varying magnetic field combinations over time.

Another potential source of misclassification comes from the limitations of quality control for the static field measurements. We only had one calibration at the end of the study for correcting the magnetometer bias. Because this bias was substantial relative to the static field bandwidth, the odds ratios for a small number of subjects were sensitive to the calibration. However, the magnetometer's bias and random imprecisions would incline the risk estimates towards the null, since any misclassifications should be nondifferential. Nonetheless, regular calibrations throughout the study would give more accurate exposure assessments and risk estimates.

The proposed hypothesis itself has several weaknesses. The hypothesis was developed by a combination of theoretical and empirical reasoning. Physical theories for peak responses to magnetic field combinations obeying the gyromagnetic equation were invoked by Blackman et al. [1985] and Liboff [1985] to explain the calcium efflux results. We did an a priori derivation of γ and the harmonic parameter n a from the static and ELF magnetic field combinations that have been reported to be biologically active in laboratory experiments.

After exploring several response functions for the static field bands, we chose the dichotomous function, because it explained the experimental data with the fewest assumptions (the principle of "Occam's razor"). Although a response declining continuously with deviations from the predicted static field resonance is more plausible physically, the functional form cannot be clearly inferred from either theory or experiment. Until the correct response function is indicated by future studies, the simplicity of the dichotomous function makes it preferable for epidemiological tests of the hypothesis.

The ELF magnetic field metrics, the bandwidth ΔB_o, and the minimum exposure duration were dictated not by theory but by the limitations of the childhood leukemia data. To avoid multiple comparisons, the bandwidth and exposure duration parameters along with the rest of the hypothesis were specified before we looked at the epidemiological data and only later varied in a sensitivity analysis.

Blackman and Most [1993] propose an equivalent formulation of this hypothesis buttressed by additional results from calcium efflux experiments. In contrast to our exposure metric, they consider only strong calcium efflux (the first column of Table 1) but also include effects from harmonics of the power frequency. Since the harmonic content of household ELF magnetic fields is substantial [Dietrich et al., 1992], the incorporation of these higher frequencies in the gyromagnetic equation (Eq. 1) is a logical extension of our hypothesis.

As hypotheses based on laboratory studies, these proposals depend on the reliability of the experimental results in Table 1. Although Blackman et al. [1982, 1985, 1987, 1990] have repeated the ELF calcium efflux experiments, the combined effect of static and ELF magnetic fields on calcium efflux has never been replicated by other investigators. Of the studies in Table 1, only the diatom mobility study has been partially replicated [Reese et al., 1991]. Attempts to replicate the original report of $^{45}Ca^{2+}$ influx with lymphocytes [Liboff et al., 1987] have been negative [Prasad et al., 1991; Yost and Liburdy, 1992].

The hypothesis has other limitations. None of these experimental studies are directly related to leukemia initiation or promotion. Further, only the calcium efflux data point at 60 Hz and 38.0 μT (Fig. 1) was taken at the exposure conditions found in Los Angeles homes. Additionally, the gyromagnetic ratios and bandwidths in Table 1 are based on a single study, so we could not determine the experimental errors of these parameter values. Therefore, the details of this empirical hypothesis may be revised as more laboratory experiments are published. An important test of the hypothesis will be whether future refinements result in stronger risk estimates.

This hypothesis also suffers from the lack of an established biophysical mechanism that can fully explain the biological findings and derive quantitative formulas for the exposure metric. Peak responses to magnetic field combinations obeying the gyromagnetic equation are observed in cyclotron resonance, nuclear magnetic resonance, electron spin resonance, and atomic and molecular spectroscopy. As is summarized in Table 4, several magnetic resonance mechanisms of these types have been proposed to explain the biological effects in Table 1. These resonances result from interactions of various magnetic moments with the magnetic field combinations.

None of the theories listed in Table 4 appears to account for the calcium efflux findings from which the 38.0 and 50.6 μT bands are derived. The gyromagnetic ratio for strong calcium efflux ($\gamma = 2.48$) corresponds to the $\gamma = 2.46$ predicted for potassium ions moving in a biological substrate by both cyclotron resonance [Liboff, 1985] and parametric resonance [Lednev, 1991] (Table 4). However, none of the theoretical resonances in Table 4 fully explains the exposures under which calcium efflux was observed. Since strong calcium efflux was found only with the ELF field oriented perpendicular to the static field [Blackman et al., 1990], cyclotron resonance and parametric resonance with their parallel orientations can be eliminated. Electron spin resonance advanced as a mechanism by Blackman et al. [1988] is not a viable explanation for calcium efflux, because the theoretical γ for electron spin in a biomolecule is too large by orders of magnitude. Lednev's mechanism is also unsatisfactory, because it occurs at subharmonics ($n < 1$), rather than the overharmonics ($n > 1$) observed with calcium efflux. Subharmonics are also a feature of "optical double resonance," which is the spectroscopic analog to Lednev's mechanism with the magnetic fields oriented perpendicularly [Happer and Gupta, 1978]. Classical magnetic resonance with a bound ion [Edmonds, 1993] should not occur at harmonic frequencies. In the magnetosome mechanism [Kirschvink, 1992], the magnetic resonance of the single-domain ferromagnetic crystal is damped away by the viscosity of the biological medium, so the response does not have narrow peaks obeying the gyromagnetic equation. Finally, any resonance with power-frequency magnetic fields should be overcome by thermal noise [Kaune, 1985; Adair, 1991, 1992a,b] unless biological amplification enhances the resonance signal sufficiently.

After rejecting the mechanisms in Table 4, we formulated a strictly empirical hypothesis that fit our exposure data and the epidemiological requirements as well as the laboratory findings. Therefore, we cannot attach any biophysical mechanism to this hypothesis.

TABLE 4. Physical Mechanisms Considered To Explain the Calcium Efflux Resulting From Perpendicularly Oriented Fields With the Parameters $\gamma = 2.48$ ($n = 1, 3, 5 \ldots$) and $\gamma = 4.96$ ($n = 1, 2 \ldots$)

Mechanism	Type of magnetic moment	Gyromagnetic ratio γ (Hz/μT)[a]	Harmonics (n)	Field orientation
Electron spin resonance [Blackman et al., 1988]	Electron spin	$gq/2m = 1.76 \times 10^5$	Multiplets from spin-spin coupling	Perpendicular
Cyclotron resonance [Liboff, 1985; McLeod and Liboff, 1986; Liboff and McLeod, 1988]	Ionic motion in helical channels	$q/m =$	1, 2 . . .	Parallel
	Li^+	13.88		
	Ca^{2+}	4.81		
	$^{45}Ca^{2+}$	4.29		
	K^+	2.47		
Parametric resonance [Lednev, 1991; Blanchard and Blackman, 1994]	Motion of bound ion (same parameters as above)	q/m	1, ½ . . .	Parallel
Classical magnetic resonance [Edmunds, 1993]	Motion of bound ion	$q/2m =$	1	Perpendicular
	Li^+	6.94		
	Mg^{2+}	3.96		
	Fe^{3+}	2.59		
	Ca^{2+}	2.40		
Double resonance [Happer and Gupta, 1978]	Motion of bound ion (same parameters as above)	q/2m	1, ½ . . .	Perpendicular
Magnetosome vibrations [Kirschvink, 1992]	Biological magnetite	Resonance damped out		Perpendicular

[a] γ in Hertz per Tesla has the same units as q/m in Coulomb per kilogram in the SI system of measurement. g, Landé g-factor for the electron = 2.00232; m, particle mass; q, particle charge.

Recently, Floderus et al. [1993] reported a significant risk of adult leukemia associated with measurements of workplace ELF magnetic fields, suggesting that the static magnetic field is not necessary to predict risk. The geomagnetic reference fields for Swedish cities range from 48.7 to 51.5 μT, which is 1.9 μT above the nearest biologically active band for 50 Hz power frequencies (Fig. 2). However, the distribution of static magnetic fields measured in workplaces is far broader than the geomagnetic reference fields [Bowman and Kardous, 1993]. Therefore, the static magnetic fields inside Swedish workplaces could be within the 42.2 μT response band predicted for the 50 Hz Swedish power supply. An important test of our hypothesis would therefore be provided by magnetometer measurements in the workplaces from Floderus et al. [1993].

CONCLUSIONS

We have generated an hypothesis that childhood leukemia is related to combinations of static and power-frequency magnetic fields. Parts of the hypothesis were developed a priori by theoretical and empirical reasoning, and parts were chosen a posteriori to allow an epidemiological test of the hypothesis with the childhood leukemia data from Los Angeles County.

The biologically active combinations of magnetic fields were associated with a significantly increasing trend of childhood leukemia in Los Angeles County. The elevated risks are based on limited magnetic field measurements and a small number of Los Angeles subjects exposed to the biologically active fields.

Although previous cancer studies in the United States found no risk associated with measurements of the ELF magnetic field magnitude alone, our findings suggest that household magnetic fields might be associated with leukemia risk if the static field's magnitude is examined along with the magnitude and frequency of the ELF field. Since this hypothesis was developed from limited findings in laboratory studies, further research on mechanisms, biophysical theory, and exposure assessment methods is needed to refine this hypothesis and test it definitively.

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