

Residential EMF Exposure and Childhood Leukemia: Meta-Analysis and Population Attributable Risk

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The controversy over the possible association between magnetic field exposure and childhood leukemia has led several researchers to summarize the literature using meta-analysis. This paper reviews these previous meta-analyses and extends them by adding results from four studies published since the most recent analysis. The analyses include odds ratio calculations based on both dichotomous and continuous exposure models, heterogeneity analysis including subgroup summaries and meta-regression, “leave one out” influence analyses, and publication bias assessments. In addition, there is a review of some of the considerations of the exposure assessments used in the studies and their implications for cross-study comparisons. Finally, the results of the analyses using dichotomous and continuous exposure model are combined with national exposure data to estimate the population attributable risk of childhood leukemia among children in the US. If an association exists, as many as 175–240 cases of childhood leukemia in the US may be due to magnetic field exposure. *Bioelectromagnetics Supplement 5:S86–S104, 2001.* © 2001 Wiley-Liss, Inc.

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INTRODUCTION

The purpose of a meta-analysis is to provide a systematic, rigorous and quantitative review of a body of literature. In the study of residential exposure to magnetic fields and the occurrence of childhood leukemia, several meta-analyses have been conducted [National Radiological Protection Board, 1992; Ahlbom et al., 1993; Washburn et al., 1994; Miller et al., 1995; Meinert and Michaelis, 1996; National Research Council, 1997; Wartenberg, 1998; Wartenberg et al., 1998]. This paper summarizes and critiques those evaluations, explores the implications of their results for making inferences about the possible association between residential exposure to magnetic fields and childhood leukemia, and predicts the magnitude of the population attributable risk in the United States (US).

What is a Meta-Analysis?

Meta-analysis is a statistical method designed to summarize and simplify a complex set of study results [Greenland, 1987, 1994, 1998; Petitti, 2000]. Typically, original studies are identified systematically from the literature, these studies are evaluated for suitability for summarization, data are extracted from each study in a consistent manner, and these data are subjected to a series of statistical analyses. Meta-analysis differs from other literature summaries in that other efforts typically are less systematic and less

comprehensive and, most often, results are not reported quantitatively. To maintain objectivity when conducting a meta-analysis, it is important for investigators to specify *a priori* a set of criteria for acceptable studies. Once studies are selected, a protocol for data extraction must be developed and implemented. Finally, a set of statistical analyses must be chosen. Typically, these include average risk estimation, heterogeneity analysis, influence analysis, and assessment of possible publication bias.

When undertaking a meta-analysis, there are several issues one must grapple with. For example, to conduct the statistical analyses of a set of studies, one must first determine a common exposure metric across which studies can be compared. If not done rigorously, this can lead to concerns about the validity of the analysis. One also must determine the specific statistical methods to be used in analyzing the data. In addition,

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there is much concern over how the heterogeneity is assessed and interpreted and whether the tests for heterogeneity have ample statistical power [Greenland, 1983; Petitti, 2000]. One must determine whether all the studies can be combined together for a single effect estimate or whether one must restrict the analyses to specific subgroups. Another concern when summarizing effects is whether dichotomous or continuous exposure response models are to be used to quantify effect sizes and whether adjustments can be made for confounders and effect modifiers. Following these analyses, one must decide how best to assess their statistical robustness, such as by conducting sensitivity or influence analyses, and how to assess the possible publication bias.

Of all the issues in the application of meta-analysis to observational studies in environmental epidemiology, the largest methodologic controversy is the comparability (and heterogeneity) of studies [Greenland, 1987; Fleiss and Gross, 1991; Dickersin and Berlin, 1992; Colditz et al., 1995; Petitti, 2000]. Comparability can be a function of design, exposure assessment, and/or adjustment for confounders and effect modifiers. The controversy focuses mainly on how one ought to assess heterogeneity, given the low statistical power of traditional methods, and how one ought to describe it [Fleiss, 1981; Greenland, 1983; DerSimonian and Laird 1986; Hardy and Thompson, 1998; Poole and Greenland, 1999; Thompson and Sharp, 1999; Petitti, 2000]. Often, one evaluates whether the data are sufficiently homogeneous to warrant a single analysis or whether one ought to limit the analyses to assessment of homogeneous subgroups. Increasingly, one of the most important goals of meta-analysis has been to try to explain the observed heterogeneity, often through subgroup analyses and related methods [Olkin, 1994; Lau et al., 1997].

Another large issue in meta-analysis is the need to apply regression models (i.e., meta-regression) to assess trend and exposure response, in preference to simple dichotomous models and adjust for confounding and effect modification [Greenland, 1987; Maclure and Greenland, 1992; Greenland and Longnecker, 1992; Berlin et al., 1993]. Limiting analyses to dichotomous exposures can obscure some patterns in the data and limit interpretations.

Below I consider these issues with respect to meta-analyses of residential magnetic field exposure and childhood leukemia.

A Review of Meta-Analyses of Residential EMF Exposure and Childhood Leukemia

As noted above, several meta-analyses have been conducted to assess the association between residential

magnetic field exposure and childhood leukemia. Because of the limited number of original epidemiologic studies conducted in this field to date and the close scrutiny the field is under, there is little controversy over the identification of studies potentially eligible for a meta-analysis. The selection of studies to include, however, has varied widely across meta-analyses. I briefly review these meta-analyses, highlighting differences, and report the estimated effect sizes in Table 1.

The first meta-analysis of residential magnetic field exposure and childhood leukemia was presented in a report of the National Radiological Protection Board of the United Kingdom [National Radiological Protection Board, 1992]. In that review, the authors excluded the first residential magnetic field and childhood leukemia study [Wertheimer and Leeper, 1979] from consideration because it was the sentinel study that raised the concern [Enterline, 1985]. They combined results from three other studies [Fulton et al., 1980; Tomenius, 1986; Savitz et al., 1988] in three separate analyses using the alternative exposure metrics of wire codes, distance from electric lines and measured magnetic fields. They found elevated average odds ratios (ORs) for each exposure metric.

In the following year, three studies of residential magnetic field exposure and childhood cancer conducted in Scandinavian were published [Feychting and Ahlbom, 1993; Olsen et al., 1993; Verkasalo et al., 1993]. In these studies, the calculated magnetic field exposures were based on proximity to electric power transmission lines and historical electrical loads on these lines and were based on nationwide cohorts. In a Letter to the Editor, the authors of these studies reported results of a meta-analysis of their three studies. They argued that these studies were more similar to one another than other studies and thus the meta-analysis would be more meaningful if limited to these studies [Ahlbom et al., 1993]. Weighting the results of each study by the inverse of its variance, they found a statistically significant doubling of the leukemia risk.

The next meta-analysis, conducted by Washburn et al. [1994], included several studies either not used or not available for previous meta-analyses [Coleman et al., 1989; Lin and Lu, 1989; London et al., 1991; Lowenthal et al., 1991; Fajardo-Gutierrez et al., 1993; Petridou et al., 1993]. The methodology in this meta-analysis differed from previous residential magnetic field meta-analyses in that individual study results based on different exposure metrics were combined into a single summary estimate of effect, rather than being stratified by exposure metric. Dichotomous cutpoints were developed for each exposure metric to facilitate this. Heterogeneity analyses were con-

TABLE 1. Summary Effect Measures From Meta-Analyses of Residential Magnetic Field Exposure and Childhood Leukemia

Reference* (no. of studies analysed)	Heterogeneity assessment	Publication bias assessment	Influence analysis	Wire codes	Spot measures	Distance	Historical calculations
					Dichotomous exposure		
NRPB (3)	—	—	—	1.4 (1.1–1.8)	1.2 (0.7–2.1)	1.3 (0.7–2.2)	—
Ahlbom et al. (3)	—	—	—	—	—	—	2.1 (1.1–4.1)
Washburn et al. (13)	Yes	—	Limited	—	—	1.5 (1.1–2.0) ^{c,d}	—
Miller et al. (1–4)	—	—	—	1.6 (1.3–2.0)	1.1 (0.7–1.7)	2.1 (1.2–3.7)	2.5 (1.0–6.0)
Meinert and Michaelis (13)	—	—	—	1.7 (1.1–2.5)	1.9 (1.1–3.3)	1.3 (0.9–1.9)	—
NRC/NAS (11)	Yes	Yes ^a	Yes	1.5 (1.1–2.1)	0.9 (0.5–1.6)	—	—
				1.4 (1.0–2.0) ^d	1.3 (0.8–2.0)	1.4 (1.1–1.8)	1.6 (1.0–2.7)
					Continuous exposure (increase in RR per 0.1 µT)		
Wartenberg et al. (5–11) dichot. (2–4) continuous	Yes ^b	Yes ^a	Yes	2.7 (0.8–8.7)	1.1 (0.9–1.3)	—	1.2 (0.9–1.5)
				(scored by spot)	—	—	—
				1.6 (0.5–4.6) ^d	—	—	—
				(scored by 24 hr)			
					Dichotomous exposure		
This report (6–13)	Yes ^b	Yes ^a	Yes	1.2 (0.9–1.6) ^d	1.3 (1.0–1.7)	1.4 (0.7–2.7)	1.3 (0.8–2.0)

^aIncludes fail-safe N and sample size needed calculations.

^bIncludes stratified analyses to identify factors explaining heterogeneity.

^cA variety of exposure metrics were combined in this summary.

^dValues with a line through them indicate substantial heterogeneity ($P \leq 0.1$); these relative risks may not be representative.

—Not Reported.

*For full references, see text.

ducted and showed that the studies combined were heterogeneous ($P = 0.02$), although this was attributed largely to one outlier, the study by Wertheimer and Leeper [1979]. Analyses without that single study were moderately homogeneous ($P = 0.14$). To assess exposure response, these authors considered six studies with exposure-response data and compared the dichotomous OR derived when all exposed categories were pooled (OR = 1.2, 95% CI 1.0–1.6) with the dichotomous OR derived using the highest exposure categories reported in each study (OR = 1.4, 95% CI 1.0–2.0). From this they inferred that either there was nondifferential misclassification or that an exposure response relationship existed. They also conducted a series of sensitivity analyses to test all of the decision rules that they used in extracting the relative risk data. These analyses showed that the assumptions had minimal impact on the results. While this was a more comprehensive meta-analysis than the previous ones, disparate exposure metrics were combined and only limited attention was paid to the observed heterogeneity.

Miller and colleagues conducted a subsequent meta-analysis in which they sought, “to examine the methodological variation used in determining EMF exposure . . . and how this variation affects interpretation of EMF risk” [Miller et al., 1995]. They used a more restricted set of studies than Washburn et al. [1994] for analysis of leukemia risk [Wertheimer and Leeper, 1979; Fulton et al., 1980; Tomenius, 1986; Savitz et al., 1988; Coleman et al., 1989; London et al., 1991; Feychting and Ahlbom, 1993]. Then, rather than pooling results across exposure metrics, as was done by Washburn et al., these investigators conducted four separate analyses, one for each exposure metric (i.e., wire codes, distance, spot measures, calculated index of magnetic field exposure) in a manner analogous to two previous meta-analyses [National Radiological Protection Board, 1992; Ahlbom et al., 1993]. This resulted in a small number of studies for each analysis. Specific cutpoints were selected for each exposure metric. Those for wire codes and distance were the same as Washburn et al., while those for magnetic fields differed. The use of subgroup analyses improved the consistency of the exposure metrics and cutpoints across studies but decreased sample size. Notably, analyses using exposure metrics of wire codes, distance, and calculated index all gave statistically significantly elevated ORs, while that using spot measures was slightly but not statistically significantly elevated.

Following this study, Meinert and Michaelis conducted a meta-analysis that was designed specifically, “. . . to investigate a potential dose-response-like

relationship by comparing analyses for different cutoff points of exposure [Meinert and Michaelis, 1996].” They considered the same set of studies as Washburn et al., but excluded from the analyses two studies used by Washburn et al. [Lin and Lu, 1989; Lowenthal et al., 1991] and also excluded one study that they found which had not been identified by Washburn et al. [Lin and Lee, 1994]. They then analysed the data for leukemia, lymphoma, CNS tumors, and all tumors. Analyses using the only random effects method were conducted for all cutpoints for which data were available from at least two different studies, resulting in 26 different ORs. They also found elevated ORs for wire codes, distance and magnetic field strength, with the wire codes and magnetic field strength results both statistically significant. In terms of the trend tests, ORs increased with decreasing distance but the results were not statistically significant, magnetic field strength did not show a monotonic response, and wire codes were available for only one cut-off point. The authors did not address adequately the large heterogeneity among the individual study results.

In 1996, the U.S. National Academy of Sciences (NAS) Committee on the Possible Health Effects of Exposure to Residential Electric and Magnetic Fields released their report which included yet another meta-analysis [National Research Council, 1997], a revised version of which has also been published in the peer-reviewed literature [Wartenberg, 1998]. The explicit goal of that analysis was to determine the role of random error in the possible association between residential magnetic fields and childhood leukemia. This meta-analysis includes all but two of the studies used in Washburn’s meta-analysis [Washburn et al., 1994], excluded due to issues of data adequacy, but included all the childhood leukemia studies used by the NRPB [National Radiological Protection Board, 1992], Ahlbom et al. [1993], Miller et al. [1995] and Meinert and Michaelis [1996].

The NAS group conducted a series of subgroup analyses and assessed both publication bias and the influence of individual studies on the summary results. In general, they found only limited to moderate heterogeneity among the studies and found elevated ORs for wire codes, wire codes and distance, calculated fields, and for all studies together when comparing the highest exposure category reported to all others. Spot magnetic field measurements, however, showed a slightly protective OR (i.e., less than 1.0). The influence analysis showed that no single study had a disproportionate effect, and the publication bias analysis indicated that many null studies would have had to have been unpublished to explain the observed results as due to random fluctuations.

When the meta-analysis included four additional studies that were published while the peer-reviewed version of the study was in process [Lin et al., 1997; Petridou et al., 1997; Tynes and Haldorsen, 1997; Michaelis et al., 1997a], only minor fluctuations in the summary ORs were found [Wartenberg, 1998]. A further analysis showed that these summary results would be changed further only if an extremely large study (several hundred to several thousand subjects, depending on exposure subgroup) reported strong negative (protective) results.

Finally, as part of its review of the EMF RAPID program for a report to the US Congress, the National Institute of Environmental Health Sciences (NIEHS) commissioned one more meta-analysis [Wartenberg et al., 1998]. This meta-analysis identified 22 studies of magnetic field exposure and childhood cancer, but excluded seven for inadequate data or design. The analyses were based on all the studies cited in the previous meta-analysis [Wartenberg, 1998] but more consideration was given to the comparability of exposures across studies, and individual study exposure-response analyses were used for the first time in a meta-analysis of exposure to magnetic fields. Efforts were made to isolate sources of heterogeneity by subgroup analysis, but no consistent pattern was detected. When exposure was dichotomized, the ORs for each exposure metric showed an elevated OR, with ORs for wire codes, calculated and measured fields combined, and proximity to electrical facilities showing statistically significant effects. The results for the dose-response analyses also showed all elevated ORs, although none were statistically significant (unless one used the fixed effects OR).

DATA AND METHODS

Since the completion of the meta-analysis conducted for NIEHS, [Wartenberg et al., 1998] four additional case-control studies of childhood leukemia have been published [Dockerty et al., 1998; McBride et al., 1999; UK Childhood Cancer Study Investigators, 1999; Dockerty et al., 1999; Green et al., 1999a, 1999b]. In this study, I extend the NIEHS meta-analysis to include these four new studies and conduct some additional analyses.

Selection of Studies

To conduct this meta-analysis, I identified all studies assessing the possible association between childhood leukemia and residential exposure to magnetic fields. Using the previous meta-analyses, I identified 22 studies. To this, I added the four most recent studies. My criteria for inclusion were that each study

reported an effect measure for the possible association of childhood leukemia with residential exposure to magnetic fields and provided data on the exposure measure used. I reviewed each study to determine whether they met these criteria. From 26 studies originally identified, seven were omitted for the following reasons:

Coghill and Steward [1996]	Data on magnetic fields not presented
Li et al. [1998]	Exposure assessment based on community proximity to lines rather than subjects' proximity to lines
Lin and Lee [1994]	Exposure related to school rather than residence
Lowenthal et al. [1991]	No data on controls; no summary effect estimate
McDowall [1986]	Children not identified separately
Michaelis et al. [1997b]	Partial data only (these data are also reported by Michaelis et al. [1997a], which is included in the meta-analysis)
Schreiber et al. [1993]	Children not identified separately

The 19 studies included in the meta-analysis are listed in Tables 2 and 3.

Exposure Assessment

Different investigators studying the possible association between exposure to electric and magnetic fields and childhood cancer defined a variety of methods of exposure classification. In some instances, ostensibly similar modes of classification (e.g., wire codes in Denver and Los Angeles) may not be truly comparable, and in other instances, ostensibly dissimilar modes of classification (e.g., wire codes in Denver and proximity to transmission lines in England) may be comparable. After careful review, I focus on four exposures metrics: (1) calculated historical transmission line fields; (2) measured magnetic fields; (3) wire codes; (4) proximity to electrical facilities.

Calculated historical transmission line fields. Six studies used some form of calculated historical magnetic field exposures. A small number of children live close to high-voltage transmission lines, experiencing unusually high residential exposure—high enough to overshadow exposures from other sources. One can

calculate with reasonable accuracy the field levels near the lines and can develop cumulative exposure estimates using historical line load data. This approach is accurate mainly for high voltage transmission lines (e.g., 230 kV) and not for lower voltage subtransmission and distribution lines. The main limitation of this metric is that few children live near such lines. Feychting and Ahlbom [1993], Olsen et al. [1993], Verkasalo et al. [1993], and Tynes and Haldorsen [1997] used this approach in similar electric power distribution systems in Scandinavia so that their estimates should be comparable. All four calculated historical time-weighted-average (TWA) field levels, although the specific cutpoints used for the epidemiologic analyses differed and the period over which the TWA was estimated varied. Generally, cutpoints closest to 0.2 μT were used in this meta-analysis.

Myers et al. [1990] used a similar approach to estimate exposure in England but summarized the data in terms of the child's calculated peak exposure over a several year period. Since peak loads are typically 1.5–4 times the annual average load, these exposure values based on peak loads were divided by 3 for comparability with other values based on average load.

The UK Childhood Cancer Study Investigators [1999, 2000] used a complicated set of measurements and calculations, including distances to circuits and line loads to determine the estimated arithmetic mean EMF exposure in the year preceding date of diagnosis. EMF exposure information was gathered from measurements at each child's home, measurements made at the child's school or other institution, a parental questionnaire on appliances in the home, the proximity and type of overhead power line nearby, and electrical company data on historical line loads and operating characteristics. These data were combined into a time-averaged estimate of the magnetic flux density. Again, a cutpoint of 0.2 μT was used for analyses in this meta-analysis.

Measured magnetic fields. Nine studies reported spot (or point-in-time) measurements [Tomenius, 1986; Savitz et al., 1988; Feychting and Ahlbom, 1993; Green et al., 1999a, b], 24- or 48-hour field measurements [Linet et al., 1997; Dockerty et al., 1998, 1999; McBride et al., 1999], both spot and 24- or 48-hour field measurements [London et al., 1991; Michaelis et al., 1997a], and two studies used personal monitors on children [McBride et al., 1999; Green et al., 1999a]. Personal monitors provide the most comprehensive assessment of a child's exposure, including for the first time measuring exposures outside the home. However, because these were available for only two studies, these data were not used in the meta-

analysis. Next best are the 24- or 48-hour measurements, which can be used to average out diurnal variations and the increase in classification accuracy of 24- or 48-hour measurements over spot measurements. However, this difference is probably small compared to the assumed errors associated in relating either type of relatively short-term measurement to long-term average exposure sometime in the past. Given the limited number of measurement comparability studies, the likely similarity of these metrics to one another relative to the other metrics, and the limited number of studies, I do not separate the 24- or 48-hour measurements from the spot measures.

Again, the cutpoints used in the analyses in the different studies vary. Some studies report data based on cutpoints selected *a priori*, others selected the cutpoints *post hoc*, and some studies reported data for both. Results using *a priori* cutpoints likely have less opportunity for bias. Unfortunately, investigators often do not state how they have chosen their cutpoints. I give preference to 24- or 48-hour measurements over spot measures when both are available. The values used for the meta-analysis were the exposures closest to 0.2 μT .

Wire codes. Wire codes reflect a set of assessments designed to categorize likely magnetic field exposure based on the size of the electric power lines outside a residence, as a proxy for electrical load on the lines, and the distance these lines are from the residence. The original Wertheimer-Leeper wire code and its various derivatives are based on very basic principles of engineering and common sense. The original 2-level code and subsequent 4-level code developed by Wertheimer and Leeper for their childhood [Wertheimer and Leeper, 1979] and adult cancer [Wertheimer and Leeper, 1982] studies, respectively, were developed for use in the Denver metropolitan area. These same wire codes were used by Savitz et al., in their subsequent study of this issue in Denver [Savitz et al., 1988], and these wire codes also have been used in other US residential exposure studies, even though some data suggest that there is substantial geographic variation in the magnetic fields in particular wire code classes (see below).

Fulton et al. [1980] modified the Wertheimer-Leeper wire code for Rhode Island, using a data-based approach. They divided the "exposure" levels of control subjects into quartiles resulting in very low, low, high, or very high exposure categories. Because Fulton's method uses the same fundamental basis as the Wertheimer-Leeper, both systems should give similar ranking of exposures although exposure class boundaries differ. To combine Fulton's data with

Wertheimer's 2-level code data, I aggregate Fulton's three lowest categories (very low, low, and high) (75% of control homes) to compare to Wertheimer's LCC (78% of control homes) while comparing Fulton's "very high" category (25% of control homes) with Wertheimer's HCC category (22% of control homes).

The analyses reported by Petridou et al. [1997] used an "adapted wire code" that is based on basic electrical engineering principles for a different distribution system. These exposure data likely differ substantially from US wire code studies and should not be used in the same analyses without adjustment. Specifically, Petridou's categories 4 and 5 were compared to the VHCC and OHCC categories of Wertheimer and Leeper's wire codes.

The wire codes used in the Linet study [Linet et al., 1997] spanned nine states in the US and thus raised questions of internal as well as external comparability. For example, while Savitz et al. [1988] reported 60% of the VHCC homes in Denver had low power spot magnetic field measurements over 0.2 μT , the corresponding figure from [Linet et al., 1997; Tarone et al., 1997] only found 40%. This could, in part, reflect urban/rural differences [Zaffanella, 1993]. In the Linet study, which reported results for eight states, there was substantial geographic variation [Tarone et al., 1997]. Twenty four hour average magnetic field measurements in each state for VHCC homes differed by over 300%, ranging from 0.082 μT to 0.267 μT . Further, for some states, 24-hour average magnetic field measurements did not increase consistently across wire code categories. In short, wire coding protocols applied to different geographic regions may provide a useful rank ordering of exposure within each region but they do not necessarily correspond to similar magnetic field levels between regions.

Both McBride et al. [1999] and Green et al. [1999a, 1999b] used wire codes based on the Wertheimer-Leeper method. The exposure cutpoint used in this meta-analysis was VHCC and OHCC versus OLCC, VLCC, and UG.

Proximity to electrical facilities. Proximity to electrical facilities in general is an indicator of magnetic field exposure, albeit very imprecise. A distance metric was used by Feychting and Ahlbom [1993], Tynes and Haldorsen [1997], Myers et al. [1990], Coleman et al. [1989], and Fajardo-Gutierrez et al. [1993]. There is greater uncertainty in comparing proximity to different types of electrical facilities than to similar types. To combine all studies reporting proximity data, I used a distance cut point of 15–20 m for distribution lines and transformers, and 50 m for transmission lines and substations. Although wire codes are based on both

distance from and type of distribution line, distance captures a large proportion of the information. To pool wire code studies with the cruder proximity studies, I included VHCC and OHCC (or HCC in the 2-level code) homes with homes within 20 m of distribution systems or 50 m of transmission systems and included OLCC, VLCC, and underground (or LCC) homes with those outside the above cut points.

Exposure Summary

There are many combinations of studies, exposure metrics, and cutpoints that could have been examined in this meta-analysis. I believe that the ones I have chosen are most valid because they were selected from an independent assessment of the exposure methodology. For measurement-based analyses, I used calculated fields over measured fields, and 24- or 48-hour measurements over spot measurements (Table 2). For proximity-based analyses, I used wire codes in preference to distance (Table 3). For consistency, for each exposure metric I selected exposure cutpoints that I believe are as close as possible to each other. For proximity to electrical facilities including wire codes, cutpoints used were VHCC + OHCC, 50 m from transmission lines and 25 m from other lines as noted in Table 2. For calculated and measured fields, cutpoints closed to 0.2 were used, as noted in Table 3.

Statistical Methods

Traditional methods for meta-analysis are used in this study [Petitti, 2000]. Calculated results include the combined effects measures, heterogeneity, influence analysis, and publication bias.

Combined effect measures and heterogeneity analysis. Meta-analysis summary statistics that incorporate the individual effect sizes use either of two statistical models: (1) fixed effects and (2) random effects. The fixed-effects model assumes that the observed ORs of the studies included are estimates of the underlying population ORs. Within-study precision (i.e., an overall treatment effect) is assessed by weighing individual study results by the inverse of the variance. The random-effects model assumes that the observed ORs are a random sample from the statistical distribution of the population ORs. An assumption of the model is that there is a sampling effect and there are differences in the true underlying ORs for each study [DerSimonian and Laird, 1986].

Model choice may be based on results of the Chi-squared (or Q-test) for homogeneity that assesses constancy of treatment effects [DerSimonian and Laird, 1986]. If the test does not reject the null hypothesis of homogeneity, then the fixed effects model is valid. If

TABLE 2. Meta-Analysis and Individual Study Results for Studies of Calculated and Measured Magnetic Fields Exposure and Childhood Leukemia*

Study*	Exposure definitions	Exposed cases	Exposed controls	Unexposed cases	Unexposed controls	Individual odds ratio	OR _{fixed effects}	Pr(Q _{HOMOG})	OR _{random effects}
All combined		241	298	3697	6000	1.31 (1.09–1.59)	1.32 (1.09–1.59)	0.29	1.34 (1.07–1.67)
Tomenius	0.3 µT spot	4	10	239	202	0.34 (0.10–1.09)	1.37 (1.13–1.65)	0.62	1.37 (1.13–1.65)
Myers	0.03 µT peak	6	6	174	271	1.56 (0.49–4.91)	1.31 (1.08–1.59)	0.23	1.34 (1.06–1.70)
Savitz	0.2 µT spot	5	16	31	191	1.93 (0.66–5.63)	1.33 (1.04–1.71)	0.13	1.38 (0.94–2.01)
London	0.27 µT 24 h	20	11	144	133	1.68 (0.78–3.64)	1.33 (1.03–1.71)	0.12	1.38 (0.93–2.06)
Feychting	0.2 µT calculated	7	46	31	508	2.49 (1.04–5.98)	1.29 (1.00–1.66)	0.20	1.32 (0.93–1.89)
Olsen	0.25 µT calculated	3	4	830	1662	1.50 (0.34–6.73)	1.36 (1.06–1.73)	0.11	1.41 (0.97–2.06)
Verkasalo	0.20 µT calculated	3	1.93	—	—	1.55 (0.29–3.81)	1.24 (1.05–1.73)	0.12	1.40 (0.95–2.08)
Linet	0.2 µT 24 h	83	70	541	545	1.19 (0.85–1.68)	1.55 (1.10–2.20)	0.16	1.49 (0.96–2.30)
Tynes	0.14 µT calculated TWA	1	14	147	565	0.27 (0.04–2.10)	1.39 (1.09–1.78)	0.23	1.47 (1.06–2.04)
Michaelis	0.2 µT 24 h	9	8	167	406	2.74 (1.04–7.21)	1.30 (1.01–1.67)	0.21	1.32 (0.93–1.88)
McBride	0.2 µT calculated	49	42	248	287	1.35 (0.86–2.11)	1.31 (1.07–1.62)	0.23	1.35 (1.04–1.75)
Dockerty	0.2 µT 24-hour interior average	5	2	35	38	2.71 (0.49–14.9)	1.31 (1.08–1.58)	0.27	1.33 (1.06–1.66)
Green	0.15 µT interior average	25	44	58	142	1.39 (0.78–2.48)	1.31 (1.07–1.60)	0.23	1.34 (1.04–1.73)
UK	0.2 µT calculated	21	23	1052	1050	0.96 (0.50–1.66)	1.37 (1.13–1.68)	0.32	1.40 (1.11–1.76)

Sample size needed to balance observed results = 8900.

Fail Safe $N = 23.72$.

*For full references, see text.

TABLE 3. Meta-Analysis and Individual Study Results for Studies of Proximity to Electrical Facilities and Childhood Leukemia

Study*	Exposure definition	Exposed cases	Exposed controls	Unexposed cases	Unexposed controls	Individual odds ratio	OR _{fixed effects}	Pr(Q _{HOMOG})	OR _{random effects}
All combined		527	610	1535	2906	1.64 (1.43–1.87)	1.18 (1.02–1.37)	0.03	1.24 (0.99–1.56)
Wertheimer	VHCC + OHCC birth address	52	29	84	107	2.28 (1.34–3.91)	1.12 (0.97–1.31)	0.13	1.15 (0.94–1.42)
Savitz	VHCC + OHCC	27	52	70	207	1.54 (0.90–2.63)	1.16 (1.00–1.35)	0.03	1.22 (0.95–1.55)
London	VHCC + OHCC	122	92	89	113	1.68 (1.14–2.48)	1.12 (0.95–1.31)	0.06	1.19 (0.93–1.50)
Linet	VHCC + OHCC	111	113	291	289	0.98 (0.72–1.33)	1.25 (1.06–1.48)	0.04	1.29 (1.00–1.67)
McBride	VHCC + OHCC	122	128	229	234	0.97 (0.72–1.32)	1.25 (1.06–1.48)	0.04	1.29 (1.00–1.67)
Green	VHCC + OHCC	12	25	67	100	0.72 (0.34–1.52)	1.21 (1.04–1.40)	0.03	1.28 (1.02–1.62)
Fulton	VHCC	42	56	131	169	0.95 (0.60–1.50)	1.21 (1.04–1.41)	0.03	1.28 (1.00–1.65)
Feychting	50 m transmission	6	34	32	520	2.87 (1.12–7.33)	1.16 (1.00–1.34)	0.06	1.19 (0.96–1.48)
Tynes	51 m transmission	9	55	139	524	0.62 (0.30–1.28)	1.22 (1.05–1.41)	0.05	1.29 (1.00–1.67)
Fajardo	20 m distribution	3	2	43	47	1.64 (0.26–10.29)	1.18 (1.02–1.37)	0.02	1.24 (0.98–1.56)
Coleman	25 m substation	3	3	81	138	1.70 (0.34–8.64)	1.18 (1.02–1.37)	0.02	1.23 (0.98–1.56)
Petridou	Categories 4,5	11	14	106	188	1.39 (0.61–3.18)	1.18 (1.02–1.37)	0.02	1.23 (0.97–1.57)
Myers	25 m	7	7	173	270	1.56 (0.54–4.53)	1.18 (1.02–1.37)	0.02	1.23 (0.97–1.56)

Sample size needed to balance observed results = 4483.

Fail Safe $N = 20.14$.

*For full reference, see text.

the test is statistically significant, homogeneity is rejected, heterogeneity is detected and the random effects model may be useful. However, often the random effects estimate does not make adequate adjustments for the heterogeneity and other methods may be needed [Poole and Greenland, 1999]. To assess heterogeneity using the homogeneity test, investigators often use a cutpoint for the *P*-value as large as 0.2 because of the low power of the test and the typically small numbers of studies available for meta-analyses.

I also conducted meta-analyses of dose-response trends for each exposure metric for which two or more studies reported results for childhood leukemia in at least three exposure categories [Berlin et al., 1993]. First, a dose-response function was estimated within each study by weighted linear regression. The dependent variable was the natural logarithm of the relative risk estimate for each exposure category. The independent variable was a score assigned to each exposure category. The weights were inversely proportional to the estimated variances of the logarithmically transformed relative risk estimates. For categories of magnetic field other than the lowest and highest, I used the midrange as the exposure score. For the lowest category, the score was 0.7 times the upper category boundary. For the highest category, the score was 1.3 times the lower category boundary.

I next conducted a test of the homogeneity of the estimated dose-response functions from the separate studies. Finally, as indicated, I combined the study specific results into summary estimates by computing inverse-variance weighted averages with random effects. The results from both the study-specific analyses and the meta-analytic summaries are expressed as the estimated relative risk for a 0.1 μT increase in estimated exposure.

Influence analysis. Influence analysis was conducted for the dichotomous results by recalculating summary indices for a set of studies leaving out one study at a time, and doing so for each study. The difference between the average risk and the average risk with one study omitted indicates the influence of the omitted study on the overall average risk and enables the researcher to determine whether any of the studies has a dominant effect on the average risk [Olkin, 1994].

Publication bias. Publication bias is the differential publication of studies based on their results. The underlying concern is that there may be many studies showing no association (i.e., null studies) that investigators are not sufficiently motivated to publish, resulting in an upward bias in the average risk of published studies. One method for investigating possible pub-

lication bias is to combine z-scores of individual published studies to assess the sensitivity of the results to possibly unpublished null studies. This enables the investigator to determine the number of additional null unpublished studies needed to reduce an observed statistically significant combined effect to non-significance, the so-called Fail Safe *N* [Cooper, 1979; Rosenthal, 1979].

For an alternative means of assessing publication bias, one can assess how large a study would be required to balance the average of reported result if they were due to random fluctuations. To do so, one can calculate the size of a single hypothetical study that would be needed to give a null average risk across all studies (i.e., an OR of 1.0), if that hypothetical study had equal numbers of cases and controls, had an exposure prevalence equal to that observed in reported studies, and had an OR equal to the reciprocal of the reported average. Unlike the Fail Safe *N*, this calculation uses the size of the effect measure, weights each study result by the inverse of its variance, hypothesizes a study with a protective rather than null effect (a plausible result if the observed effects are due to random variation), and seeks a null rather than non-significant combined effect.

Investigation of heterogeneity. One goal of a meta-analysis is to see if characteristics of studies are related to their results, particularly if testing shows substantial heterogeneity. The characteristics may pertain to aspects of study design and conduct, the nature of the exposures, or population characteristics. When the number of studies is small and their characteristics are highly correlated, as in these analyses, the utility of stratification is somewhat limited.

In Tables 4 and 5, I report possible sources of heterogeneity separately for two groups of studies listed in Tables 2 and 3. For each of six characteristics (study design, country in which studies was conducted, year of publication, exposure metric, maximum age of subjects, and method of control selection), I divide the studies into two groups and compute for each group the random-effects OR and the *P*-value for the Q-test for homogeneity [Olkin, 1994; Lau et al., 1997]. If the ORs differ and each subgroup is homogeneous, then this characterization, in part, appears to explain the overall heterogeneity.

I also investigate the six characteristics simultaneously using meta-regression separately for proximity metrics and measurement characteristics. To do so, I define a binary design matrix for each of the six characteristics. Then, I regress the logarithm of the OR on the design matrix, weighing by the inverse of the variance of the logarithm of the OR. The resulting beta

TABLE 4. Stratification by Study Characteristics of Results for Measured and Calculated Magnetic Fields

Characteristic	Homogeneity	Odds ratio	Homogeneity	Odds ratio
All studies	0.3	1.34 (1.07–1.67)	—	—
Study design	0.2	Case-control (11)	Cohort/Nested case control (3)	1.90 (1.07–3.39)
		US (3)	Other (11)	
Country	0.6	1.30 (0.97–1.76)	0.2	1.36 (0.97–1.83)
Year of publication	0.3	1993 and before (7)	After 1993 (7)	1.27 (0.99–1.62)
		Measured (7)	Calculated (5)	
Magnetic field strength	0.2	1.39 (0.96–2.00)	0.4	1.31 (0.98–1.76)
		≤ 14 (11)	>14 (3)	
Maximum age of subjects	0.6	1.32 (1.08–1.61)	<0.1	1.17 (0.40–3.42)
		Random digit dialing (4)	Population-based data (10)	
Control selection	0.8	1.32 (1.01–1.72)	0.1	1.32 (0.96–1.93)

Number in parenthesis indicates number of studies in each group out of the 14 total studies considered.

coefficients are the logarithms of the ORs for the design variables and reflect their relative importance.

Estimating the population attributable risk. To determine the possible impact of the observed risk to US population, it is possible to conduct a quantitative risk assessment by calculating the population attributable risk and annual number of cases expected. This is done by combining the average study risk with the prevalence of exposure [Rothman and Greenland, 1998]. Using the random-effects OR, I calculate the attributable risk (or attributable fraction) as (OR-1)/OR. Then, by multiplying this number by the prevalence of exposure among children in the US, I estimate the population attributable risk, or the pro-

portion of the total number of cases observed that might be due to EMF exposure and the number of cases expected annually in the US [Wartenberg, 1999].

RESULTS

Results for Dichotomous Exposure Classifications

Individual study and meta-analysis results using the exposure proximity and measurement calculation classifications described above are presented in Tables 2 and 3, Figures 1 and 2, respectively, and summarized in Table 11. In Tables 2 and 3, the first line of the table presents totals for all studies

TABLE 5. Stratification by Study Characteristics of Results for Proximity to Electrical Facilities

Characteristic	Homogeneity	Odds ratio	Homogeneity	Odds ratio
All studies	<0.1	1.24 (0.99–1.56)	—	—
Study design	0.1	Case-control (11)	Cohort/nested case control (2)	1.10 (0.62–1.96)
		US (5)	Other (8)	
Country	<0.1	1.37 (0.98–1.90)	0.2	1.09 (0.79–1.50)
Year of publication	0.3	1993 and before (8)	After 1993 (5)	0.94 (0.78–1.15)
		Wire codes (8)	Distance (5)	
Proximity metric	<0.1	1.22 (0.96–1.56)	0.1	1.39 (0.71–2.70)
		≤ 14 (8)	>14 (4)	
Maximum age of subjects	0.1	1.12 (0.88–1.41)	<0.1	1.71 (0.93–3.13)
		Random digit dialing (4)	Population-based data(9)	
Control selection	0.1	1.21 (0.84–1.71)	0.1	1.28 (0.92–1.78)

Number in parenthesis indicates number of studies in each group out of the 13 total studies considered.

Calculated and Measured Magnetic Fields

Odds Ratios and 95% Confidence Intervals

(in chronological order)

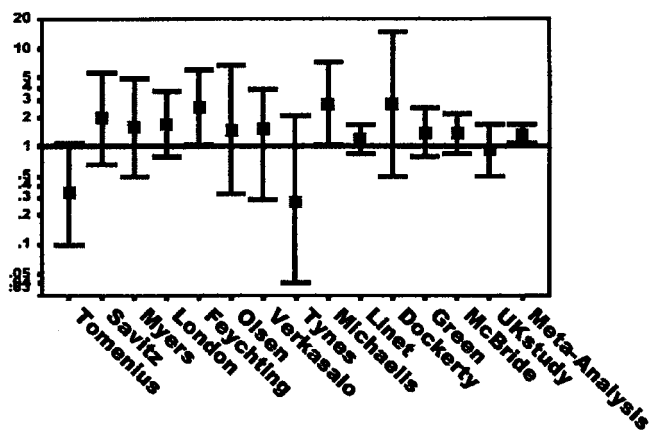


Fig. 1. Calculated and measured magnetic fields.

combined. That is, it shows the number of subjects, the crude OR for all studies pooled and the fixed-effects and random-effects estimates for all studies combined as well as the *P*-value for the *Q*-test for homogeneity.

Table 2 and Figure 1 present results for calculated and measured magnetic fields. The first line of the table shows the total number of subjects by disease and exposure status, the combined fixed- and random-effects ORs and the *P*-value for the *Q*-test for homogeneity. The combined OR is elevated and statistically significant (1.3, 95% CI 1.1–1.6), and the studies are homogeneous (*P* = 0.4). Each subsequent line of the table presents name of the primary study author the exposure metric and cutpoint, the number of subjects and study specific OR. Then, for the fixed effects, random effects and *Q*-test columns, the combined results are for all of the studies except the study named in that row (the leave one out statistics). Overall, the most influential study is the Linet study [Linet et al., 1997], which reduces the average OR by about 10%. Publication bias is unlikely given a Fail Safe *N*, the number of additional null studies needed to result in a nonstatistically significant average risk, that is greater than 23 and a needed sample size of 8900. A stronger effect is seen for the calculated magnetic field data than the measured magnetic field data only (detailed results not shown; some results are reported in Table 11).

For proximity to electrical facilities, in Table 3 and Figure 2, using the random effects model I found an elevated but not statistically significant OR (1.2, 95% CI 1.0–1.6) and moderate to strong heterogeneity (*P* = 0.03). Due to the heterogeneity, the average risk is not an adequate representation of the studies. Removal

Proximity to Electrical Facilities

Odds Ratios and 95% Confidence Limits

(in chronological order)

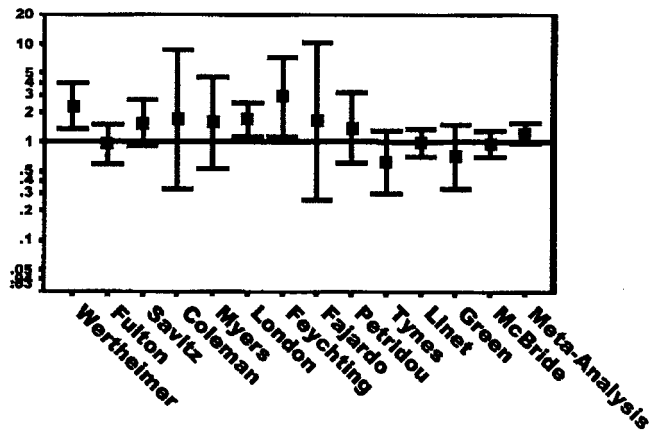


Fig. 2. Proximity to electrical facilities.

of the Wertheimer and Leeper study [1979], line 2 in Table 3, increases the homogeneity by the greatest amount, but the *P*-value is still only 0.13 and the OR decreases by less than 10%. Overall, these results were not sensitive to deletion of individual studies.

Publication bias seems unlikely, as shown by a Fail Safe *N* of greater than 20 and a needed sample size to negate the findings of over 4400 subjects. Results using only wire code data were similar (detailed results not shown) as were those for distance only (detailed results not shown).

Investigation of Heterogeneity by Stratification

Results of the heterogeneity analyses are reported for those using calculated and measures fields (Table 4) and for proximity to electrical facilities (Table 5). Studies with calculated and measured magnetic fields considered as a single group and unstratified show limited evidence of heterogeneity (*P* = 0.3). Only study design shows differences in the ORs between the two strata of at least 20%. For study design, one group is made up of the studies that are cohort or nested case control designs, that are Scandinavian studies, that use calculated rather than measured magnetic fields, that are similar to one another and that show higher ORs than the other studies. This is the most useful split in explaining the heterogeneity although it is not clear what aspect of the studies is most likely responsible for the difference.

Among the results for proximity to electrical facilities unstratified, there is substantially greater evidence of overall heterogeneity (*P* = 0.03). In the stratified analyses, there is evidence that the heterogeneity

TABLE 6. Meta-Regression Results

Characteristic (reference/alternative)	OR for measured and calculated fields	OR for proximity to electrical facilities
Intercept	0.66 (0.17–2.57)	1.48 (0.95–2.29)
Design (case–control/cohort or nested case control)	3.61 (0.94–13.88)	0.79 (0.27–2.32)
Country (US/other)	1.11 (0.52–2.37)	1.07 (0.46–2.45)
Year (≤ 1993 / >1993)	0.84 (0.43–1.65)	0.59 (0.34–1.01)
Exposure Metric (measured/calculated; wire codes/distance)	0.62 (0.23–1.62)	1.24 (0.52–2.95)
Controls (other/random digit dialing)	0.74 (0.25–2.25)	1.10 (0.48–2.49)
Age limit (<15 / ≥ 15)	3.05 (0.83–11.23)	0.99 (0.40–2.46)

may be attributable to study characteristics. However, even after stratification, many of the subgroups are still not homogeneous. The one exception is stratification by year of publication in which both strata are homogeneous and there is a statistically significant elevation of risk for those studies published through 1993 but those after 1993 show no elevation of risk. This suggests that other than year of publication the stratification factors are not helpful in explaining the heterogeneity.

The results of the meta-regressions are shown in Table 6. When all characteristics were entered into the regression for either measured/calculated fields or wire codes/distance, none of the coefficients were statistically significant. In part, this reflects a limitation of the small sample size. The direction of most of the effects differ depending on which exposure metric is used, also suggesting that this approach is of limited value for these data.

Results for Exposure-Response Modeling

To conduct exposure-response modeling, one must extract results for each exposure category. The study specific data are reported in Tables 7–9 and the summary risk estimates in Tables 1 and 11.

Spot measurements of magnetic fields. Savitz [1987, 1988], Savitz et al. [1988], London et al. [1991], Feychting and Ahlbom [1993], and Linet et al. [1997] reported results for leukemia in more than two categories of magnetic field spot measurements. The results reported by Savitz et al. were the arithmetic means of the measurements taken near the front door, in the child's bedroom, and in the parents' bedroom in the residence occupied at the time of diagnosis. The results reported by London et al. were for the child's bedroom in the residence occupied longest in

TABLE 7. Results Extracted From Studies of Exposure-Response Trends for Childhood Leukemia and Spot Measurements of Magnetic Fields

First author	Exposure range (μT)	Assigned value (μT) (see text)	Cases	Controls	Relative risk (95% confidence interval)
Savitz	<0.065	0.0455	21	134	1.
	0.065–0.099	0.0825	4	28	0.91 (0.29–2.86)
	0.100–0.249	0.1750	4	33	1.35 (0.53–3.45)
	≥ 0.250	0.3250	2	12	2.13 (0.63–7.22)
London	<0.032	0.0217	67	56	1.
	0.032–0.067	0.0495	34	28	1.01 (0.55–1.87)
	0.068–0.124	0.0960	23	14	1.37 (0.65–2.92)
	≥ 0.125	0.1625	16	11	1.22 (0.52–2.83)
Linet	<0.065	0.0455	206	215	1.
	0.065–0.099	0.0820	92	98	0.96 (0.65–1.40)
	0.100–0.199	0.1495	107	106	1.15 (0.79–1.65)
	0.200–0.299	0.2495	29	26	1.31 (0.68–2.51)
	0.300–0.399	0.3495	14	11	1.46 (0.61–3.50)
	0.400–0.499	0.4495	10	2	6.41 (1.30–31.73)
≥ 0.500	0.6500	5	5	1.01 (0.26–3.99)	
Feychting	<0.10	0.063	19	207	1.
	0.10–0.19	0.145	1	67	0.2 (0.01–0.9)
	≥ 0.20	0.260	4	70	0.6 (0.2–1.8)

TABLE 8. Results Extracted From Studies of Dose-Response Trends for Childhood Leukemia and Wire Codes Scored by Spot Measurements of Magnetic Fields

First author	Wire code category	Assigned value (μT) (see text)	Cases	Controls	Relative risk (95% confidence interval)
Savitz (Savitz, 1988; Savitz et al., 1993)	Buried + VLCC	0.030	33	106	1.
	OLCC	0.051	38	102	1.20 (0.70–2.05)
	OHCC	0.090	20	44	1.46 (0.76–2.82)
	VHCC	0.216	7	8	2.81 (0.95–8.33)
London	Buried + VLCC	0.017	31	38	1.
	OLCC	0.022	58	75	0.95 (0.53–1.70)
	OHCC	0.029	80	68	1.44 (0.81–2.56)
	VHCC	0.060	42	24	2.15 (1.08–4.28)

a specified etiologic period, the definition of which varied with age at diagnosis. The results reported by Feychting were the average of the measurements in the room closest to the line, the room farthest from the line and a central room. The results reported by Linet were a weighted average of measurements taken in the child's bedroom, the family room, the kitchen, and the room in which the mother slept during the index pregnancy. The extracted results are summarized in Table 7. The combined results are consistent when analyzed in this manner, as shown by the high P -value for the homogeneity test statistic ($P=0.3$) and the identical values of the random-effects and fixed-effects summaries (OR = 1.1, 95% CI 0.9–1.3).

Wire codes scored by spot measurements of magnetic fields. Savitz [1987, 1988], Savitz et al. [1988], Savitz and Kaune [1993], and London et al. [1991] reported results for leukemia in more than two wire code categories and reported summary values of magnetic field spot measurements for those categories. Similarly, London et al. [1991] and Linet et al. [1997] report results for leukemia in more than two wire code categories and reported summary values of magnetic field 24-hour measurements for those categories.

These data permit an analysis in which each wire code category is assigned an exposure score based on the field measurements in that category from the same study. This approach [Poole and Ozonoff 1996] takes advantage of the fact that there was far less missing data for the wire codes than for the measured fields. The extracted results are summarized in Tables 8 and 9.

Risks for all reported results are positive but none are statistically significant. The resulting relative risk for wire codes scored by spot measures (OR = 2.7, 95% CI 0.8–8.7) is considerably larger than the others but is far less precise and not very homogeneous ($P=0.1$). The result for wire codes scored by 24-hour measures (OR = 1.6, 95% CI 0.5–4.6) is less homogeneous ($P=0.02$) than others.

Calculated magnetic fields. Feychting and Ahlbom [1993], Verkasalo et al. [1993], Olsen et al. [1993], and Tynes and Haldorsen [1997] reported results for leukemia in more than two calculated magnetic field categories. Various algorithms used by the investigators to determine the calculated fields. The extracted data are reported in Table 10. The results are homogeneous ($P=0.2$) and show a small but not statistically significant elevation of risk (OR = 1.2, 95% CI 0.9–1.5).

TABLE 9. Results Extracted From Studies of Exposure-Response Trends for Childhood Leukemia and Wire Codes Scored by 24-hour Bedroom Measurements of Magnetic Fields

First author	Wire code category	Assigned value (μT) (see text)	Cases	Controls	Relative risk (95% confidence interval)
London	Buried + VLCC	0.0475	33	106	1.
	OLCC	0.0650	38	102	1.20 (0.70–2.05)
	OHCC	0.0720	20	44	1.46 (0.76–2.82)
	VHCC	0.1150	7	8	2.81 (0.95–8.33)
Linet	Buried + VLCC	0.072	175	175	1.
	OLCC	0.118	116	114	1.07 (0.74–1.54)
	OHCC	0.136	87	87	0.99 (0.67–1.48)
	VHCC	0.207	24	26	0.88 (0.48–1.63)

TABLE 10. Results Extracted From Studies of Exposure-Response Trends for Childhood Leukemia and Calculated Magnetic Fields

First author	Exposure range (μT)	Assigned value (μT) (see text)	Cases	Controls	Relative risk (95% confidence interval)
Feychting (0.2 μT upper cutpoint)	<0.100	0.070	27	475	1.
	0.100–0.199	0.145	4	33	2.1 (0.6–6.1)
	≥ 0.200	0.260	7	46	2.7 (1.0–6.3)
Feychting (0.3 μT upper cutpoint)	<0.100	0.070	27	475	1.
	0.100–0.299	0.195	4	47	1.5 (0.4–4.2)
	≥ 0.300	0.390	7	32	3.8 (1.4–9.3)
Verkasalo	<0.01	0.007	—	—	1.
	0.01–0.19	0.100	32	—	0.89 (0.61–1.3)
	≥ 0.40	0.520	3	—	1.6 (0.32–4.5)
Olsen (0.25 μT upper cutpoint)	<0.10	0.070	829	1658	1.
	0.10–0.24	0.170	1	4	0.5 (0.1–4.3)
	≥ 0.25	0.325	3	4	1.5 (0.3–6.7)
Olsen (0.40 μT upper cutpoint)	<0.10	0.070	829	1658	1.
	0.10–0.39	0.245	1	7	0.3 (0.0–2.0)
	≥ 0.40	0.520	3	1	6.0 (0.8–44)
Tynes	<0.05	0.035	134	532	1.
	0.05–0.13	0.095	10	26	1.5 (0.7–3.3)
	≥ 0.14	0.182	4	21	0.8 (0.3–2.4)

Summary. In summary, exposure metrics of wire codes (scored by spot measurements and 24-hour measurements), spot measurements and calculated fields, all analyses but those of wire codes gave similar random effects ORs (2.7, 1.6, 1.1, and 1.2, respectively), as shown in Table 11.

Population Attributable Risk (PAR)

Finally, I conduct a quantitative risk assessment by calculating the population attributable risk. This is a prediction of the impact of residential magnetic field exposure predicated on the assumptions that: (a) the exposure causes leukemia in children; (b) the studies are accurate and representative; (c) the exposure-response follows a log-linear relationship. Using expo-

sure data developed from surveys of homes throughout the US, I have both distributions of wire codes and spot measured magnetic fields [Zaffanella, 1993; Zaffanella and Kalton, 1998]. For wire codes, it was reported that 28% of homes have ordinary high (OHCC) or very high (VHCC) current configurations. For spot measurements, the data were reported to follow approximately a lognormal distribution with a mean of 0.09 μT and a standard deviation of 2.2 μT .

Using the relative risks of 1.4 for OHCC or higher wire codes and 1.1 per 0.1 μT for spot measured magnetic fields, as reported in the NIEHS meta-analysis [Wartenberg et al., 1998], and the reported annual 2,200 cases of leukemia cases to children under 15 years of age (source: Leukemia Society of America),

TABLE 11. Summary of NIEHS Meta-Analyses (Wartenberg et al., 1998)

Criterion	Index	Measured/calculated Fields			Proximity to Source		
		Dichotomy	Continuous		Dichotomy	Continuous	
			Spot measurements	Calculated fields		Wire codes scored by spot	Wire codes scored by 24 h
Strength	Summary RR ^a	1.4 (1.0–2.0)	1.1 (0.9–1.3)	1.2 (0.9–1.5)	1.4 (1.1–1.8)	2.7 (0.8–8.7)	1.6 (0.5–4.6)
Consistency	% of positive studies (number of studies)	80% (10)	75% (4)	75% (4)	73% (11)	100% (2)	50% (2)
Publication bias	Homogeneity	0.2	0.3	0.2	0.1	0.1	0.02
	Fail-safe N	7	—	—	30	—	—
Influence analysis	Subjects needed	>6000	—	—	> 3400	—	—
	Homogeneity	0.11–0.50	—	—	0.04–0.20	—	—
	Relative risk	1.2–1.6	—	—	1.3–1.5	—	—

^aRandom effects model (DerSimonian et al., 1986).

TABLE 12. Population Attributable Risk for Children in the United States

Stage of risk assessment	Wire codes	Measurements
Hazard ID		Group 2B carcinogen
Exposure assessment	28% \geq OHCC ^a	Lognormal (0.09, 2.2) ^b
Exposure response ^c	RR = 1.4	RR = 1.1 per 0.1 μ T
Risk characterization	PAR #cases	8% ~175
		11% ~240

^aZaffanella (Zaffanella, 1993).

^bZaffanella (Zaffanella et al., 1998).

^cWartenberg (Wartenberg et al., 1998).

one can calculate the number and proportion of cases attributable (PAR) to residential magnetic field exposure each year. Based on the wire code data, I predict about 175 cases, or 8%, attributable to residential magnetic field exposure in the US. Based on the spot measurement data, I predict about 240 cases, or 11%, attributable to magnetic field exposure in the US (Table 12). From a policy perspective, these are substantial numbers, if somewhat uncertain.

DISCUSSION

The goals of a meta-analysis are threefold. First, a meta-analysis is used to identify and review all studies conducted on a specific topic. Second, a meta-analysis is used to assess the consistency and comparability (homogeneity) of results of each of the identified studies. Third, if the studies are sufficiently similar, meta-analytic tools are used to combine estimates from individual studies into a composite estimate with greater statistical power than the individual studies. While the advantage of combining estimates to a "more reliable bottom line" is often seen as a primary objective of meta-analysis, careful attention has to be given to the review of the individual studies and the consistency of the contributing studies. If this is not done, the combined risk estimate may result in a false sense of reliability and closure even though the actual estimate of risk is very uncertain and unrepresentative.

First, results from the meta-analyses in which the exposure data are dichotomized generally are positive, and several are statistically significant. In most cases, none of the individual studies are particularly (or disproportionately) influential. This is important because many people believe there are no data to support an association between residential magnetic field exposure and childhood leukemia. To the contrary, the data strongly and relatively consistently support such an association, although the estimated magnitude of the risk is moderate. Limitations due to design, confounding, or other biases may suggest alternative interpretations.

There is moderate heterogeneity, statistically, in the results using a variety of measures of proximity to electrical facilities, but not for those using measured or calculated magnetic fields. When I attempted to isolate the source of the heterogeneity by stratification, I found that the year of study showed the greatest difference for the proximity analyses. That is, studies published up through 1993 showed a stronger association than those published thereafter. Age of subjects also differs greatly. For the studies with measured and calculated fields, the differences by year of publication were small, as were difference by age, although there is a substantial difference by study design not seen in the proximity/distance studies. None of the factors investigated showed consistent and substantial confounding. Thus, after sacrificing detail on any apparent exposure-response relationship by using a dichotomized analysis, there appears to be a fairly consistent association of leukemia risk with (dichotomized) residential exposure.

My analyses also provide little evidence for publication bias. The number of unpublished null studies needed to balance the average risk of those published (the Fail-Safe *N*) generally were considerably greater than the number published. However, for studies in which the results were not statistically significant, this index is not meaningful. Similarly for the statistic concerning the number of subjects needed, only an extremely large and negative (protective) study could reverse the observed results.

The exposure response meta-analyses represent a more sophisticated approach to assessing the consistency of study results and provide more specific information about effects of exposure. These analyses were conducted for exposure metric-disease outcome pairs. In order to be sure of combining only those studies with similar enough exposure assessment methods to be meaningful from an engineering standpoint, it was necessary to limit the number of studies that could be combined in any one comparison. In each such grouping therefore, there were only two to four studies. All ORs were elevated but none were statistically

significant. Heterogeneity in all but the spot measurements was fairly large ($P < 0.2$). Information provided in these studies was too limited to allow me to determine the reason for heterogeneity in wire codes and spot measures, other than suggesting the obvious effects of seasonal and other temporal variations in energy use patterns. Similarly, there were no systematic differences in wiring practices in different geographical locations that would permit application of a simple correction factor to make wire code determinations more comparable in different regions.

When heterogeneity is present, it should be reported, and average risk estimates are unrepresentative. Explanation of the heterogeneity in terms of characteristics of the studies may provide more insight than the summary estimate itself. If there are a sufficient number of studies, a thorough analysis of study characteristics and results can provide particularly useful insights possibly relating these characteristics directly to the results. In such a study-rich meta-analysis, the homogeneity P values and comparisons between fixed effects and random effects estimates are preliminary analyses, conducted as a prelude to a serious analysis of the study characteristics and their associations with the studies' results. Our efforts in this direction were limited by only a few studies with exposure-response information and substantial heterogeneity across exposure metrics. Detailed analysis of factors contributing to outcome is precluded due to lack of data. In these situations, one often relies on indirect indicators of sources of error in the data.

In reaching final conclusions about the interpretation of these studies, one must consider four factors: the number of studies in an analysis, the heterogeneity, the effect size, and the sensitivity (robustness). Overall, I see largely positive results with small to moderate effect sizes. The results are robust to study deletion but there is considerable heterogeneity. These summaries are unlikely to be change by additional studies unless those studies are extremely large and produce markedly different results. If one chooses to use these summary estimates for interpretation, given the widespread exposure to magnetic fields they suggest perhaps as much as a 15–25 % increase in the childhood leukemia rate, which is a large and important public health impact.

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APPENDIX: DISCUSSION AT THE WORKSHOP

Neutra asked how the attributable risk of 23% translates to individual childhood accumulated risk. Wartenberg estimated that the childhood risk would be about 10% more than the base risk, i.e. between one in 1,000 and one in 10,000. Stolwijk objected that this kind of assessment assumes that there is a zero threshold and that most of the risk is actually accumulated by people or children receiving EMF exposures below 1 mG (0.1 μ T). Wartenberg replied that he also performed a dichotomous estimate, classifying subjects as either unexposed or exposed, and the risk increased by a factor of two in this new analysis. Wartenberg thought that when one considers all the uncertainties involved in these estimates, the two results essentially agree.

Stolwijk remarked that there were very important mitigation consequences depending on which of the

two models one accepts—either a model that assumes a threshold of zero or a model that assumes a threshold of around 2 mG, because mitigation generally addresses EMF sources on above 2 mG. People often propose to mitigate these levels of exposure, he said, but most of the EMF attributable risk would not be eliminated with this type of mitigation if, in fact there was a threshold of zero. Neutra agreed that this is a really important point that needs to be clarified. DelPizzo noted that in the Swedish study the cumulative distribution of the exposure of cases and controls living in single family homes diverged from a very low cutpoint (0.1 mG). He argued that if there were a clear threshold higher than about a fraction of one mG, the two curves would overlap up to the threshold and then diverge.

Bowman commented that if one were estimating the wrong metric, heterogeneity between studies using a quantitative assessment of exposure, would not imply inconsistency with a causal association. He said he was not sure the same could be said for studies using wire codes, since wire codes are so poorly understood. He also pointed out that, since the logistic model assumes no intercept, using a partially exposed population as the reference group underestimates the slope (he drew a graphic example). In their meta-analysis for occupational studies, Bowman continued, he and his colleagues subtracted the exposure of the reference group from each point. Using this approach, they get a fit with no intercept and a bigger slope.

Langholtz asked if, by integrating under Bowman's curve to calculate the population attributable risk (PAR), one implicitly makes the assumption that all childhood leukemia is attributable to electromagnetic field exposure. DelPizzo remarked that the quantity plotted on the vertical axis represents the odds ratio rather than the incidence. Therefore, he said, the incidence is not zero even if exposure is zero. Wartenberg agreed and explained that the area under the curve represents the total number of cancers attributable to EMF exposure and that therefore the intercept represents the rate among nonexposed subjects.

Buffler questioned the wisdom of attempting PAR estimates before having resolved all the doubts, which still linger, about EMF epidemiology. Wartenberg reminded her that he had prefaced his presentation by saying, “if one believes it's causative.” Savitz said that this exercise, though performed with the scanty information that now available, should be remembered and considered a beginning at generating a pooled estimate. However, he continued, this exercise relies heavily on assumptions that may or may not be good, and the result may or may not be right either. He thought that Wartenberg's work in carrying the

meta-analysis through all the logical steps to the estimate of attributable cases was useful.

Savitz also said that he understood the National Academy of Sciences rules require making a dichotomous decision regarding hazard identification before proceeding to the next stages. However, he thought that this procedure was not helpful if the answer to the hazard identification question was neither “yes” or “no,” but rather “maybe,” as he believed to be the case with EMF. He thought that by assuming varying degrees of possibility one can find a range of estimates, and finding such a range, he believes, is a useful exercise. However, he also recognized that once estimates are generated, people tend to forget the process that generated them and that the estimates are tentative, no matter how emphatically the researchers emphasize it. Therefore, he sympathizes with Buffler’s concern over generating PAR estimates when one is not sure that the risk exists, especially since such estimates can fuel hysteria. In order to address the problem of potential hysteria, he agreed with Wartenberg that one should

keep stating the same caveats over and over and keep describing the nature of the exercise. These sorts of estimates are generated all the time, he continued, in committees and behind closed doors, but he believes that the process should be explicit and discussed openly.

Wartenberg noted that experts continue to receive questions from the public concerned about EMF exposure, such as whether or not to buy a house near power lines. He thought that attempting a rough estimate of PAR helps to put the EMF question into context by allowing some comparison with other risks, even if a straight numerical comparison cannot be done. Rather than fuel hysteria, Wartenberg said, these estimates suggest that EMF is not one of the risk factors that require aggressive response. He thought that it is useful to be able to say that, even if EMF is causally related to by leukemia, we certainly cannot conclude, based on the information we have, that the majority of all leukemia cases are due to EMF exposure.