

## RESIDENTIAL MAGNETIC FIELDS AS A RISK FACTOR FOR CHILDHOOD ACUTE LEUKAEMIA: RESULTS FROM A GERMAN POPULATION-BASED CASE-CONTROL STUDY

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**Our objective was to investigate whether exposure to residential power-frequency (50 Hz) magnetic fields above 0.2  $\mu$ T increases a child's risk of leukaemia and to confirm or reject a finding from a previous German study on this topic, which reported increased leukaemia risk with exposure to stronger magnetic fields during the night. A population-based case-control study was used, covering the whole of the former West Germany. Residential magnetic fields were measured over 24 hr for 514 children with acute leukaemia identified by the German Childhood Cancer Registry and 1,301 control children taken from population registration files. Magnetic fields above 0.2  $\mu$ T were relatively rare in Germany (only 1.5% of the study population). Childhood leukaemia and 24 hr median magnetic fields were only weakly related (OR = 1.55, 95% CI 0.65–3.67). A significant association was seen between childhood leukaemia and magnetic field exposure during the night (OR = 3.21, 95% CI 1.33–7.80). A dose-response-relationship was observed after combining the data of all German studies on magnetic fields and childhood leukaemia. The evidence for an association between childhood leukaemia and magnetic field exposure in our study comes from a measure of exposure during the night. Despite the large size of our study, the results are based on small numbers of exposed children. If the observed association stands, the effect on a population level in Germany would be small.**

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**Key words:** electromagnetic fields; leukaemia; childhood cancer; case-control study; epidemiology; environmental exposures

During the last 2 decades, a number of epidemiological studies have explored the association between childhood leukaemia and residential exposure to power-frequency electromagnetic fields (EMFs). Although there are inconsistencies across studies, reviews have suggested that there is a small excess leukaemia risk with magnetic field exposure above 0.2  $\mu$ T.<sup>1–5</sup> Based on these findings and epidemiological studies that observed an association between adult chronic lymphoblastic leukaemia and occupational exposure to EMFs,<sup>6</sup> an international working group convened by the U.S. National Institute of Environmental Health Sciences (NIEHS) rated exposure to power-frequency magnetic fields as “possibly carcinogenic to humans” using the International Agency for Research on Cancer criteria for classifying potential carcinogens.<sup>4</sup> However, so far, there is no convincing supportive laboratory evidence for this rating, and the absence of a plausible biological mechanism of disease causation limits the evidence derived from epidemiological studies.<sup>4</sup>

From 1993 to 1997 we performed 2 smaller EMF studies embedded in population-based case-control studies carried out by the German Childhood Cancer Registry (GCCR), one in the north-western part of Germany (Lower Saxony) and one in Berlin, and then pooled the 2 sets of results.<sup>7,8</sup> Exposure was assessed by measurements of the magnetic field over 24 hr in the child's bedroom. Based on 176 children with acute leukaemia and 414 control children, we observed an elevated odds ratio (OR) of 2.3 with a wide 95 percent confidence interval (95% CI) of 0.8–6.7 due to the small number of children exposed to median magnetic fields above 0.2  $\mu$ T (9 cases, 8 controls). When the analysis was restricted to the median magnetic field measured during the night, the OR based on the

0.2  $\mu$ T cut-off point increased to 3.8 (95% CI 1.2–11.9). The association was strongest for children under the age of 5 years.

Because of these inconclusive results, we expanded the magnetic field measurements to a large-scale population-based epidemiological study on a variety of potential risk factors for childhood cancer covering the whole of the former West Germany, including densely populated areas like Hamburg, the Ruhr district and Munich.<sup>9,10</sup> Before we started conducting measurements, we set up defined hypotheses and planned an analysis strategy that will be described in Material and Methods below. The primary intentions of the extended study were (i) to contribute to the ongoing discussion on this topic by achieving more stable estimates for the leukaemia risk associated with average exposure to residential magnetic fields under German conditions, (ii) to confirm or reject the results of our previous studies regarding exposure during the night and (iii) to explore whether adjustment for different confounding factors changes the results.

### MATERIAL AND METHODS

Briefly, our EMF study involved cases and controls participating in a large-scale case-control study carried out between 1993 and 1997. The study consisted of 2 parts: a nation-wide component (NW component)<sup>9</sup> and one restricted to geographic areas around nuclear installations and selected control regions (NI component).<sup>10</sup> Measurements of residential magnetic fields started in November 1997 and continued until December 1999. Cases were identified from the nation-wide GCCR Registry at the University of Mainz, which has been estimated to be more than 95% complete.<sup>11</sup> Controls were selected from complete files of local resident registration offices.

#### Study basis

The NW component of the case-control study comprised children with acute leukaemia, non-Hodgkin's lymphoma and solid tumours. Cases were eligible if one of these diseases was diagnosed when the child was younger than 15 years between October 1992 and September 1994 and if he or she lived in the former West Germany on the date of diagnosis. The NI component was embedded in an ecological study investigating childhood malignancies in the vicinity of German nuclear installations. The study population comprised cases with childhood acute leukaemia or non-Hodgkin's lymphoma aged 15 years or less, born after 1 July

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1975 and, on the date of diagnosis, living in a nuclear installation area (*i.e.*, at most, 15 km away from a nuclear installation) or a matched control region. The diagnostic period of the NI component was from January 1980 to September 1994, but cases diagnosed before January 1990 and their corresponding controls were excluded from EMF measurements. This was done to avoid extremely long time periods between the date of diagnosis and the date of the measurement. Some cases who met the inclusion criteria of both components were counted only once, in the analysis of the total sample.

For both components, one control matched by gender, date of birth and community (smallest administrative unit in Germany) was selected for each case. A list of 4 addresses of children of the same gender and with a birth date as close as possible to a given date (the birth date of the corresponding case but changed slightly to prevent identification by the local resident registration office) was requested from the registration office of the community in which the case lived on the date of diagnosis. We randomly chose 1 control from this list. If the chosen family did not participate, we contacted another family from the remaining names on the list. We checked that no case family (who might have been sampled as a potential control) was selected as a control.

For each control, the date of diagnosis of the corresponding case was defined as the reference date (both date of diagnosis and reference date will be referred to as reference date hereafter). Information on potential risk factors was collected by both self-administered questionnaire and subsequent telephone interview. During this interview, we asked for all addresses where the child lived between the birth date and the reference date.

The EMF study, which started after completion of the original case-control study, comprised only cases with acute leukaemia. Since we adopted a frequency-matched design for the EMF study,<sup>12,13</sup> all controls were eligible, even if they were originally matched to a case with a non-Hodgkin's lymphoma or a solid tumour. To avoid overlap with our previous German EMF studies in Lower Saxony and Berlin, children whose families had already participated in these studies were excluded from the current study. This concerned children of the NW component who lived in West Berlin at the date of diagnosis (they partially formed the study basis of our previous EMF study in Berlin<sup>8</sup>), children of the NW component who had a reference date before July 1993 and lived in Lower Saxony at the date of diagnosis and children living in the vicinity of a nuclear installation located in Lower Saxony.<sup>7</sup> For the following reasons, participants in the original study were also excluded from the EMF study: the reference date was before 1 January 1990, the residence where the child lived longest before the reference date was out of Germany or the parents refused to give former addresses during the telephone interview.

#### Measurements

Measurements over 24 hr were conducted at 2 fixed locations, one under the mattress of the child's bed and one in the living room at a place removed from any electrical appliance. In the child's bedroom, the Physical Systems FW2a (Physical Systems, Inc., Bradenton, FL) field meter was used to record magnetic field intensity at 50 Hz. The EMDEX II (EnerTech, Campbell, CA) field meter, calibrated at 50 Hz with a response to frequencies ranging from 40 to 800 Hz, was used in the living room; this additional measurement was made for quality purposes. To obtain information on the spatial distribution of the magnetic field, the field technicians performed short-term measurements with the EMDEX II connected to a measurement wheel, recording a value approximately every 30 cm while walking very slowly through all rooms of the residence. Moreover, the field technicians determined if there were any power lines, transformers or substations located near the residence.

Spot measurements were conducted to identify sources of elevated magnetic fields. We used them as 1 of 3 exposure variables in our previous studies; but since we observed a poor agreement

between 24 hr measurements and spot measurements<sup>14</sup> and childhood leukaemia was not related to spot measurements in our former<sup>8</sup> and in other<sup>4</sup> studies, they were not used to estimate exposure in the current study.

Magnetic field intensity was recorded in 3 dimensions, from which we calculated the root mean square (often called the resultant) magnitude at 50 Hz. For analytical purposes, we calculated arithmetic and geometric means, SDs and several percentiles (including the median) of each measurement over 24 hr. The median during the night (night-time value) was calculated from the data recorded between 10 PM and 6 AM; the daytime median was based on data acquired between 6 AM and 10 PM.

According to the design of the previous German EMF studies,<sup>7,8</sup> the address where the child lived longest before the reference date was used for measurements. If more than 1 residence fulfilled this criterion, *e.g.*, if a 2-year-old child lived in 2 different residences over a period of 1 year, we performed measurements in all relevant dwellings. Multiple measurements for 1 participant were later combined to a single data record by calculating the means of the measurement parameters. All measurements were conducted by field technicians from the *Forschungsverbund*. The engineers were blinded to case or control status; however, sometimes it might have been obvious that the child was a case.

#### Statistical analysis

As in our previous studies, the median of the 24 hr measurement in the child's bedroom was defined as a proxy for the child's average exposure to magnetic fields. To compare our results with those from studies in the United States,<sup>15,16</sup> Canada,<sup>17</sup> New Zealand<sup>18</sup> and the United Kingdom,<sup>19</sup> we also calculated ORs using the arithmetic mean of the measurement. The second parameter for confirmatory analysis was the night-time value, as described above. The cut-off point to discriminate between exposed and non-exposed subjects was 0.2  $\mu$ T. To explore a possible dose-response relationship, we defined 4 categories with cut-off points at 0.1, 0.2 and 0.4  $\mu$ T.

ORs and 95% CIs were computed with logistic regression models using the PHREG procedure of SAS (Cary, NC) software, release 6.12. According to the frequency-matched design of the EMF study, data were stratified for gender, age (age groups of 1 year) and year of birth. All analyses were additionally adjusted for socio-economic status (high, other), which was estimated on the basis of family net income and level of parental education. A few families, particularly parents of controls, refused to give their income; therefore, socio-economic status was estimated on the basis of the parental occupational history. Frequency-matched analyses were also adjusted for degree of urbanisation (urban, mixed, rural) to compensate for ignoring the matching for community in the original case-control study and for study component (NI component only, NW component or both). Further potential confounders considered in additional analyses were residential mobility (0, 1,  $\geq 2$  moves between birth date and date of diagnosis), season of measurement, type of residence (single-family homes/farms, double-family homes/row-houses, apartment buildings with 3 to 10 parties, apartment buildings >10 parties) and monthly family net income (5 levels). These factors were related to the occurrence of elevated magnetic fields in earlier studies.<sup>4,20</sup>

#### RESULTS

According to the eligibility criteria, the EMF study population comprised 847 cases and 2,127 controls (Table I). Sixty-four cases and 86 controls were excluded since the residence where they lived longest before the reference date was not known or was out of Germany. Of 2,935 addresses relevant for measurements (there were 108 subjects with 2 relevant residences and 1 subject with 4 relevant residences), families in 1,853 residences participated (63.1%). Reasons for non-participation were refusal (18.6%), no appointment with the family could be made (14.1%; *i.e.*, the family had no phone and did not respond to letters, the family did not

**TABLE I** – RESPONSE RATE AMONG CURRENT OCCUPANTS<sup>1</sup> CONTACTED REGARDING MEASUREMENTS OF RESIDENTIAL MAGNETIC FIELD

	Residences of cases			Residences of controls		
	n	%	%	n	%	%
Eligible	847	100.0		2,127	100.0	
Residential history unknown	20			22		
Lived longest out of Germany	44			64		
Contacted	783	92.4	100.0	2,041	96.0	100.0
No measurement could be conducted	263			722		
Participated	520	61.4	66.4	1,319	62.0	64.6
Erroneous recordings	4			14		
Measurement at wrong address	2			4		
Included in analysis	514	60.7		1,301	61.2	

<sup>1</sup>Study participant's family still lived in 67.7% of all relevant residences.

**TABLE II** – DISTRIBUTION OF CASES AND CONTROLS BY GENDER, AGE, SOCIO-ECONOMIC STATUS, MONTHLY FAMILY NET INCOME, DEGREE OF URBANISATION, TYPE OF RESIDENCE, RESIDENTIAL MOBILITY AND STUDY COMPONENT

	Cases (n = 514)	Controls (n = 1301)	p
Gender			
Male	304 (59.1%)	779 (59.9%)	
Female	210 (40.9%)	522 (40.1%)	0.77
Age (years)			
0–4	290 (56.4%)	635 (48.8%)	
5–9	153 (29.8%)	401 (30.8%)	
10+	71 (13.8%)	265 (20.4%)	<0.01
Socio-economic status			
Other	374 (72.8%)	880 (67.6%)	
High	140 (27.2%)	421 (32.4%)	0.03
Monthly family net income			
<1,000 Euro	21 (4.2%)	43 (3.5%)	
1,000–2,000 Euro	299 (59.9%)	584 (47.9%)	
2,000–3,000 Euro	134 (26.9%)	420 (34.5%)	
>3,000 Euro	45 (9.0%)	171 (14.0%)	<0.01
Unknown	15	83	
Degree of urbanisation			
Urban	174 (33.9%)	489 (37.6%)	
Mixed	188 (36.6%)	440 (33.8%)	
Rural	152 (29.6%)	372 (28.6%)	0.31
Type of residence			
Single family houses/farms	222 (43.2%)	563 (43.3%)	
Duplexes/row-houses	134 (26.1%)	403 (31.0%)	
Small apartment buildings (3–10 units)	132 (25.7%)	285 (21.9%)	
Large apartment buildings (>10 units)	26 (5.1%)	50 (3.8%)	0.09
Number of residences (residential mobility)			
1	344 (66.9%)	895 (68.8%)	
2–3	163 (31.7%)	384 (29.5%)	
>3	7 (1.4%)	22 (1.7%)	0.60
Study part			
NW component	360 (70.0%)	1,086 (83.5%)	
NI component	78 (15.2%)	115 (8.8%)	
Both components	76 (14.8%)	100 (7.7%)	<0.01

speak German, the new owner or tenant of the residence could not be traced, the address was not complete or wrong) or the building was pulled down or renovated and improved (4.2%). Because the family of the study participant had moved, 949 residences (32.3%) were inhabited by new owners or tenants (hereafter called new tenants). There were no differences between case and control families; however, there were large differences regarding participation: of 1,986 families still living in the relevant residence, 1,479 participated (74.5%), but only 356 of 949 new tenants (37.5%) approved the measurement. Eighteen measurements were not included in the analysis because of erroneous recordings, *i.e.*, malfunctions of the measurement instrument, the instrument was inadvertently placed too close to an electrical appliance or the family agreed to only short-term measurements. In all, exposure information was available for 514 cases and 1,301 controls (Table I).

Table II gives the distribution of cases and controls by gender, age, socio-economic status, monthly family net income, degree of urbanisation, type of residence, residential mobility and study component. Differences in age and study component distribution

were expected and were due to the study design since we included matched partners of cases with solid tumours (all children with a solid tumour were participants of the NW component and, on average, were older at date of diagnosis than leukaemia cases).<sup>9</sup> Differences between cases and controls were also observed with respect to socio-economic status. This was due to a higher response of controls with high socio-economic status than controls with other socio-economic status. Hence, all analyses were adjusted for that factor. Despite the strong association with family net income, case or control status was only moderately associated with type of residence.

Table III gives the results of our primary analyses. As described in Material and Methods, our confirmatory hypothesis focused on the median magnetic field of the 24 hr measurement in the child's bedroom and on the night-time value. While the association between childhood leukaemia and magnetic fields was weak on the basis of median magnetic fields, it was pronounced based on exposure at night. The difference between night-time and day-time exposures became more marked after incorporating both magnetic

TABLE III—OR FOR CHILDHOOD ACUTE LEUKAEMIA BY EXPOSURE TO RESIDENTIAL MAGNETIC FIELDS (MFS, PRIMARY ANALYSIS)

	<0.2 $\mu$ T	$\geq$ 0.2 $\mu$ T	<0.1 $\mu$ T	0.1 to <0.2 $\mu$ T	0.2 to <0.4 $\mu$ T	$\geq$ 0.4 $\mu$ T
Median MF <sup>1</sup>						
Cases	505	9	472	33	6	3
Controls	1,283	18	1,210	73	15	3
Adjusted OR (95% CI) <sup>2</sup>	1.00	1.55 (0.65–3.67)	1.00	1.15 (0.73–1.81)	1.16 (0.43–3.11)	5.81 (0.78–43.2)
<i>p</i> value		0.32		0.54	0.77	0.09
<i>p</i> value for 2-tailed test for trend						0.34
Arithmetic mean MF <sup>1</sup>						
Cases	500	14	456	44	11	3
Controls	1,277	24	1,188	89	21	3
Adjusted OR (95% CI) <sup>2</sup>	1.00	1.69 (0.83–3.46)	1.00	1.34 (0.90–2.01)	1.45 (0.67–3.14)	5.94 (0.80–44.1)
<i>p</i> value		0.15		0.15	0.35	0.08
<i>p</i> value for 2-tailed test for trend						0.07
Daytime value <sup>3</sup>						
Cases	504	10	464	40	7	3
Controls	1,279	22	1,196	83	18	4
Adjusted OR (95% CI) <sup>2</sup>	1.00	1.35 (0.60–3.07)	1.00	1.32 (0.87–2.02)	1.10 (0.43–2.78)	3.44 (0.59–20.2)
<i>p</i> value		0.47		0.19	0.85	0.17
<i>p</i> value for 2-tailed test for trend						0.28
Night-time value <sup>4</sup>						
Cases	502	12	468	34	7	5
Controls	1,289	12	1,219	70	8	4
Adjusted OR (95% CI) <sup>2</sup>	1.00	3.21 (1.33–7.80)	1.00	1.42 (0.90–2.23)	2.53 (0.86–7.46)	5.53 (1.15–26.6)
<i>p</i> value		0.01		0.13	0.09	0.03
<i>p</i> value for 2-tailed test for trend						0.01

<sup>1</sup>Derived from 24 hr measurement in the child's bedroom in the residence where the child lived longest before the reference date.—<sup>2</sup>OR and respective 95% CI from logistic regression analyses stratified for year of birth, age groups of 1 year and gender and additionally adjusted for degree of urbanisation (urban, mixed, rural), study component (NI component only, NW component only or both) and socio-economic status (high, other).—<sup>3</sup>Median magnetic field between 6 AM and 10 PM derived from the 24 hr measurement in the child's bedroom.—<sup>4</sup>Median magnetic field between 10 PM and 6 AM derived from the 24 hr measurement in the child's bedroom.

field characteristics in the same logistic regression model; at 0.2  $\mu$ T, the OR for night-time exposure increased to 3.69 (95% CI 1.32–10.3), while the OR for daytime decreased to 0.77 (95% CI 0.29–2.03). As can also be seen from Table III, the prevalence of magnetic fields exceeding 0.2  $\mu$ T in Germany was very low, and only 27 subjects (1.5%) were exposed to average magnetic fields above this value [24 subjects (1.3%) during the night]. Only 8 (29%) of these 27 median magnetic fields above 0.2  $\mu$ T were produced by high-voltage transmission lines.<sup>14</sup>

Adjustment for other potential confounding factors had only a small effect on ORs. After including the season of measurement, residential mobility and type of residence in the logistic regression models, the ORs were slightly lower; however, the statistically significant association between childhood leukaemia and exposure during the night remained. The respective ORs are shown in Table IV. When we restricted the analysis to children who lived in a single home between date of birth and reference date (including a few who lived for the entire reference period in homes for which we conducted 24 hr measurements), the association was even more pronounced (Table IV). When we examined the data for children aged 4 years or younger and children aged 5 years or older, we observed a pattern similar to that in our previous EMF studies: the risk was highest for younger children (Table IV).<sup>8</sup> The ORs restricted to the major morphological subgroup of leukaemia, acute lymphoblastic leukaemia (ALL), are shown in Table IV, allowing comparison with studies that involved only cases with ALL.

Ten cases and 1 control with Down syndrome participated in our EMF study, and 2 of the cases had daytime as well as night-time exposures above 0.2  $\mu$ T. Excluding these children from the study, like Linet *et al.*<sup>16</sup> did in the U.S. study, led to lower and less precise risk estimates (Table IV). Both exposed cases with Down syndrome had median and night-time magnetic fields ranging from 0.2 to 0.25  $\mu$ T.

Table V gives the results for the combined risk estimates after pooling the current study with our previous EMF studies in Lower

Saxony and Berlin.<sup>7,8</sup> The logistic regression model involved the former East and West Germany as an additional independent variable and study setting (Berlin, Lower Saxony, NI component only, NW component only or both) as a further dummy variable for adjustment. All combined analyses included children with Down syndrome. The methods for exposure assessment were similar for all 3 studies, except that we used the FW2 field meter in the current study while the EMDEX II was used in the former studies. As can be seen in Table V, the leukaemia risk was statistically significant for median magnetic fields of 0.4  $\mu$ T and above. For the night-time value, we observed a clear dose-response relationship (2-tailed *p* for trend < 0.01). Nevertheless, this has to be interpreted with care since the pooled analyses combined the current replication study with the hypothesis-generating studies.

## DISCUSSION

### Strengths and limitations

One strength of our study is that it was population-based because cases were identified from an almost complete nation-wide cancer registry and controls were drawn at random from complete files of population registries. Since in Germany registration is compulsory for all residents, these files provide an excellent sampling frame for epidemiological studies. Furthermore, our study was embedded in a large-scale case-control study on a variety of risk factors for childhood cancer; therefore, we had very detailed information on potential confounding factors. Our comprehensive method for measuring magnetic fields enabled us to identify the source of elevated magnetic fields and to compare those measured in the child's bedroom to those obtained in other rooms of the dwelling. The large study population was another strength of the study, but in hindsight, it was not large enough under German conditions of environmental exposure to EMF.

When we calculated the sample size of the study, we assumed a prevalence of magnetic fields above 0.2  $\mu$ T of about 3%, which

TABLE IV – ADDITIONAL ANALYSIS INVOLVING POTENTIAL CONFOUNDING FACTORS ON SUBSETS OF DATA (EXPLORATORY ANALYSIS)

	<0.2 µT	≥0.2 µT	<0.1 µT	0.1 to <0.2 µT	0.2 to <0.4 µT	≥0.4 µT
Additional potential confounding factors						
Median MF <sup>1</sup>						
Cases	505	9	472	33	6	3
Controls	1,283	18	1,210	73	15	3
Adjusted OR (95% CI) <sup>2</sup>	1.00	1.49 (0.62–3.55)	1.00	1.16 (0.73–1.83)	1.12 (0.41–3.04)	5.26 (0.69–40.2)
<i>p</i> value		0.37		0.52	0.83	0.11
Night-time value <sup>3</sup>						
Cases	502	12	468	34	7	5
Controls	1,289	12	1,219	70	8	4
Adjusted OR (95% CI) <sup>2</sup>	1.00	3.21 (1.31–7.84)	1.00	1.44 (0.92–2.28)	2.58 (0.87–7.70)	5.33 (1.09–26.0)
<i>p</i> value		0.01		0.11	0.09	0.04
Analysis restricted to children with a single residence						
Median MF <sup>1</sup>						
Cases	343	6	320	23	4	2
Controls	891	13	842	49	11	2
Adjusted OR (95% CI) <sup>4</sup>	1.00	1.59 (0.55–4.59)	1.00	1.23 (0.71–2.14)	1.06 (0.32–3.56)	11.6 (0.83–160)
<i>p</i> value		0.39		0.45	0.92	0.07
Night-time value <sup>3</sup>						
Cases	339	10	316	23	7	3
Controls	896	8	849	47	6	2
Adjusted OR (95% CI) <sup>4</sup>	1.00	4.35 (1.49–12.8)	1.00	1.60 (0.91–2.81)	3.07 (0.93–10.1)	15.6 (1.35–182)
<i>p</i> value		0.01		0.10	0.07	0.03
Analysis restricted to children aged 4 or younger						
Median MF <sup>1</sup>						
Cases	285	5	265	20	3	2
Controls	629	6	594	35	5	1
Adjusted OR (95% CI) <sup>4</sup>	1.00	2.10 (0.59–7.40)	1.00	1.30 (0.72–2.35)	1.21 (0.28–5.26)	12.7 (0.92–174)
<i>p</i> value		0.25		0.38	0.80	0.06
Night-time value <sup>3</sup>						
Cases	283	7	262	21	4	3
Controls	631	4	601	30	3	1
Adjusted OR (95% CI) <sup>4</sup>	1.00	4.48 (1.20–16.7)	1.00	1.74 (0.95–3.19)	2.75 (0.60–12.7)	14.9 (1.20–185)
<i>p</i> value		0.03		0.07	0.19	0.04
Analysis restricted to cases with ALL						
Median MF <sup>1</sup>						
Cases	443	9	417	26	6	3
Controls	1,283	18	1,210	73	15	3
Adjusted OR (95% CI) <sup>4</sup>	1.00	1.81 (0.76–4.34)	1.00	1.04 (0.64–1.70)	1.36 (0.50–3.69)	6.24 (0.85–45.8)
<i>p</i> value		0.18		0.87	0.55	0.07
Night-time value <sup>3</sup>						
Cases	441	11	411	30	6	5
Controls	1,289	12	1,219	70	8	4
Adjusted OR (95% CI) <sup>4</sup>	1.00	3.36 (1.35–8.37)	1.00	1.48 (0.92–2.39)	2.49 (0.80–7.73)	6.19 (1.29–29.7)
<i>p</i> value		0.01		0.11	0.11	0.02
Primary analysis excluding children with Down syndrome						
Median MF <sup>1</sup>						
Cases	497	7	466	31	4	3
Controls	1,282	18	1,209	73	15	3
Adjusted OR (95% CI) <sup>4</sup>	1.00	1.25 (0.49–3.19)	1.00	1.09 (0.68–1.73)	0.80 (0.26–2.51)	5.99 (0.81–44.2)
<i>p</i> value		0.65		0.72	0.70	0.08
Night-time value <sup>3</sup>						
Cases	494	10	462	32	5	5
Controls	1,288	12	1,218	70	8	4
Adjusted OR (95% CI) <sup>4</sup>	1.00	2.75 (1.09–6.96)	1.00	1.36 (0.86–2.15)	1.85 (0.57–6.07)	5.63 (1.17–27.0)
<i>p</i> value		0.03		0.19	0.31	0.03

<sup>1</sup>Derived from the 24 hr measurement in the child's bedroom in the residence where the child lived longest before the reference date. MF, magnetic field. <sup>2</sup>OR and respective 95% CI from logistic regression analyses stratified for year of birth, age groups of 1 year and gender and additionally adjusted for degree of urbanisation (urban, mixed, rural), study component (NI component only, NW component only or both) and socio-economic status (high, other) and for residential mobility (1 residence, 2 to 3 residences, more than 3 residences), season of measurement (summer, autumn/spring, winter) and type of residence (single family/farms, duplexes/row-houses, small apartment buildings, large apartment buildings). <sup>3</sup>Median magnetic field between 10 PM and 6 AM derived from 24 hr measurement in the child's bedroom. <sup>4</sup>OR and respective 95% CI from logistic regression analyses stratified for year of birth, age groups of 1 year and gender and additionally adjusted for degree of urbanisation (urban, mixed, rural) and socio-economic status (high, other).

seemed reasonable based on our previous studies in Lower Saxony and Berlin and further measurement activities by the *Forschungsverbund*.<sup>21</sup> However, the observed prevalence among the control group was only 1.4% (95% CI 0.7–2.0%),<sup>14</sup> higher than in rural

Lower Saxony (0.9%) but considerably lower than in Berlin (5.8%).<sup>8</sup> It was more than 5 times lower than in the North American studies<sup>15–17</sup> and slightly lower than in the UK study,<sup>19</sup> for which the prevalence was 2%. From a statistical point of view, the

TABLE V - POOLED OR FOR CHILDHOOD ACUTE LEUKAEMIA BY EXPOSURE TO RESIDENTIAL MAGNETIC FIELDS (MF)<sup>1</sup>

	<0.2 $\mu$ T	$\geq$ 0.2 $\mu$ T	<0.1 $\mu$ T	0.1 to <0.2 $\mu$ T	0.2 to <0.4 $\mu$ T	$\geq$ 0.4 $\mu$ T
Median MF <sup>2</sup>						
Cases	672	18	629	43	11	7
Controls	1,689	26	1,595	94	21	5
Adjusted OR (95% CI) <sup>3</sup>	1.00	1.58 (0.83–3.03)	1.00	1.08 (0.73–1.61)	1.19 (0.55–2.57)	3.53 (1.01–12.3)
<i>p</i> value		0.16		0.69	0.67	0.05
Arithmetic mean MF <sup>2</sup>						
Cases	667	23	606	61	17	6
Controls	1,678	37	1,560	118	32	5
Adjusted OR (95% CI) <sup>3</sup>	1.00	1.51 (0.86–2.65)	1.00	1.28 (0.90–1.80)	1.33 (0.71–2.50)	3.02 (0.82–11.2)
<i>p</i> value		0.15		0.16	0.37	0.10
Night-time value <sup>4</sup>						
Cases	669	21	625	44	14	7
Controls	1,698	17	1,607	91	12	5
Adjusted OR (95% CI) <sup>2</sup>	1.00	2.80 (1.42–5.52)	1.00	1.33 (0.90–1.97)	2.40 (1.07–5.37)	4.28 (1.25–14.7)
<i>p</i> value		<0.01		0.15	0.03	0.02

<sup>1</sup>Pooled analysis of current study and our 2 previous German studies.<sup>7,8</sup> <sup>2</sup>Derived from 24 hr measurement in the child's bedroom in the residence where the child lived longest before the reference date. <sup>3</sup>OR and respective 95% CI from logistic regression analyses stratified for year of birth, age groups of 1 year and gender and additionally adjusted for degree of urbanisation (urban, mixed, rural), socio-economic status (high, other), part of Germany (West and West Berlin, East Berlin) and study setting (Lower Saxony, Berlin, NI component only, NW component only or both). <sup>4</sup>Median magnetic field between 10 PM and 6 AM derived from 24 hr measurement in the child's bedroom.

unexpectedly low prevalence decreased the statistical power of our study and, hence, limited the precision of our risk estimates. From a public health perspective, however, it means that even if the association between childhood leukaemia and residential magnetic fields stands, only few German children would be affected.

Besides the low number of residences with average magnetic fields exceeding 0.2  $\mu$ T, our study has 2 major drawbacks. One is the relatively low response rate. About 65% of all families approved the measurement. There were no differences between cases and controls; however, the population of our EMF study was already a subset of a case-control study that had response rates of 84% among cases eligible for the EMF study and 67% among controls. Therefore, bias introduced by non-participation cannot be ruled out. A few studies have addressed the problem of selection bias in EMF investigations.<sup>4,22,23</sup> They demonstrated that elevated risks may, to some extent, be due to differences between the case and control groups regarding socio-economic status, but this did not explain the observed association entirely. In our EMF study, socio-economic status was only moderately associated with the occurrence of magnetic fields above 0.2  $\mu$ T. In Germany, this may be due to the fact that, although stronger magnetic fields occur more often in apartment buildings, only in urban areas was the type of residence associated with family income. We found a somewhat stronger association between 5-level monthly family net income and magnetic fields, with higher magnetic fields for the lowest income category.<sup>14</sup> However, of 4 families among this income category for which we obtained stronger magnetic fields, there were 1 case and 3 controls. Another noticeable finding was that after we combined the data of all German EMF studies and calculated risk estimates separately for high as well as other socio-economic status, the respective ORs were 1.53 (95% CI 0.39–6.00, high) and 1.67 (95% CI 0.78–3.56, other) for the median of the 24 hr measurement and 3.89 (95% CI 0.88–17.2, high) and 3.00 (95% CI 1.34–6.70, other) for the night-time value. Hence, the risk estimates were similar for both strata of socio-economic status; however, they were less precise for subjects with higher socio-economic status. In conclusion, selection bias remains a concern; however, we found no evidence that it explains our findings.

Another limitation of our study is the long time lag between the aetiologically relevant time period and the measurement period. Due to economical reasons, we decided to await the results of the 2 smaller studies<sup>8</sup> before we expanded the EMF research. While the reference dates of the current study were between 1990 and 1994, it was late 1997 when we started the measurements. Moreover, we assessed exposure in the residence where the child lived longest before the reference date; because some families had

moved before the reference date, for some subjects the time lag was >10 years. For 50.3% of subjects, the time lag was <5 years (cases 50.6%, controls 50.2%). We tried to compensate this weakness, at least partially, by carrying out very comprehensive measurements. To avoid falsely classifying subjects as positive, we identified the source that produced the stronger magnetic field and considered the stability of the measured values over time during an expert meeting. For some exposed subjects, particularly those exposed to stronger magnetic fields produced by indoor sources, measurements were repeated in December 1999 (and all stronger magnetic fields were confirmed). Furthermore, we aimed at reducing the number of false-negative subjects by excluding renovated and improved buildings and a few residences where proximate power lines had been removed. Exposure misclassification cannot be excluded, but it is likely to be independent of case or control status (non-differential misclassification) and, therefore, to dilute an effect instead of creating a spurious one.<sup>24</sup> However, due to the small number of exposed subjects in our study, this cannot be taken for granted: if we assume that only a handful of subjects were misclassified, then, even if the misclassification probability is equal for cases and controls, it could have happened by chance that more cases than controls were falsely classified as exposed, which leads to a spurious association; but this is rather speculative. Our overall risk estimates were confirmed by ORs calculated for the subset of subjects who lived in a single residence. In conclusion, we acknowledge the limitation of the long time lag between the aetiologically relevant time period and the measurement period; however, it is unclear if and how this affected our findings.

Down syndrome is associated with an increased risk of developing childhood leukaemia and is considered as being causal.<sup>25</sup> The relative risk is high, around 30-fold,<sup>26</sup> and was even higher in our own study,<sup>27</sup> which may be an indication not to include this high-risk group in EMF studies. Children with Down syndrome were excluded from the EMF study of the National Cancer Institute<sup>16</sup> but not from other studies.<sup>4,15,18,19</sup> Two of 9 exposed cases in our study were children with Down syndrome. Both had the common B-cell precursor form of ALL (cALL); they were 1 and 6 years old on the date of diagnosis. As shown in Table IV, exclusion of children with Down syndrome led to substantially lower ORs for median magnetic fields between 0.1 and 0.4  $\mu$ T. The OR for median magnetic fields above 0.4  $\mu$ T, however, was only marginally altered, and we still observed a conspicuous association between childhood leukaemia and magnetic field exposure during the night.

Despite the high risk, not all children with Down syndrome develop a haematological malignancy, and the causal pathway from the genetic disorder to the first clinically evident symptoms

of acute leukaemia is not entirely understood.<sup>28</sup> Hence, exposure to magnetic fields as a potential post-natal promotional effect cannot be excluded. In conclusion, the observation that 2 of 9 exposed leukaemia cases were children with Down syndrome was unexpected; however, we think that arguments to exclude them from the analyses are not convincing.

#### Interpretation of results

Our study provides evidence for a weak association between childhood leukaemia and exposure to residential power-frequency magnetic fields. An explanation for this association remains unclear. The role of chance, bias and confounding has been stressed again and again,<sup>3,4</sup> and in our study an impact of these factors cannot be ruled out and no one of them alone can explain our findings. Our finding for average exposure to residential magnetic fields goes along with earlier studies on this topic that conducted long-term magnetic field measurements and lies within the confidence boundaries of the 3 large studies in the United States,<sup>16</sup> Canada<sup>17</sup> and the United Kingdom (although for the latter no effect was observed).<sup>19</sup> As in our previous studies,<sup>8</sup> the association was strongest for younger children, a finding that was also seen in a Canadian study.<sup>29</sup> Our risk estimates also correspond very well with those of a pooled analysis by Ahlbom *et al.*,<sup>20</sup> who reported ORs of 1.08, 1.11 and 2.00 for exposure categories 0.1 to <0.2, 0.2 to <0.4 and  $\geq 0.4$   $\mu\text{T}$ , respectively. The respective combined ORs from pooled analysis of all 3 German studies (Table V) are 1.08, 1.19 and 3.53.

Our attention was particularly drawn to our finding that the association between childhood leukaemia and magnetic field exposure at night was consistently stronger than the association between childhood leukaemia and average magnetic field exposure. Four possible explanations came to mind; it was a chance finding, it was due to some kind of bias, it resulted from the use of an exposure measure that reflected the child's individual exposure to magnetic fields more appropriately or it was aetiologically relevant.

We explored leukaemia risk and exposure to magnetic fields at night in 2 earlier studies,<sup>7,8</sup> and a major aim of this third study was to test this rather new hypothesis. Although our study confirmed our previous findings, even in our pooled analysis only 38 subjects were exposed to night-time magnetic fields above 0.2  $\mu\text{T}$ . Thus, the CIs of our risk estimates are relatively wide. Nevertheless, our study consists of 4 parts, which were carried out in different, partially overlapping German regions and for different, partially overlapping diagnostic periods but showed consistently that the strongest associations were observed for exposure to magnetic fields at night. Thus, it appears that chance is an unlikely explanation; but admittedly, this is only one study with few exposed subjects. The investigators of the U.S. study<sup>16</sup> considered night-time exposure to be an alternative exposure measure.<sup>30</sup> For the median magnetic field during the night, they reported an OR of 1.50 (95% CI 0.94–2.74, 90–100th percentile compared to the 0–49th percentile). The respective figure for the median over 24 hr was 1.28 (95% CI 0.81–2.05). With that, the association between leukaemia and magnetic fields became stronger after restricting the relevant exposure to the night-time period; however, the association from the U.S. study was weaker than the association from the combined German studies.

As described above, particularly non-participation might have biased the results. This is an overall concern but an unlikely explanation for our consistent finding that the link between leukaemia and magnetic fields was stronger when only exposure at night was taken into account. In all, 16 cases and 15 controls were exposed to magnetic fields above 0.2  $\mu\text{T}$  on average as well as during the night; only 2 cases but 11 controls were exposed on average but not at night; while 5 cases and 2 controls were exposed only at night. This pattern was consistent for all study parts.

The limitations of different methods for exposure assessment in this field have been thoroughly discussed.<sup>4</sup> A weakness of the

measurements is that they were conducted stationary within the residence at 1 point in time, which is after the date of diagnosis, but were used to estimate the subject's individual past exposure. Exposure at night is probably the most appropriate measurement because misclassification is reduced, exposure being recorded when the child is there with the instruments. During night-time, stationary measurements and personal dosimetry do not differ; in both cases, the instrument is located near the child's bed.

Finally, our finding of an excess leukaemia risk with magnetic field exposure during the night might be of aetiological relevance. It has been hypothesized that exposure to higher magnetic fields suppresses the nocturnal production and release of the hormone melatonin, which is assumed to have oncostatic capabilities;<sup>31,32</sup> however, the melatonin hypothesis has been proposed for breast cancer and hormone-dependent cancers rather than leukaemia.<sup>33,34</sup> Nevertheless, young children have higher melatonin levels than adults;<sup>35</sup> therefore, effects caused by reduced melatonin concentrations might be more marked. So far, there is weak supportive evidence for the melatonin hypothesis from human laboratory studies.<sup>4</sup>

It might also be of aetiological relevance that 2 of our exposed children with leukaemia had a known pre-natal genetic abnormality. Wiemels *et al.*<sup>36</sup> reported that childhood ALL is frequently initiated by a chromosomal translocation event *in utero* but a secondary post-natal event is required for full leukaemogenesis. Environmental exposures might provoke or promote evolution of the "pre-leukaemic" clone.<sup>37</sup> Exposure to magnetic fields might belong to these post-natal events.

#### Conclusions

The main outcomes of our EMF study are as follows: (i) in Germany, average magnetic fields above 0.2  $\mu\text{T}$  are rare, so even if the association between magnetic field exposure and childhood leukaemia should stand, the effect on a population level would be relatively small; (ii) fewer than one-third of all stronger magnetic fields were caused by high-voltage powerlines, meaning that only a minor fraction of potentially magnetic field-related leukaemia cases would be attributable to powerlines; (iii) we found no convincing confounding factor that could explain the observed association; and (iv) although our study shows an association between childhood leukaemia and exposure to residential magnetic fields, it is neither a proof nor a breakthrough.

The evidence for an association between childhood leukaemia and magnetic fields in our study comes from a measure of the child's exposure during the night. With the current study, we confirm the findings of our previous studies. Despite the large size of our study, risk estimates were imprecise since only few subjects were exposed to magnetic fields exceeding 0.2  $\mu\text{T}$  at night. Since other studies have measured magnetic fields over 24 hr, there are further opportunities to explore the association between childhood leukaemia and magnetic field exposure at night.

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## REFERENCES

1. Angelillo IF, Villari P. Residential exposure to electromagnetic fields and childhood leukaemia: a meta-analysis. *Bull World Health Organ* 1999;77:906–15.
2. Greenland S, Sheppard AR, Kaune WT, Poole C, Kelsh MA. A pooled analysis of magnetic fields, wire codes and childhood leukemia. *Epidemiology* 2000;11:624–34.
3. Meinert R, Michaelis J. Meta-analyses of studies on the association between electromagnetic fields and childhood cancer. *Radiat Environ Biophys* 1996;35:11–8.
4. Portier CJ, Wolfe MS (eds). National Institute of Environmental Health Sciences Working Group Report. Assessment of health effects from exposure to power-line frequency electric and magnetic fields. NIH Publ 98-3981. Research Triangle Park, NC: NIEHS, 1998.
5. Repacholi MH, Greenebaum B. Interaction of static and extremely low frequency electric and magnetic fields with living systems: health effects and research needs. *Bioelectromagnetics* 1999;20:133–60.
6. Kheifets LI, Afifi AA, Buffler PA, Zhang ZW, Matkin CC. Occupational electric and magnetic field exposure and leukemia. *J Occup Environ Health* 1997;39:1074–91.
7. Michaelis J, Schüz J, Meinert R, Menger M, Grigat JP, Kaatsch P, et al. Childhood leukemia and electromagnetic fields: results of a population-based case control study in Germany. *Cancer Causes Control* 1997;8:167–74.
8. Michaelis J, Schüz J, Meinert R, Zemann E, Grigat JP, Kaatsch P, et al. Combined risk estimates for two German population-based case-control studies on residential magnetic fields and childhood acute leukemia. *Epidemiology* 1998;9:92–4.
9. Kaatsch P, Kaletsch U, Meinert R, Miesner A, Hoisl M, Schüz J, et al. German case control study on childhood leukemia—basic considerations, methodology and summary of the results. *Klin Padiatr* 1998;210:185–91.
10. Kaatsch P, Kaletsch U, Meinert R, Michaelis J. An extended study on childhood malignancies in the vicinity of German nuclear power plants. *Cancer Causes Control* 1998;9:529–33.
11. Kaatsch P, Haaf G, Michaelis J. Childhood malignancies in Germany—methods and results of a nationwide registry. *Eur J Cancer* 1995;31A:993–9.
12. Brookmeyer R, Liang KY, Linet M. Matched case-control designs and overmatched analyses. *Am J Epidemiol* 1986;124:693–701.
13. Neuhäuser M, Becher H. Improved odds ratio estimation by post hoc stratification of case-control data. *Stat Med* 1997;16:993–1004.
14. Schüz J, Griget JP, Störmer B, Rippin G, Brinkmann K, Michaelis J. Extremely-low-frequency magnetic fields in residences in Germany: distribution of measurements, comparison of two methods for assessing exposure, and predictors for the occurrence of magnetic fields above background level. *Radiat Environ Biophys* 2000;39:233–40.
15. London SJ, Thomas DC, Bowman JD, Sobel E, Cheng TC, Peters JM, et al. Exposure to residential electric and magnetic fields and risk of childhood leukemia. *Am J Epidemiol* 1991;134:923–37.
16. Linet MS, Hatch EE, Kleinerman RA, Robison LL, Kaune WT, Friedman DR, et al. Residential exposure to magnetic fields and acute lymphoblastic leukemia in children. *N Engl J Med* 1997;337:1–7.
17. McBride ML, Gallagher RP, Theriault G, Armstrong BG, Tamaro S, Spinelli JJ, et al. Power-frequency electric and magnetic fields and risk of childhood leukemia in Canada. *Am J Epidemiol* 1999;149:831–42.
18. Dockerty JD, Elwood JM, Skegg DC, Herbison GP. Electromagnetic field exposures and childhood cancers in New Zealand. *Cancer Causes Control* 1998;9:299–300.
19. UK Childhood Cancer Study Investigators. Exposure to power-frequency magnetic fields and the risk of childhood cancer. *Lancet* 1999;354:1925–31.
20. Ahlbom A, Day N, Feychting M, Roman E, Skinner J, Dockerty J, et al. A pooled analysis of magnetic fields and childhood leukemia. *Br J Cancer* 2000;83:692–8.
21. Stamm A, Zemann E. Low-frequency magnetic fields: exposure assessment for epidemiological studies. In: Brinkmann K, Kärner H, Schaefer H. *Electromagnetic compatibility of biological systems*, vol. 4. Berlin: vde-Verlag (1995).
22. Gurney JG, Davis S, Schwartz SM, Mueller BA, Kaune WT, Stevens RG, et al. Childhood cancer occurrence in relation to power line configurations: a study of potential selection bias in case-control studies. *Epidemiology* 1995;6:31–5.
23. Hatch EE, Kleinerman RA, Linet MS, Tarone RE, Kaune WT, Auvinen A, et al. Do confounding or selection factors of residential wiring codes and magnetic fields distort findings of EMF studies? *Epidemiology* 2000;11:189–98.
24. Breslow NE, Day NE. *Statistical methods in cancer research. The analysis of case-control studies*. IARC Sci Publ 32. Lyon: IARC, 1980.
25. Pui C. Childhood leukemias. *N Engl J Med* 1995;332:1618–30.
26. Little J. *Epidemiology of childhood cancer*. IARC Sci Publ 149. Lyon: IARC, 1999.
27. Schüz J, Kaatsch P, Kaletsch U, Meinert R, Michaelis J. Association of childhood cancer with factors related to pregnancy and birth. *Int J Epidemiol* 1999;28:631–9.
28. Shen JJ, Williams BJ, Zipursky A, Doyle J, Sherman SL, Jacobs PA, et al. Cytogenetic and molecular studies of Down syndrome individuals with leukemia. *Am J Hum Genet* 1995;56:915–25.
29. Green LM, Miller AB, Agnew DA, Greenberg ML, Li J, Villeneuve PJ, et al. Childhood leukemia and personal monitoring of residential exposures to electric and magnetic fields in Ontario, Canada. *Cancer Causes Control* 1999;10:233–43.
30. Auvinen A, Linet MS, Hatch EE, Kleinerman RA, Robison LL, Kaune WT, et al. Extremely low-frequency magnetic fields and childhood acute lymphoblastic leukemia: an exploratory analysis of alternative exposure metrics. *Am J Epidemiol* 2000;152:20–31.
31. Reiter RJ. Antioxidant actions of melatonin. *Adv Pharmacol* 1997;38:103–17.
32. Reiter RJ. Reported biological consequences related to the suppression of melatonin by electric and magnetic field exposure. *Integr Physiol Behav Sci* 1995;30:314–30.
33. Stevens RG. Electric power use and breast cancer: a hypothesis. *Am J Epidemiol* 1987;125:556–61.
34. Baldwin WS, Barrett JC. Melatonin: receptor-mediated events that may affect breast and other steroid hormone-dependent cancers. *Mol Carcinog* 1998;21:149–55.
35. Brzezinski A. Melatonin in humans. *N Engl J Med* 1997;336:186–95.
36. Wiemels JL, Cazzaniga G, Daniotti M, Eden OB, Addison GM, Masera G, et al. Prenatal origin of acute lymphoblastic leukaemia in children. *Lancet* 1999;354:1499–503.
37. Greaves M. Molecular genetics, natural history and the demise of childhood leukaemia. *Eur J Cancer* 1999;35:173–85.