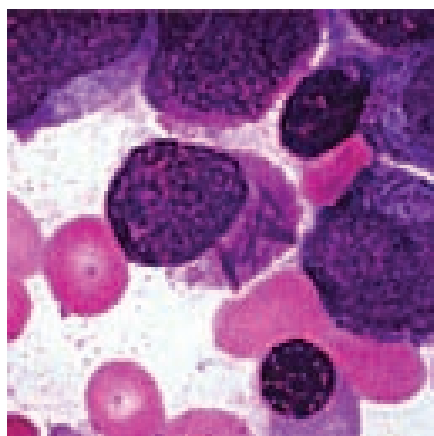


Joachim Schüz

Childhood leukemia and low-frequency

Results of a comprehensive German epidemiological study



Introduction

Weak magnetic fields in the low-frequency range (EMF) (particularly in the area of power supply) have been associated for some 20 years with cancer. The starting point was a case-control study conducted in Denver and published in 1979 (Wertheimer and Leeper 1979) claiming that children living near high-voltage transmission lines showed a three times increased risk to die from leukemia. Since then, worldwide numerous studies on this controversial topic were carried through, the early ones being highly heterogeneous in design, exposure registration, evaluation strategy as well as results. However, the scientific controversy mainly derives from the fact that the magnetic field strengths (mostly magnetic fields above 0.2 μT) judged as a 'strain' by epidemiology many times lay below the limit value of 100 μT . Consequently, there is no known mechanism being capable to explain carcinogenicity of these very weak magnetic fields.

During the nineties, this topic was also dealt with by research groups confronting the issue by means of large-scale exposure measurements. Measurements of the magnetic field over longer time periods in big study populations were conducted in the United States, Canada, Great Britain and Germany (Linet et al. 1997; McBride et al. 1999; UKCCSI 1999; Michaelis et al. 1998). In the four Scandinavian countries

the magnetic field strain was estimated according to historical capacity utilisation data of overhead cables. Two independent meta-analyses on EMF and childhood leukemia based upon original data of the conducted studies in 2000 drew consistent conclusions. Ahlbom et al. (2000) pooled the methodically more convincing studies observing a two-fold increased leukemia risk at 0.4 μT and higher, but not below. Greenland et al. (2000) pooled all available studies and reported on a statistically significantly elevated odds ratio of 1.7 at magnetic field strengths above 0.3 μT . Based upon this report, in 2001 an international committee of experts founded by the International Agency for Research on Cancer (IARC) classified low-frequency magnetic fields as 'possibly carcinogenic to humans' (IARC Monography No80, in press). An important role in this evaluation played among others the results of a comprehensive extension of the EMF study in Germany published in early 2001 (Schüz et al. 2001 a). These results will be summarised in the following.

Leukemia in children

Leukemia is the most frequent form of childhood cancer with a quota of about 35% of all malignancies. In Germany, every year out of 13.2 million children aged 15 years or less about 620 fall ill with leukemia. This is equivalent to an incidence of 4.8 childhood leukemia cases in 100,000



Leukemia magnetic fields

children per year. The chances for curing today are at about 80% in total. The prognosis for children suffering from acute lymphoblastic leukemia (ALL) - about 85% of childhood leukemia cases - is considerably better than for children with acute myeloid leukemia (AML) for whom the five-year survival rate even lies below 60%. The remaining 15% of childhood leukemias are more or less cases of AML. Only very few children suffer from chronic leukemia or a lymphoblastic-myeloid combination. Cancer registries collecting data on childhood cancer for several decades now, for the 20th century report no significant increase of leukemia cases. In Germany, in the years 1995 to 1999 a small increase was observed. However, whether it is an actual increase of incidence rates or whether the small increase of recent years must be seen in the context of random temporal variations will become clear in the next few years. In Germany, cases of childhood cancer are systematically covered since 1980 (since 1991 as well those of the new federal states) by the German Childhood Cancer Registry at the Institute of Medical Statistics and Documentation of the University Mainz. With a reference population of more than 13 million children the German Childhood Cancer Registry is the worldwide biggest childhood cancer registry.

For most childhood leukemia cases no predisposition by mutated genes is known.

The most important predisposition is a Down syndrome. Studies on family clusters give no evidence for those; the only exception is a high concordance rate of leukemia in identical twins during the first year after birth. As a verified environmental risk factor of leukemia are seen only high doses of ionising radiation. There is a huge number of hypotheses on leukemia genesis in children, particularly associated with infectious diseases; but ultimately, none of these approaches could (until now) be confirmed. In summary, we must admit that the cause of more than 90% of all childhood leukemia cases is unclear (Greaves 1999).

Methodical approach of the German EMF study

The EMF study was integrated into a case-control study conducted between 1992 and 1997 in Western Germany by the German Childhood Cancer Registry. Cases were all children who fell ill with leukemia between January 1990 and September 1994 aged 15 years or less. The control group was randomly selected supported by local resident registration offices. The children were of the same age and gender and were living in the same community as the matching case. Whereas the first German study presented measurements for 173 cases and 414 controls, the extended study added to that further 514 cases and 1301 controls. Cooperation part-

ner of the Childhood Cancer Registry for the EMF study was the Research Association Electromagnetic Compatibility of Biological Systems at the Technical University Braunschweig conducting measurements for both studies.

For determination of the magnetic field strength at the residences three measurement methods were applied. For the 24-hs measurement in the child's bedroom a measurement device of the type Physical Systems FW2a was placed under the mattress of the child's bed. The magnetic field at 50 Hz and at 16 2/3 Hz was recorded three-dimensionally in a one-second interval for calculating the resulting magnetic field intensity. The 24-hs measurement in the reference room (24-hs control measurement) was made by means of a measurement device of the EMDEX II type. For positioning the second device a room was looked for where the child spent the most time apart from the bedroom. The control measurement was made for quality purposes, for it would give evidence for possible measurement artefacts and device interferences. The third measurement was aimed to determine site field distribution applying a measurement wheel connected to a EMDEX II device. The magnetic field was measured while the field technician moved very slowly through the rooms (short-time measurement). The objective of this measurement was to find proof of field sources. Whereas at the 24-hs meas-

urement more than average magnetic field strength was recorded, the spatial distribution allowed to draw conclusions on the fact whether the higher magnetic field strength was caused by an external (f.e. overhead cables) or an internal (f.e. fuses) field source and/or a field source in the low-frequency or high-frequency range. By means of this method, not only new knowledge on field sources prevailing in Germany was gained, it also served to confirm the quality standard. To a certain extent it was possible to judge whether the magnetic field recorded at the time of measurement was representative for the aetiologically relevant time period prior to diagnosis. Measurements were conducted between December 1997 and December 1999.

Results I: Measurement phase

Evaluations concerning the frequency of stronger magnetic fields ($>0.2 \mu\text{T}$) and on conditions under which stronger magnetic fields were more probable were limited to the group of control family house-

holds of the nationwide study, since these represented the general population within the epidemiological study. Field source analysis referred to all successfully conducted measurements of the EMF II study (Schüz et al. 2000).

The prevalence of median magnetic fields $>0.2 \mu\text{T}$ of the EMF II study lay at 1.4% (95% confidence interval (CI): 0.7-2.0%). Thus, it was above the prevalence of the control group of the Lower Saxony study (0.9%), but lower than the prevalence of median magnetic fields of the Berlin control group (West: 3.5%; East: 10.3%). Studies in the USA and Canada showed between five- and tenfold higher prevalences. Reasons for this are the differences between energy distribution system, energy consumption per head and grounding methods. A British study demonstrated a prevalence of 2%. More than three-fourths of all German households had a median magnetic field below $0.05 \mu\text{T}$. The highest measured median was about $0.7 \mu\text{T}$. Median magnetic fields of $>0.4 \mu\text{T}$ were measured only at about every 500th residence (prevalence 0.2%). During the night the average magnetic field strain was smaller than at daytime; the prevalence of nocturnal magnetic fields $>0.2 \mu\text{T}$ lay at 0.9%.

Magnetic fields $>0.2 \mu\text{T}$ were more frequent in apartment buildings. Whereas the median magnetic field only in every 200th single family house lay at $>0.2 \mu\text{T}$ (0.5%), this was the case at every 17th large apartment building (>10 parties; 6.0%). As well magnetic fields $>0.2 \mu\text{T}$ were measured more frequently for families of the lowest income class; here, the age of the respective house could have been the crucial factor. On the whole, we could not determine good indicators for a prognosis on a higher magnetic field strain at a given residence. Ultimately, only a magnetic field measurement can provide evidence for that.



High-voltage transmission lines were responsible for less than a third of all magnetic fields $>0.2 \mu\text{T}$. At none of the residences being at a distance of more than 50 m from a high-voltage transmission line a higher magnetic field emitted by this line could be proved. Out of the 25 residences where a high-voltage transmission line was led past in a distance of 5 m or nearer, only in 8 a magnetic field of $>0.2 \mu\text{T}$ was measured. The existence of a high-voltage transmission line in the vicinity of the house alone was no indicator of a higher magnetic field exposure. One indicator, however, is the capacity utilisation of the line. In none of the residences a magnetic field of $>0.2 \mu\text{T}$ was caused by a medium-voltage line (10–60 kV), by a transformer or by a transformer station. Low-voltage overhead cables alone never were the primary magnetic field source, either; however, in some of the residences the connection of the cable with the house supply led to stronger magnetic fields. In individual cases, also a grounding cable (380 V) was the magnetic field source, though cable drilling to the most part neutralises the developing magnetic field. Internal field sources, i.e. riser wires and out-of-date electrical installations also could produce average magnetic fields $>0.2 \mu\text{T}$ caused by unbalances at the three conductors.

Short-time measurements under German conditions only partially allow to draw conclusions on an average day strain. In countries like the United States where the main part of stronger magnetic fields is caused by overhead cables with a relatively stable magnetic field strength over the day, a good correlation between short-term and 24-hs measurements were shown. Sources in the low-voltage range show much stronger temporal variations meaning that a short-term measurement possi-

bly will record an atypical day segment. However, just magnetic fields from sources in the low-voltage range were the dominating cause of stronger magnetic fields in Germany.

Results: Risk analyses

Table 1 shows the results for the a priori defined basic hypotheses. For the median of the 24-hs measurement in the child's bedroom based upon 9 cases (1.8%) and 18 controls (1.4%) $>0.2 \mu\text{T}$ there is an adjusted odds ratio of 1.55 being statistically insignificant. At the four-scale exposure set-up, the odds ratio for magnetic fields between 0.1 and 0.4 μT is scarcely increased. Only in 3 cases (0.6%) and 3 controls (0.2%) a median magnetic field (0.4 μT) was measured. This results in a nominally high odds ratio of 5.81; however, the extremely wide confidence interval encloses the 1 reflecting the statistical uncertainty of the risk estimate. Looking only at nighttime magnetic fields, it stands out that compared to the 24-h median exactly one-third more cases, but also one-third less controls were exposed to magnetic fields $>0.2 \mu\text{T}$. Based upon 12 exposed cases (2.3%) and 12 exposed controls (0.9%) there is an odds ratio of 3.21. This result is statistically significant (p value: <0.01); the 95% confidence interval ranges from 1.33 to 7.80. At the four-scale exposure categorisation of the nighttime value there are odds ratios of 1.42 for the category 0.1– $<0.2 \mu\text{T}$ (p value: 0.13), of 2.53 for the category 0.2– $<0.4 \mu\text{T}$ (p value: 0.09) and 5.53 for the category $>0.4 \mu\text{T}$ (p value: 0.03). The test for trend concerning the nighttime value is statistically significant (p value test for trend: 0.01). For children younger than 5 years the observed association was stronger than for older children.

Table 2 shows the results after combining the two German studies. With meas-

urements over 24 hs for 2405 participants, among them 690 families with a child suffering from leukemia and 1715 control families, the pooled German study is the worldwide biggest study on the question whether childhood leukemia diseases are associated with residential magnetic fields. For the median of the 24-hs measurement at $>0.2 \mu\text{T}$ based upon 18 cases (2.6%) and 26 controls (1.5%) there is an adjusted odds ratio of 1.58. At a multi-scale exposure categorisation there are practically no increased odds ratios for the categories 0.1– $<0.2 \mu\text{T}$ and 0.2– $<0.4 \mu\text{T}$, but for the highest exposure category $>0.4 \mu\text{T}$ based on 7 cases (1.0%) and 5 controls (0.3%) there is an odds ratio of 3.53. This risk estimate is statistically significantly increased (p value: 0.05). At the nighttime value $>0.2 \mu\text{T}$ a strong association is observed: the odds ratio based upon 21 cases (3.0%) and 17 controls (1.0%) lies at 2.80 and is statistically significantly increased (p value <0.01). A trend toward increased risk at increased exposure is shown by the multi-scale exposure categorisation during the night (p value for trend <0.01).

Until now, none of the epidemiological studies considered environmental exposure to magnetic fields of 16 2/3 Hz (railroad traffic). At one half of the residences being representative for general population a median magnetic field of only 0.002 μT or less was measured almost reaching the limits of measurement devices. Only at 7 residences of the control group a median of $>0.2 \mu\text{T}$ was measured; this corresponded to a prevalence of stronger magnetic fields of 0.6%. A summary of magnetic field strengths at 16 2/3 Hz and at 50 Hz for magnetic fields $>0.2 \mu\text{T}$ showed a total prevalence of 2.2% (95% CI 1.4%–3.0%). Based upon the magnetic fields alone at 16 2/3 Hz there were odds ratios of 1.93 (95% CI 0.42–9.01) for the median of the

Table 1: Evaluation of the second German EMF study

	<0,2µT	≥0,2µT	<0,1µT	0,1-<0,2µT	0,2-<0,4µT	(0,4µT
Median 24-hs measurement child's bedroom						
cases	505	9	472	33	6	3
controls	1.283	18	1.210	73	15	3
CI (95%-KI)*	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)
nighttime value (median 22-6 hs)						
cases	502	12	468	34	7	5
controls	1.289	12	1.219	70	8	4
CI (95%-KI)*	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)

* adjusted odds ratios for age, sex, year of birth, socio-economic status, region type and study

Table 2: Evaluation of the combined German studies

	<0,2µT	≥0,2µT	<0,1µT	0,1-<0,2µT	0,2-<0,4µT	(0,4µT
Median 24-hs measurement child's bedroom						
cases	672	18	629	43	11	7
controls	1.689	26	1.595	94	21	5
CI (95%-KI)*	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)
nighttime value (median 22-6 hs)						
cases	669	21	625	44	14	7
controls	1.698	17	1.607	91	12	5
CI (95%-KI)*	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)

* adjusted odds ratios for age, sex, year of birth, socio-economic status, region type and study (four-scale) and Eastern/Western Germany (Berlin)



24-hs measurement and of 1.71 (95% CI 0.23-12.5) for the nighttime value. There was no association shown for short-term increased magnetic fields as occur in the vicinity of railroad tracks at passing-by trains. At combining magnetic field strengths at 16 2/3 Hz and 50 Hz risk analyses showed only a slight impact of the 16 2/3-Hz magnetic fields on the total result. This is not surprising in view of the rare occurrence of higher 16 2/3-Hz magnetic fields. The odds ratios for 50-Hz magnetic fields scarcely change at simultaneously considering the 16 2/3-Hz magnetic fields (Schüz et al. 2001b).

Detailed confounder analyses showed no evidence for a significant impact of any of the examined factors. Of particular importance was the fact that all calculation models showed the statistically significant impact of the nighttime value. Even the residence type having stood out as a strong predictor of magnetic fields >0.2 µT had little influence on risk analyses. The reason for this was that though it was strongly associated with magnetic fields, there was no strong enough connection with the case-control status of the participating family. Also traffic density was to be considered as a possible interference. Should air pollution connected with traffic density (especially through benzol and diesel) increase the risk for children to develop leukemia, and should traffic density be particularly high in regions where also magnetic fields >0.2 µT more frequently occur, then air pollution caused by traffic could be the causal factor standing behind an association between childhood leukemia and magnetic fields. It is also possible that the coexistence of both factors increases the risk for leukemia. It is conceivable that in this combination benzol acts as a cancer initiating factor and magnetic field as a cancer promoting factor. For none of the two hypotheses our study or the mentioned meta-analyses of Ahlbom and Greenland (see above) found serious evidence.

Summary

Because of the observations concerning nocturnal magnetic field exposure and because of the good correspondence of our results with other studies on this issue our study can be seen as evidence for a statistical association between magnetic fields and childhood leukemias. A biologic explanation for this observation is not known. Strong points of our study are the big study population and the high-quality recording of exposure. A weak point of the study is the relatively low participation rate. Though measurements could be conducted for about two-thirds of all families that had been addressed, because of participation refusal in the initial study only for about half of the study population magnetic field exposure could be registered. Further weaknesses of the study are the relatively long time period between diagnosis and date of measurement as well as the small case numbers for exposures above 0.2 µT being of course a positive finding with respect to general population exposure.

However, even if the observed association is causal, only about 1% of all childhood leukemia cases in Germany would be the result of exposure to low-frequency magnetic fields. The reason for this is the low prevalence of higher residential magnetic fields. Thus, the cause for the majority of all childhood leukemia cases remains unclear.

Addition

A detailed final report on the EMF study can be downloaded for free at the homepage of the Institute of Medical Statistics and Documentation. The address is: <http://info.imsd.uni-mainz.de/presse2001.html>.

The study was funded by the German Federal Ministry for Environment, Nuclear Safety and Nature Preservation. Responsible for scientific consulting was the Federal Office for Radiation Protection.

The study was conducted as a coopera-

tion between the Research Association Electromagnetic Compatibility of Biological Systems (Prof. Dr. Ing. Dr. Ing. h.c. Karl Brinkmann, Dipl.Ing. Jan Peter Grigat) and the Institute of Medical Statistics and Documentation (Prof. Dr. med. Jörg Michaelis, Dr. Joachim Schüz). We wish to express our heartfelt thanks to the other co-workers of the study. In particular, we very much appreciate the help of the families who were willing to participate in this study.

Dr. Joachim Schüz, Institute of Medical Statistics and Documentation, University Mainz

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