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Evidence for Childhood Cancers (Leukemia)

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I. INTRODUCTION

The International Agency for Research on Cancer (IARC) concluded in 2001 that power-frequency magnetic fields are a possible human carcinogen (Group 2B). This classification was based on the evidence from epidemiological studies of childhood leukemia. The panel rated the evidence from all other types of cancer, from long-term animal experiments and mechanistic studies as inadequate. The IARC working group decided that the association between power frequency magnetic fields and childhood leukemia can be interpreted as only limited evidence because bias and confounding cannot be ruled out.

Since the seminal work of Wertheimer and Leeper (1979) many epidemiological studies of childhood cancer and residential exposure to power-frequency EMFs were published, not counting some studies about electrical appliances and cluster observations. Although these studies make up an impressive body of evidence, there is an ongoing discussion whether the observed relationships between exposure to power-frequency EMFs and childhood cancer (in particular leukemia) can be causally interpreted. Based on the comparatively few empirical studies virtually hundreds of commentaries, reviews and meta-analyses have been produced, more often than not increasing confusion instead of clarifying the issue. In 2000 two pooled analyses of childhood leukemia, the endpoint most often studied, have been published, one (Ahlbom et al., 2000) that was restricted to 9 studies that fulfilled a number of strict inclusion criteria (a defined population base for case ascertainment and control selection and using measurements or historical magnetic field calculations for exposure assessment), and another (Greenland et al., 2000) including also wire-code studies. Both pooled analyses got essentially the same result: a monotonously increasing risk with increasing power-frequency (50Hz/60Hz) magnetic field levels. These pooled analyses were the bases for the IARC working group decision.

Typically, if an agent is classified as a Group 2B carcinogen, precautionary measures are taken at workplaces and special care is recommended if it is present in consumer products (e.g. lead, styrene, benzofuran, welding fumes). Concerning power-frequency EMFs the WHO International EMF Program made the following exceptional statement: "In spite of the large number data base, some uncertainty remains as to whether magnetic field exposure or some other factor(s) might have accounted for the increased leukaemia incidence." (WHO Fact Sheet 263, 2001). This is the line of arguments that has been unswervingly followed by the electrical power industry since the early 1980's. An endless chain of factors allegedly

responsible for the 'spurious' positive association between power-frequency EMF exposure and cancer has been put forward, leading to nothing except waste of energy and money. The statement of WHO is scientifically flawed because there is no finite number of empirical tests to refute it. It is always possible that some factor not yet tested could be responsible, however low the probability that it remained obscure for such a long time. In the last years, due to the fact that no confounding factor has been found that explains the increased leukemia risk, a slight change of arguments can be discerned that consists of pointing out the very low proportion of children (less than 1%) exposed to power frequency fields associated with a significantly increased risk. In fact, both pooled analyses concluded that there is little indication of an increased risk below 3 to 4 mG magnetic flux density.

Since the evaluation of IARC several other epidemiological studies have been published that corroborate the earlier findings and strengthen the evidence of an association. It becomes increasingly less likely that confounding factors exist that operate all over the world and still remained undetected.

In the following chapters we will present the epidemiological evidence, discuss potential biases and demonstrate that from a worst-case scenario the evidence compiled so far is consistent with the assumption of a much greater proportion of leukemia cases attributable to power frequency field exposure than previously assumed. The key problem identified is the lack of a bio-physical model of interaction between very weak ELF EMFs and the organism, tissues, cells, and biomolecules.

II. EPIDEMIOLOGICAL STUDIES OF POWER-FREQUENCY EMF AND CHILDHOOD CANCER

Table 11-4 gives a synopsis of studies on childhood cancer and exposure to power-frequency EMF, Table 11-5 presents the main findings of these investigations. Most often assessment of exposure was by measurements with 16 studies measuring for at least 24 hours up to 7 days, and 9 studies with spot measurements. Eleven studies used distance from power lines as a proxy (some in combination with spot measurements) and 11 studies used wire codes (solely or in addition to other methods) classified according to the Wertheimer-Leeper or Kaune-Savitz methods or some modifications thereof accounting for specific power grid conditions. Several investigations covered more than one endpoint with hematopoietic cancers the most

frequently included malignancies (overall 37 studies), followed by nervous system tumors (13 studies) and other cancers (10 studies). All childhood cancer cases were assessed by 9 investigations.

The most restrictive criteria for combining the evidence for an association between ELF magnetic fields (MF) exposure and childhood leukemia were applied by Ahlbom et al., (2000) that included 9 investigations. Table 11-1 shows the results of these investigations for the exposure category ≥ 4 mG (against < 1 mG as reference category). The studies included 3,203 children with leukemia, 44 of which were exposed to average flux densities of 4 mG or above. Thus only 1.4% of children with leukemia and less than 1% of all children in the studies were exposed that high in accordance with measurement samples from the general population in Europe, Asia and America (Brix et al., 2001; Decat et al., 2005; Yang et al., 2004; Tomitsch et al. 2010; Zaffanella, 1993; Zaffanella & Kalton, 1998).

Meta-analyses of wire-code studies (Greenland et al., 2000; Greenland 2003; Wartenberg, 2001) revealed similar results for childhood leukemia with estimates of risks around 2 for very high current codes but with considerable heterogeneity across studies.

Table 11- 1: Results from nine studies included in Ahlbom et al. (2000) updated according to Schüz (2007) of residential MF exposure and risk of childhood leukemia

Country	Odds-Ratio[*] (95%-CI)	Observed Cases
Canada	1.55 (0.65−3.68)	13
USA	3.44 (1.24−9.54)	17
UK	1.00 (0.30−3.37)	4
Norway	0 cases / 10 controls	0
Germany	3.53 (1.01−12.3)	7
Sweden	3.74 (1.23−11.4)	5
Finland	6.21 (0.68−56.9)	1
Denmark	2 cases / 0 controls	2
New Zealand	0 cases / 0 controls	0
Overall	2.08 (1.30 – 3.33)	49

[*] 24-h geometric mean MF flux density of ≥ 4 mG against <1 mG

In 2010 Kheifets et al. published a pooled analysis of studies that appeared after the analyses of Ahlbom et al. (2000) and Greenland et al. (2000). This analysis included data from Bianchi et al. (2000) , Kabuto et al. (2006), Kroll et al. (2010), Lowenthal et al. (2007), Malagoli et al. (2010), Schüz et al. (2001), and Wünsch-Filho et al. (2011). For this pooled analysis the data from Bianchi et al. (2000) were extended by 5 years. Table 11-2 gives an overview of the results of this pooled analysis.

Table 11- 2: Results from the pooled analysis of 7 (6) studies of residential MF exposure and risk of childhood leukemia (Kheifets et al. 2010a) and of the earlier pooled analysis of 9 other studies (Ahlbom et al. 2000). Shown are odds ratios (95% confidence interval) adjusted for age, sex, SES and study.

Exposure category	Kheifets et al. 2010a	Kheifets et al. 2010a without Brazil	Ahlbom et al. 2000
<1 mG (ref)			
1-2 mG	1.07 (0.81 – 1.41)	1.15 (0.83 – 1.61)	1.08 (0.89 – 1.31)
2-4 mG	1.22 (0.78 – 1.89)	1.20 (0.67 – 2.17)	1.11 (0.84 – 1.47)
≥4 mG	1.46 (0.80 – 2.68)	2.02 (0.87 – 4.69)	2.00 (1.27 – 3.13)
>200 m (ref)			
100-200 m	1.20 (0.90, 1.59)		
50-100 m	1.30 (0.89, 1.91)		
≤50 m	1.59 (1.02, 2.50)		

In addition to studies investigating the risk of leukemia in relation to power frequency MF the hypothesis has been examined that effects on relapse and survival in newly diagnosed acute lymphoblastic leukemia occur (Foliart et al. 2006, 2007). There was a significantly increased hazard ratio for death at exposures ≥3 mG that was based on four deaths only.

The only other endpoint except leukemia and other hematopoietic diseases that has been investigated in several studies is nervous system tumors. The number of cases studied is too low to allow a differentiation according to diagnostic subgroups. Several papers have investigated childhood CNS tumors amongst other endpoints, including leukemia (Wertheimer & Leeper, 1979; Tomenius, 1986; Savitz et al., 1988; Feychting & Ahlbom, 1993; Olsen et al., 1993; Verkasalo et al., 1993; Tynes & Haldorsen, 1997; UKCCS, 1999; 2000; Draper et al., 2005; Kroll et al., 2010), whereas others have solely investigated CNS tumors (Gurney et al., 1996; Preston-Martin et al., 1996; Schüz et al., 2001b; Saito et al., 2010). In most cases the time window was restricted to the postnatal period. Exposure was assessed based on residential proximity to overhead power lines, measurements and wiring

configurations of houses. In a meta-analysis of childhood brain tumor studies (Wartenberg et al., 1998) estimates of risk were similar whether based on calculated fields (OR 1.4, 95% CI: 0.8 – 2.3), measured fields (OR 1.4, 95% CI: 0.8 – 2.4), wire codes (OR 1.2, 95% CI: 0.7 – 2.2), or proximity to electrical installations (OR 1.1, 95% CI: 0.7 – 1.7). The few studies published after this review do not change these figures substantially. Kheifets et al. (2010) report a pooled analysis of 10 studies using measured or calculated fields. The results are summarized in Table 11-3.

Table 11- 3: Summary of results from a pooled analysis of 10 studies of residential MF exposure and risk of childhood brain tumors (Kheifets et al. 2010b). Shown are odds ratios (95% confidence interval) adjusted for age and sex.

Exposure category	Type of measurement		
	Long-term	Calculated fields	Spot
<1 mG (ref)			
1-2 mG	1.13 (0.69 - 1.87)	1.06 (0.53 - 2.11)	1.16 (0.79 - 1.72)
2-4 mG	0.94 (0.43 - 2.06)	0.56 (0.19 - 1.60)	1.21 (0.67 - 2.18)
≥4 mG	1.35 (0.39 - 3.71)	1.21 (0.53 - 2.78)	0.68 (0.26 - 1.80)
Exposure category	Type of home exposure		
	Home at diagnosis	Longest lived-in	Birth home
<1 mG (ref)			
1-2 mG	0.89 (0.60 - 1.31)	1.42 (0.79 - 2.56)	1.03 (0.59 - 1.80)
2-4 mG	0.77 (0.44 - 1.36)	0.86 (0.28 - 2.65)	0.79 (0.34 - 1.80)
≥4 mG	1.08 (0.54 - 2.16)	2.19 (0.57 - 8.44)	1.14 (0.52 - 2.49)

III. DISCUSSION

With overall 42 epidemiological studies published to date power frequency EMFs are among the most comprehensively studied environmental factors. Except ionizing radiation no other environmental factor has been as firmly established to increase the risk of childhood leukemia, but for both there are ongoing controversies. Although data from atomic bomb survivors and radiotherapy of benign diseases (ringworm, ankylosing spondylitis, and thymus enlargement) clearly indicate a causal relationship between exposure and leukemia, for other conditions like living in the vicinity of nuclear power plants, diagnostic x-rays, exposure secondary to the Chernobyl incident evidence is less clear and therefore no agreement has been reached so far. Concerning power frequency EMFs few deny that the relationship is real and not due to chance, but still there is a discussion whether or not this association can be causally interpreted. Still the possibility that confounding, exposure misclassification, and selection and other biases are responsible for the observed relationship is mentioned as an argument against a causal interpretation. Furthermore, it is often claimed that even if the exposure is causally related, due to the low attributable fraction no expensive measures to reduce exposure are warranted.

The Environmental Health Criteria 238 (WHO 2007) summarizes:

> Scientific evidence suggesting that everyday, chronic low-intensity (above 0.3–0.4 μT) power-frequency magnetic field exposure poses a health risk is based on epidemiological studies demonstrating a consistent pattern of increased risk for childhood leukaemia. Uncertainties in the hazard assessment include the role that control selection bias and exposure misclassification might have on the observed relationship between magnetic fields and childhood leukaemia. In addition, virtually all of the laboratory evidence and the mechanistic evidence fail to support a relationship between low-level ELF magnetic fields and changes in biological function or disease status. Thus, on balance, the evidence is not strong enough to be considered causal, but sufficiently strong to remain a concern.
> Although a causal relationship between magnetic field exposure and childhood leukaemia has not been established, the possible public health impact has been calculated assuming causality in order to provide a potentially useful input into policy. However, these calculations are highly dependent on the exposure distributions and other assumptions, and are therefore very imprecise. Assuming that the association is causal, the number of cases of childhood leukaemia worldwide that might be attributable to exposure can be estimated to range from 100 to 2400 cases per year. However, this represents 0.2 to 4.9% of the total annual incidence of leukaemia cases, estimated to be 49 000 worldwide in 2000. Thus, in a global context, the impact on public health, if any, would be limited and uncertain. (pp.11-12)

Concerning preventive measures with respect to long-term effects it is stated:

> Implementing other suitable precautionary procedures to reduce exposure is reasonable and warranted. However, electric power brings obvious health, social and economic benefits, and precautionary approaches should not compromise these benefits. Furthermore, given both the weakness of the evidence for a link between exposure to ELF magnetic fields and childhood leukaemia, and the limited impact on public health if there is a link, the benefits of exposure reduction on health are unclear. Thus the costs of precautionary measures should be very low. (p.13)

The sequence of arguments is as follows:

- There are possible biases, exposure misclassification and confounding that could lead to spuriously increased risks

- There is no support from animal experiments and mechanistic studies for the association found in epidemiological investigations

- Therefore the association cannot be causal interpreted

- Even if the association is causal the number of attributable cases is low because of the small proportion of exposed children

- Therefore only low-cost precautionary measures are warranted.

In the following sections we will challenge these arguments.

A. The association between power frequency MF and childhood leukemia

After the pooled analyses of Ahlbom et al. (2000) and Greenland et al. (2000) were published several other epidemiological investigations were conducted that did not change the conclusions of an association between power frequency MF and childhood leukemia. Seven of these additional investigations were included in a pooled analysis by Kheifets et al. (2010a). Seven other studies were excluded for several reasons: because only distance to power lines was assessed, because data were not available in time etc. Overall the results of all studies taken together speak in favor of an association between exposure to power frequency MF and childhood leukemia (see Table 11-5).

B. Confounding

A confounder is a factor that is associated with the agent in question as well as with the disease. Hence a confounder must be a risk factor for the disease. Concerning childhood leukemia it was clear from the very beginning that any suggested confounder must be purely

speculative since there is no established environmental risk factor except ionizing radiation. Even if a condition can be found that is strongly associated with exposure to power frequency fields, if it is not associated with childhood leukemia it cannot confound the relationship. In the homogenous case, i.e. the association between EMF exposure and the confounder does not depend on disease status, and the confounder - leukemia association is independent of exposure to power frequency EMFs, even a stronger assertion can be proven: power frequency EMF remains a risk factor if the risk associated with the confounder is smaller than that associated with power frequency EMFs. Equation (1) gives the bias-factor for the homogenous case and dichotomous exposure variables (that can, however, easily be extended to categorical or continuous exposure variables):

$$B_F = \frac{1 + \pi_F(\Psi_{AF}\Psi_{DF} - 1)}{[1 + \pi_F(\Psi_{AF} - 1)][1 + \pi_F(\Psi_{DF} - 1)]} \tag{1}$$

(π_F is the prevalence of the confounder, Ψ_{DF} is the odds ratio for the confounder with respect to the disease, and Ψ_{AF} is the odds ratio of the agent in question with respect to the confounder). From this equation it is immediately clear that if either Ψ_{DF} or Ψ_{AF} or both are 1 there is no bias (i.e. the confounder is no risk factor for the disease and/or the agent in question is not associated with the confounder). This equation can be used to obtain limiting conditions for the odds ratio of the confounder given specific associations with power frequency fields. This has been done by Langholz (2001).

Langholz (2001) investigated factors that have been proposed as possible confounders based on data from Bracken et al. (1998). None of these factors on their own explain the power frequency EMF - leukemia relationship. It has been criticized (Greenland, 2003) that too far reaching conclusions have been drawn based on the failure to discover a single factor that may explain the relationship, because combinations of such factors have not been addressed. However, even considering combinations of confounders it is unlikely that confounding alone explains the relationship between power frequency EMFs and childhood leukemia.

Because of the rather small relative risks of around two for average exposure to ≥ 3 to 4 mG magnetic flux density or very high current codes there is, however, a possibility that bias due to a combination of confounding and other errors account for the increased risk. It will be shown in the last section that the most important aspect is the exposure metric. A much higher risk may be associated with exposure to power frequency fields. If this is actually the case the problem of bias of other provenience disappears.

Because the increased risk from high levels of exposure to power frequency EMFs is found all over the world a confounder explaining this increased risk must not be quite strong and associated with magnetic fields of various sources but must also be present everywhere in the world. It is virtually impossible that such a risk factor has not yet been detected. Therefore, confounding alone as an explanation for the relationship with leukemia can practically be ruled out.

C.   Exposure misclassification

Disregarding chance variations, non-differential exposure misclassification (i.e. misclassification that does not depend on disease status) always leads to an underestimation of the risk. The methods applied to calculate or measure MF in the residences of children are unlikely producing a bias that depends on the disease status (they have usually been done blinded to the case or controls status). Hence, if exposure misclassification was present this will rather have reduced the overall risk estimate. Different effects must be considered whether sensitivity (the probability that a child that was exposed is correctly classified as exposed) or specificity (the probability that a child that was not exposed is correctly classified as not exposed) is affected by the assessment method. The bias depends on six parameters (the exposure prevalence, the true odds ratio, the sensitivity and specificity in cases and controls). A thorough analysis of the effect of different types of exposure misclassification reveals that the vast majority of cases result in a bias towards the zero hypothesis. For low exposure prevalence the impact of a lack of specificity is greater than that of a lack of sensitivity, while for large exposure prevalence the opposite is the case. Considering that high levels of magnetic fields have a low prevalence an increase of specificity (i.e. reducing the number of false positives) has a greater impact on the reduction of bias than of increasing sensitivity (i.e. reducing the number of false negatives). This could explain why odds ratios tend to increase if longer measurements are applied.

Overall, exposure misclassification is a very unlikely cause of a bias in the direction of a higher odds ratio.

D.   Selection bias

In studies that were relying on individual measurements selection bias may have played an important role. Participation rates were sometimes lower in controls and especially for families with lower SES. Schüz et al. (2001b) calculated in a simulation study that about two

thirds of the increased risk could be due to selection bias. Although Wartenberg (2001) applying a meta-regression could not establish any aspect of study methodology that could account for the variation across studies, it is possible that the proportion of children exposed to high levels of MF has been underestimated in some studies.

The biased odds ratio can be factored into the true odds ratio and a bias factor. The bias factor is often called the selection odds ratio. It can be estimated if there are some data on exposure for non-participants. In the study from Brazil (Wünsch-Filho et al. 2011) measurements of magnetic flux density at the front door of participating and non-participating cases and controls have been conducted that allow computation of the bias factor. It turned out to be 1.08, which indicates a slight bias towards an increased risk. The specific conditions of the study in Brazil (e.g. restriction to cases and controls that did not move to a district outside Sao Paulo, inclusion of children less than 9 years, differences in age distribution of participants and non-participants) do not allow generalization to other studies. However, due to the fact that studies that were registry based obtained essentially the same results speak against a distorting selection bias.

E.   Exposure metric

After measurements of MF over 24 hours or even longer periods were introduced lower risk estimates for measured fields as compared to estimates from wire codes were noted. This observation was termed the "wire code paradox". Although much of the discrepancies disappeared after the pooled analyses (Ahlbom et al., 2000; Greenland et al., 2000), and also the comprehensive meta-analysis of Wartenberg (2001) could find no support for a systematic effect, still in some investigations there was indeed a stronger relationship to estimates from wire codes as compared to measurement. Bowman et al. (1999) and Thomas et al. (1999) published a thorough analysis of this aspect based on data of the Californian childhood leukemia study (London et al., 1991). They correctly noted the different error structure associated with measured fields and calculated fields from the wire codes that are more stable over time. They further pointed to the fact that the bias introduced by basing the risk estimate on exposure variables that are unbiased but prone to statistical variation will be towards the null. It can be shown that this bias is inversely related to the conditional variance of the exposure metric. Hence the higher the variance of the used exposure metric, conditional on the true one, the greater the bias of the risk estimate.

Up to now most considerations put forward were directed towards identification of factors and methodological issues that would explain a spurious relationship between power frequency EMFs and childhood leukemia. Hardly anyone asked the question: "Why is the risk estimated so low?" This question should, however, been asked because there are a number of intriguing facts: First of all, in developing countries with low levels of electrification childhood leukemia incidence is manifold lower as compared to industrialized regions (Parkin et al., 1998). Although registry data in developing countries are less reliable and sparse the difference is too pronounced to be due to underreporting. The time trend of childhood leukemia in industrialized countries suggests that childhood leukemia in the age group below 4 to 5 years of age is essentially a new phenomenon that emerged in the 1920s. Milham and Ossiander (2001) suggest that the acute lymphoblastic leukemia peak is due to electrification. Given the evidence of the pooled analyses, risk increases as a function of average MF flux density reaching significance at the far end of the exposure distribution for children exposed to an average of 3 to 4 mG. This result is clearly not in line with the hypothesis that much if not all of childhood leukemia (at least for the most prevalent ALL type in the age group of 2 to 4 years) is due to power frequency EMFs. Obviously there are two conclusions possible: either the hypothesis is wrong or the data must be reinterpreted.

Another difficulty arises due to the fact that animal studies and in vitro tissue culture investigations provided equivocal evidence for a causal relationship between power frequency EMFs and cancer. There is a fundamental problem in clarifying the etiological role of the exposure in the development of leukemia. According to present theory (Greaves 1999; 2002; 2003; 2006; Wiemels et al., 1999) childhood leukemia is a consequence of several (at least two) genetic events one of which already occurred before birth. Factors affecting childhood leukemia may therefore be related to different critical exposure windows: the preconceptional, the prenatal, and the postnatal period. Preconceptional factors may affect the mother and the grandmother during pregnancy with the mother, as well as the father during spermatogenesis. During the prenatal period exposure of the mother during pregnancy and exposure of the fetus may differentially affect the first stage of the disease. In fact, there is evidence that at birth around 1% of children show genetic deviations in cord blood cells (Wiemels et al., 1999; Eguchi-Ishimae et al., 2001; Mori et al., 2002) that could lead to leukemia conditional on them surviving and on additional genetic or epigenetic events. While the frequency of these deviations at birth might have been overestimated it is still manifold higher than the cumulative probability of childhood leukemia. Given this higher incidence of

early genetic events, a causal factor for childhood leukemia need not be directly genotoxic and not even mutagenic. A slight but continuous shift of the balance towards survival and proliferation of deviating clones will be sufficient to dramatically increase the incidence. Experimental investigations were generally insufficient to cover such effects.

Assuming that there is an exposure metric, intimately connected to average magnetic flux densities, and actually related to that condition responsible for the increased incidence of childhood leukemia, how does such a metric look like? Actually it is easy to derive the necessary conditions for such an exposure metric from bias considerations. There are only two such conditions that must be met:

     a. The conditional expectancy $E(x|z) = z$ (or equal to a linear function of z); where x is the unknown exposure metric and z is the logarithm of the true average magnetic flux density the child is exposed to.

     b. The conditional variance $V_{x|z}$ must be inversely related to z.

Based on the pooled analysis of Ahlbom et al. (2000) and assuming average magnetic flux density follows a log-normal distribution with mean 0.55 mG and a geometric standard deviation of 1, using the complete data set of cases and controls, the results of the pooled analysis can be reconstructed. However, *by varying the magnitude of the variance and the slope of the logistic function relating the purported exposure metric to the probability of developing childhood leukemia up to 80% of all cases can be attributed to the exposure.*

Fig.1 shows one of such Monte Carlo analyses. It can be seen that the bias of the risk estimate related to average MF flux density decreases as the level increases, however, the bias with respect to the assumed exposure metric reaches a factor of about 25 at levels above the third quartile. Of course, the precision of the actual measurements is much lower than indicated in the figure that is constructed by sampling from a theoretical log-normal distribution. However, this does not affect the validity of the argument since imprecisions in the average flux density lead to a bias towards 1. Therefore, the argument even holds in the absence of a relevant imprecision in measurements. The simulation was performed in such a way that exactly the same number of cases and controls are allocated to the average flux density categories as reported in Ahlbom et al. (2000) while varying the relationship between the theoretical alternative exposure metric that has the features a. and b. outlined above. Assuming that this correct metric is causally related to childhood leukemia, attributable

fractions between 1% and 80% are calculated dependent on the relationship between the average MF flux density and this assumed metric.

While of course this analysis does not prove the assumption that most of childhood leukemia is due to electrification, it demonstrates that the data obtained so far do not contradict this assumption. It is of crucial importance to analyze existing measurement data for aspects of the exposure that are in line with conditions a. and b. stated above. These exposure conditions may be analyzed by in vitro studies to asses their potential the facilitate transformation of already genetically damaged cells.
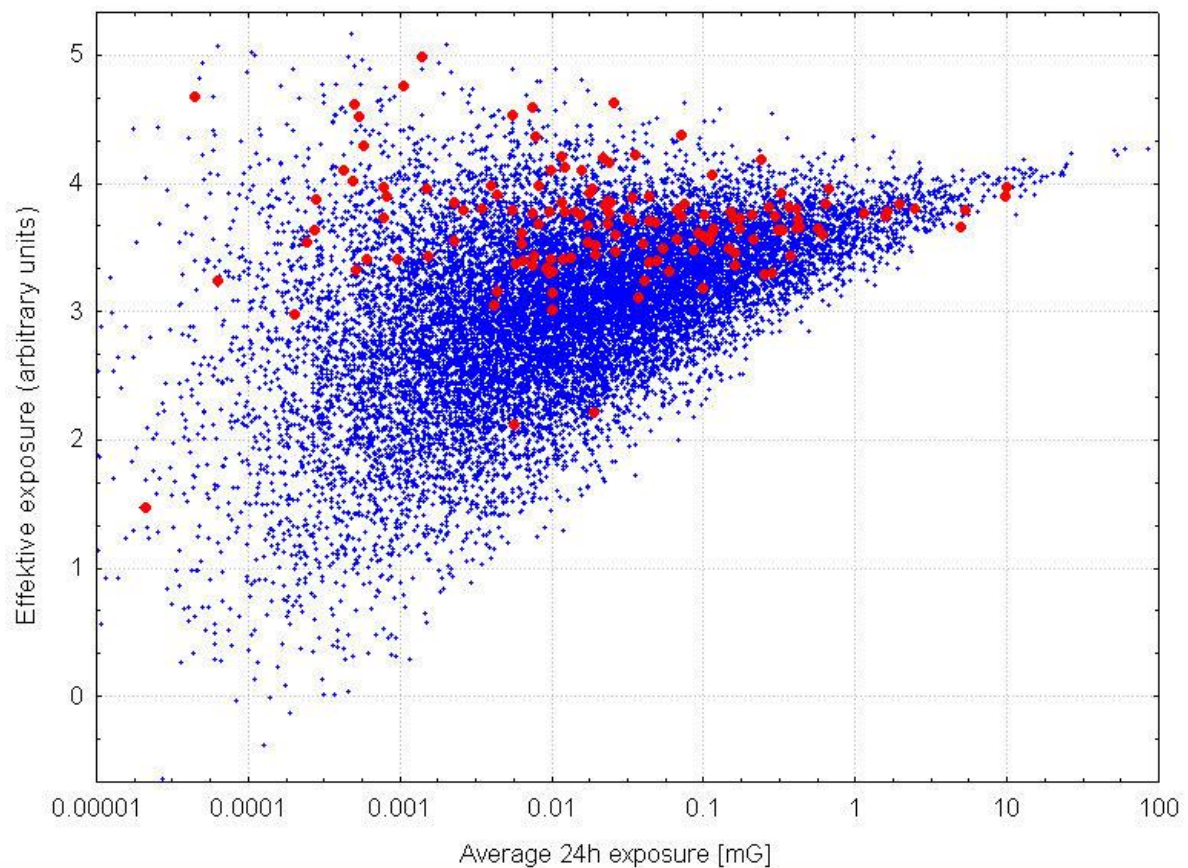
Fig. 1: Results of Monte Carlo simulation under the assumption of a log-normal distribution of average magnetic flux densities in the homes of children that are related to an assumed ‚effective' exposure metric that follows the conditions a. and b. mentioned in the text. Blue are controls and red children with leukemia. The purported ‚effective' exposure metric is associated with an attributable fraction of 80% and the odds-ratio for the highest quartile is around 50.

IV.   CONCLUSIONS

The only endpoint studied so far in sufficient detail is childhood leukemia. Brain and nervous system tumors were also studied in some detail but due to the diversity of these tumors no conclusions can be drawn.

Childhood leukemia is the most frequent childhood malignancy that peaks in the age group of 2 to about 5 years. This peak seems to have been newly evolved in the early quarter of the 20th century and may be due to electrification. This assumption is supported by the absence of this peak or it being much less pronounced in developing countries.

An overview of existing evidence from epidemiological studies indicates that there is a continuous increase of risk with increasing levels of average magnetic field exposure. Risk estimates reach statistical significance at levels of 3 to 4 mG. A low number of children are exposed at these or higher levels.

As an alternative interpretation of the association of leukemia with power frequency MF contact currents have been put forward (Kavet et al. 2000). Indeed, considering that a correlation between the magnitude of contact currents in the homes (e.g. in the bathtub) has been found and dosimetry indicates that high levels of internal fields could exist in the bone marrow of children touching metallic water fixtures, the hypothesis has some empirical support. However, a report from an epidemiological investigation in California (Does et al. 2011) could find no indication that contact currents play a decisive role while results for MF flux densities are in line with the previous findings of an increased risk with increasing exposure to power frequency MF in the homes.

I have pointed out (Kundi 2006) that under four conditions (temporal relation, association, environmental equivalence, and population equivalence) epidemiological evidence alone is sufficient to suggest disease causation. This is in line with the hazard assessment of IARC that specifies the default rule for assessing an agent as carcinogenic if there is sufficient evidence from epidemiological studies. Support from animal experiments or mechanistic studies is not necessary in these cases. Evidence from epidemiological studies is considered sufficient if a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence.

In the studies of childhood leukemia and residential exposure to power frequency magnetic fields measurements have been conducted after diagnosis. This is a violation of the condition

of temporal relation. However, these measurements can be considered an estimate of the exposure during the etiologically relevant period. But still it would result in some exposure misclassification. Because this type of misclassification is non-differential it can only reduce the observed association. Furthermore, support comes from studies with calculated fields that cover the relevant period. Therefore, the epidemiological evidence can be considered to fulfill the criterion.

Due to the small fraction of homes with very high exposure levels single studies have often insufficient power to detect an effect of the assumed magnitude of a doubling of the risk at levels around 3-4 mG. Therefore, meta-analyses and pooled analyses are important to investigate whether the association is due to chance. These analyses show a statistically significant association. There is no indication of a threshold but some investigations found reduced risks at intermediate levels, which might be due to inconsistencies in the sources that account for these exposure levels. There is sufficient evidence of an association that is apparent based on measurements, calculations, wire codes and other proxies for exposure.

Most studies used matching by at least sex and age, some added other potential confounders like region, SES, number of siblings etc. Care has been applied in most investigations to have the same population base for cases and controls. Studies investigating potential confounders did not reveal any factor other than exposure to power frequency MF that could be responsible for the observed association. There is only one cohort study (Verkasalo et al. 1993). This study, although with only 140 childhood cancer cases, is in line with the assumption of an association. An important analysis using the case-specular method supports the assumption of population and environmental equivalence (Ebi et al. 1999). Because the etiology of childhood leukemia is still not clear it is difficult to directly test the features most relevant for assessing the ceteris paribus condition. One investigation (Yang et al. 2008) indicates that power frequency MF may interact with specific genetic conditions. These results can be interpreted in two ways: the risk of leukemia from exposure to MF may be increased only in individuals harboring some specific polymorphism, on the other hand it is possible that exposure increases the genetic instability independently of an already increased instability due to a genetic polymorphism leading to a greater probability of developing the disease. At present there is no evidence to discriminate between these possibilities. If the first interpretation is valid different fractions of children harboring the relevant genetic condition would result in differences in the observed risk and thus some studies could have violated the population equivalence principle. Only in this case, it would be failure to detect an effect and

not a spuriously increased risk. Overall, there is no reason to assume that the principles of population and environmental equivalence has been violated in such a way that spuriously increased risks could have resulted.

For all these reasons it can be concluded that there is sufficient evidence from epidemiological studies of an increased risk from exposure to power frequency MF that cannot be attributed to chance, bias or confounding. Therefore, according to the rules of IARC such exposures can be classified as a group 1 carcinogen.

It has to be stressed, however, that according to the rules of IARC the working groups may up- or down-grade the classification upon consideration of the overall evidence. The IARC working group considered the lack of supporting evidence from animal experiments and in vitro studies as sufficient to down-grade the classification to 2B. Although it is not possible to discuss this aspect in this context, there are several problems with this view: first, there is no animal model for ALL, the most frequent childhood leukemia type; second, animal studies are difficult due to the fact that procedures usually applied, i.e. exposure levels just below the acute toxicity level, cannot be followed for MFs due to muscle and nerve excitations accompanying such exposures; third, at levels relevant for human long-term exposure in vitro experiments would have to detect extremely rare cellular events to account for the increased risk observed in epidemiological investigations, which is impossible using methods available to date. Therefore, strong and consistent support from such studies can neither be expected nor demanded. Consequently, lack of support from such evidence cannot be used as an argument to down-grade the classification based in epidemiology.

Considering the possibility that aspects of exposure to power frequency EMFs that have not yet been detected may account for a greater proportion of cases than assumed there are two necessary steps to be taken: Concerted efforts must be undertaken to scrutinize existing data and collect new ones that should reveal whether or not exposure metrics exist that show the necessary conditions for an effective exposure metric; and, second, precautionary measures must be delineated that result in a reduction of all aspects of exposure to power frequency EMFs.

Exposure guidelines of IEEE and ICNIRP are solely derived from immediate effects such as nerve and muscle excitations. These guidelines are indeed sufficient to protect from such acute effects (although indirect effects from contact currents cannot be ruled out). Evidence for long-term chronic effects has been collected in the past decades and has reached a state

that it cannot longer be denied that these effects are real. Only under very exceptional and remote conditions of a combination of several unknown confounders, selection bias and differential exposure misclassification the established relationship could be spurious. These combinations must have been present all over the world. There is no other risk factor identified so far for which such unlikely conditions have been put forward to postpone or deny the necessity to take steps towards exposure reduction. As one step in the direction of precaution, measures should be implemented to guarantee that exposure due to transmission and distribution lines is below an average of about 1 mG. This value is arbitrary at present and only supported by the fact that in many studies this level has been chosen as a reference.

- The balance of evidence suggests that childhood leukemia is associated with exposure to power frequency EMFs either during early life or pregnancy

- Considering only average MF flux densities the population attributable risk is low to moderate, however, there is a possibility that other exposure metrics are much stronger related to childhood leukemia and may account for a substantial proportion of cases. The population attributable fraction ranges between 1-4% (Kheifets et al., 2007) 2-4% (Greenland & Kheifets 2006), and 3.3% (Greenland 2001) assuming only exposures above 3 to 4 mG are relevant. However, if not average MF flux density is the metric causally related to childhood leukemia the attributable fraction can be much higher. Calculating a guideline level based on the unit-risk approach leads to a level close to 1 mG.

- Other childhood cancers except leukemia have not been studied in sufficient detail to allow conclusions about the existence and magnitude of the risk

- IEEE guideline levels are designed to protect from short-term immediate effects, long-term effects such as cancer seem to be evoked by levels several orders of magnitudes below current guideline levels

- Precautionary measures are warranted that should reduce all aspects of exposure, because at present we have no clear understanding of the etiologically relevant aspect of the exposure

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Table 11- 4: Synopsis of childhood cancer epidemiologic studies (1979 – 2012)

Study	Country/Period/Study Type	Exposure assessment	Interval diagnosis - measurement	Interval measurement cases-controls	Confounders considered & matching variables(m)	Case/control selection
Wertheimer & Leeper 1979	Greater Denver area, Colorado/ 1950-1973/ Case-control	wire-codes by inspection (not blinded) of surroundings of residences occupied at birth and time of death	retrospective (1976-1977) assessment	all assessments within 22 days	age (m), sex, urbanization, SES, family pattern, traffic	344 cancer deaths (age<19) from files, matched controls from next entry in birth register or from alphabetical list
Fulton et al. 1980	Rhode Island/1964-1978/Case-control	power lines (<45.72m from residences) assessed and MF calculated as combined weighted average (based on Wertheimer-Leeper measurements)	retrospective (1979) assessment	all assessments within same period	age(m), SES	119 leukemia patients (age<20) from Rhode Island hospital files; 240 control addresses from birth register

Study	Country/Period/Study Type	Exposure assessment	Interval diagnosis - measurement	Interval measurement cases-controls	Confounders considered & matching variables(m)	Case/control selection
Tomenius 1986	Stockholm county/ 1958-1973/ Case-control	inspection of visible electrical constructions within 150m of dwellings occupied at birth and diagnosis date; spot measurements at the door of the dwellings (blinded to case status)	retrospective (~1981) assessment	all assessments within same period	age(m), sex(m), district(m)	716 tumor cases (660 malignant, 56 benign) from cancer registry (age<19), matched controls from entry into birth register just before or after index case from same church district
Savitz et al. 1988	Five-county Denver area, Colorado/1976-1983/Case-control	wire-code of homes occupied prior to diagnosis (blinded to case status); spot measurements at the front door, in child's and parent's bedrooms and other rooms of frequent occupancy; interviews of mothers (in some cases fathers or adopted mothers)	retrospective (~1985) assessment	all assessments within same period	age±3y (m), sex(m), area(m), SES, traffic density, maternal age, maternal smoking	356 cancer cases (age<15) from cancer registry (71% interviewed, 36% measurements, 90% wire codes); 278 controls (79% resp.rate) from RDD (80% interviewed, 75% measurements, 93% wire codes)

Study	Country/Period/Study Type	Exposure assessment	Interval diagnosis - measurement	Interval measurement cases-controls	Confounders considered & matching variables(m)	Case/control selection
Coleman et al. 1989	Four boroughs near London/1965-1980/ Case-control	historical exposure by type and distance of electricity supply within 100 m of residences; distance to center of building assessed blinded to case status; calculations according to peak winter load of the power lines	retrospective assessment	all assessments within same period	age(m), sex(m), year of diagnosis(m)	84 leukemia cases (age<18) and 141 cancer controls from cancer registry
Myers et al. 1990	Yorkshire/1970-1979/ Case-control	assessment of overhead power lines within a distance depending on type of power line (100-500m) of home at birth; flux densities calculated from line load data and distance to center of dwelling	retrospective (1981-1989) assessment	all assessments within same period	age(m), sex(m), district(m), house type	374 cancer cases (age<15) from registries; 588 controls from nearest entry in birth register of the same district
London et al.	Los Angeles County,	24-h MF	measurements	all	age±1 or 2 or	232 leukemia cases

Study	Country/Period/Study Type	Exposure assessment	Interval diagnosis - measurement	Interval measurement cases-controls	Confounders considered & matching variables(m)	Case/control selection
1991	CA/1980-1987/Case-control	measurements (IREQ/ EMDEX) at location of child's bed; EF, MF and static magnetic field spot measurements; Wertheimer-Leeper wire code (all facilities within 46m; blinded to case status); interviews with parents about use of appliances etc.	1987-1989	assessments within same period	3y(m), sex(m), ethnicity(m), indoor pesticides, hair dryers, black&white TV, fathers occupational exposure to chemicals	(70% part.rate) from LA County Cancer Surveillance Program (age<11); 232 matched controls (90% part.rate) – 65 as friends of cases, others by RDD (5 digits cases, last 2 random)
Verkasalo et al. 1993	Finland/ 1970-1989/ Retrospective Cohort	estimated magnetic flux density from high-voltage power lines in the center of the building	cumulative and max. flux density any time between birth and diagnosis	n.a.	age, sex, calendar period	68300 boys and 66500 girls (age<20) identified having lived any time after birth in a house with a distance < 500m from a 110, 220, or 400 kV power line and an estimated flux density exceeding 0.1mG; 140 cancer cases from follow-up in cancer registry through 1990.
Feychting &	Sweden/1960-	calculations (blinded)	the year	all	age(m), sex(m),	142 cancer cases within

Study	Country/Period/Study Type	Exposure assessment	Interval diagnosis - measurement	Interval measurement cases-controls	Confounders considered & matching variables(m)	Case/control selection
Ahlbom 1993	1985/Nested Case-control	based on historical load data, wire configuration and distance from 220 and 400kV power lines and spot measurements (several rooms, 5-min measurements, main current turned on and off)	closest to date of diagnosis	assessments within same period	parish(m), year of diagnosis, apartment/single house, traffic (NO$_2$)	the study base of children (age<16) living on a property <300m from any 220 or 400kV power line; 558 matched controls from the study base.
Olsen et al. 1993	Denmark/1968-1986/Case-control	calculations based on estimated historical load of overhead transmission lines, transmission cables, and substations (50-400 kV)	retrospective up to 9 mo before birth	all assessments within same period	age(m), sex(m)	1707 cancer cases from registry (age<15) and 4788 matched controls from population register
Fajardo-Gutierrez et al. 1993	Mexico City/not specified/Case-control	interview with parents including assessment of distance and type of transmission and distribution lines, power substations etc.	n.a.	n.a.	age±2y(m), SES	81 leukemia cases from two hospitals; 77 controls from orthopedics or traumatology department

Study	Country/Period/Study Type	Exposure assessment	Interval diagnosis - measurement	Interval measurement cases-controls	Confounders considered & matching variables(m)	Case/control selection
Coghill et al. 1996	England/1986-1995/ Case-control	E- and H-field probes designed for the study measured 24 h in the bedroom; data used only for the period 20:00 to 08:00	retrospective	parallel measurements in case and control homes	age(m), sex(m)	56 leukemia cases (age<15) from various sources (media advertising, self-help groups, Wessex Health Authority) and 56 controls
Gurney et al. 1996	Seattle area, Washington/1984-1990/Case-control	wire-code by inspection of homes (blinded for case status) occupied within 3 y before diagnosis, electrical appliances by interview with mothers and mailed questionnaire	retrospective (1989-1994) assessment	all assessments within same period	age±2y(m), sex(m), area of residence(m), race, mothers education, family history of brain tumors, ETS, living on a farm, head/neck x-ray, head injury, epilepsy, fits	133 brain-tumor cases (age<20) (74% part.rate) by Cancer Surveillance System; 270 controls by RDD (79% part.rate)

Study	Country/Period/Study Type	Exposure assessment	Interval diagnosis - measurement	Interval measurement cases-controls	Confounders considered & matching variables(m)	Case/control selection
Preston-Martin et al. 1996	Los Angeles County, California/1984-1991/ Case-control	wire-code and outside spot measurements of homes occupied from conception to diagnosis (blinded for case status); 24h measurements in child's bedroom and another room for a subset; electrical appliances, occupation etc. by interviews with mothers	retrospective (1990-1992) assessment	all assessments within same period	age±1y(m), sex(m), year of diagnosis, SES, parents occupation, building type	298 brain tumor cases (age<20) (68% part.rate); 298 controls by RDD (70% part.rate)
Tynes & Haldorsen 1997	Norway/1965-1989/Nested Case-control	cohort (age <15) living in a ward crossed by a high-voltage power line (≥45kV in urban, ≥100kV in rural areas) in at least one of the years 1960, 1970, 1980, 1985, 1987, 1989.	Calculated historical fields	n.a.	age(m), sex(m), muni-pality(m), SES, type of building, number of dwellings	500 cancer cases (94%) from cancer registry; 2004 controls (95%) randomly selected from cohort

Study	Country/Period/Study Type	Exposure assessment	Interval diagnosis - measurement	Interval measurement cases-controls	Confounders considered & matching variables(m)	Case/control selection
Petridou et al. 1997	Greece/1993-1994/Case-control	distance to transmission and distribution lines, field calculation	n.a.	n.a.	age(m), sex(m), region(m), maternal age, education etc.	117 childhood leukemia cases (age<15) (77% of eligible) and 202 controls (68% of eligible)
Michaelis et al. 1997a	Lower Saxony, Germany/1988-1993/ Case-control	24h measurements (EMDEX II) in the child's bedroom and living room in dwellings where the child lived longest (not blinded to case status); perimeter measurements (measurement wheel) with recordings every foot (~30cm) when walking through the rooms and outside the house where the child lived for at least 1 y.	measurements 1992-1995	all measurements within same period	age±1y(m), sex(m), SES, urbanization	129 leukemia cases (age<15) (59% part.rate) from register; 328 controls (167 from same district, 161 from random district) (53% part.rate) from government registration files

Study	Country/Period/Study Type	Exposure assessment	Interval diagnosis - measurement	Interval measurement cases-controls	Confounders considered & matching variables(m)	Case/control selection
Michaelis et al. 1997b	Berlin/1991-1994/ Case-control (pooled with data from Michaelis et al. 1997a)	as above	not specified	not specified	age±1y(m), sex(m), SES, urbanization, age at diagnosis, West/East Germany	47 leukemia cases (age<15) (59% part.rate) from register; 86 controls (28% part.rate) from government registration files
Linet et al. 1997	Illinois, Indiana, Iowa, Michigan, Minnesota, New Jersey, Ohio, Pennsylvania, and Wisconsin/1989-1994/Case-control	24h measurements (EMDEX C) in child's bedroom (blinded to case status); spot measurements in the residences and at the front door; wire coding of residences of residentially stable case-control pairs	~2 years	all measurements within same period	age(m), ethnicity(m), 8-digits phone number(m), sex, SES, time of measurem., urbanization, type of residence, birth order, birth weight, mother's age, medical x-ray	638 ALL cases (age<15) from register of Children's Cancer Group (78% part.rate); 620 controls from RDD (63% part.rate).

Study	Country/Period/Study Type	Exposure assessment	Interval diagnosis - measurement	Interval measurement cases-controls	Confounders considered & matching variables(m)	Case/control selection
Li et al. 1998	Taipei Metropol. Area (3 districts), Taiwan/ 1987-1992/ Ecological	high voltage transmission lines (69 -345kV) were mapped to 124 administrative regions; households with ≥50% intersecting a buffer zone of 100m around transmission lines	n.a.	n.a.	age (5y groups), calendar year	28 leukemia cases from registry in a study base of ~121.000 children (age<15); 7 cases within 21 cases outside a 100m corridor each side of a transmission line
Dockerty et al. 1998	New Zealand/1990-1993/Case-control	24h measurements (Positron) in child's bedroom and another room (only for leukemia cases); interview with mothers	1-2 years	all measurements within same period	age(m), sex(m), SES, maternal smoking, living on a farm	303 cancer cases (age<15) from 3 registries (88% part.rate) – 121 leukemia cases; 303 controls from birth register (68% part.rate)

Study	Country/Period/Study Type	Exposure assessment	Interval diagnosis - measurement	Interval measurement cases-controls	Confounders considered & matching variables(m)	Case/control selection
UKCCS 1999	England, Scotland & Wales/1991(92)-1994(96)/Case-control	spot measurements (EMDEX II) in child's bedroom, 90 min measurements in main family room, 48h measurements (20% of case-control pairs) at child's bedside; school measurements; weighted averages from info obtained by questionnaire; adjustments from historical load data	~2 years	<4 months in 98% of case-control pairs (spot), within 4 weeks (48h measurem.)	age (m), sex(m), district(m), deprivation index	2226 cancer cases (age<15) from registry (59% part.rate); 2226 matched controls from registry
McBride et al. 1999	Canada (5 provinces)/ 1990-1994(95)/Case-control	48h personal measurements (Positron), 24h measurements in child's bedroom	9 months average	2 months average	age±3-6mo (m), sex(m), area(m), maternal age, maternal education,	399 leukemia cases (age<15) (90% part.rate) from treatment centers and registry; 399 matched

Study	Country/Period/Study Type	Exposure assessment	Interval diagnosis - measurement	Interval measurement cases-controls	Confounders considered & matching variables(m)	Case/control selection
		(75% cases, 86% controls); wire codes (78% cases, 85% controls) and residence perimeter and front door measurements (64% cases, 74% controls) (blinded to case status) (EMDEX C); interviews with parents			income, ethnicity, number of residences	controls (76% part.rate) from health insurance/family allowance rolls
Green et al. 1999a	Greater Toronto Area, Canada/1985-1993/ Case-control	48h personal measurements (Positron); spot measurements in child's bedroom and two other rooms; wire codes; interviews with parents	2-3 y average	~5 mo average	age±1y (m), sex(m), family income, siblingship, residential mobility, insecticides, mother's medication and exp. prior or during pregn.	201 leukemia cases (age<15) from hospital record (64% part.rate); 406 controls from telephone marketing list (10,000 residences) (63% part.rate)
Green et al. 1999b	Greater Toronto Area, Canada/1985-1993/ Case-control	as above	2-3 y average	~5 mo average	as above	88 leukemia cases (age<15) from hospital record; 133 controls

Study	Country/Period/Study Type	Exposure assessment	Interval diagnosis - measurement	Interval measurement cases-controls	Confounders considered & matching variables(m)	Case/control selection
						from telephone marketing list (10,000 residences)
Schüz et al. 2001a	West Germany/1993(90)-1997(94)/Case-control	24h measurements (FW2a) under mattress of child's bed; 24h measurements (EMDEX II) in living room; perimeter measurements with recordings every foot (~30cm) when walking through the rooms			age(m), sex(m), community(m), SES, year of birth, urbanization, residential mobility, season, type of residence	514 leukemia cases (age<15) from cancer registry (61% of eligible) and 1301 controls from population registry (61% of eligible)
Schüz et al. 2001b	Lower Saxony/1988 – 1993 & Western Germany/1992-1994/ Case-control	as above			age(m), sex(m), community(m), SES, urbanization	64 cases of CNS tumors (age<15) from registry and 414 controls from population registry

Study	Country/Period/Study Type	Exposure assessment	Interval diagnosis - measurement	Interval measurement cases-controls	Confounders considered & matching variables(m)	Case/control selection
Mizoue et al. 2004	Japan/1992-2001/Ecological	classification of 294 districts according to their proximity to high voltage power lines (66 and 220V); proportion of area of district (0%, <50%, >50%) within ±300m of a power line	n.a.	n.a.	age (5y groups)	14 cases (age<15) of hematopoietic malignancies identified from two hospitals (all that treated these malignancies)
Draper et al. 2005	England & Wales/ 1962-1995/Case-control	computed distance from nearest overhead power line (132kV, 275kV, 400kV) of residence at birth	n.a.	n.a.	age±6mo(m), sex(m), district(m), SES	29081 cancer cases (age<15) identified from several registries (88% of total); 29081 controls from birth registers
Perez et al. 2005	Cuba (Habana)/1996-2000/Case-control	spot measurements inside and outside (Bell 4090), measurement of ionizing radiation	not specified	not specified	age(m), sex(m), school(m)	unknown number of leukemia cases (age<15) and controls

Study	Country/Period/Study Type	Exposure assessment	Interval diagnosis - measurement	Interval measurement cases-controls	Confounders considered & matching variables(m)	Case/control selection
Kabuto et al. 2006	Tokyo, Nagoya, Kyoto, Osaka and Kitakyushu metropolitan areas (Japan)/1999-2001/Case-control	7 days continuous MF measurement (EMDEX Lite) in child's bedroom; spot measurements in- and outside the house (EMDEX II)	~13 mo	~3 days	age±(≤)1y(m), sex(m), region(m), population size(m), father's and mother's education	321 ALL/AML cases (age<15) from several registries of childhood cancer study groups (49% part.rate); 634 controls from residential registry (29% part.rate)
Mejia-Arangure et al. 2007	Mexico-City/1995-2003/Case-control	spot measurements (EMDEX II) at the front door; wire coding (blinded to case status)	not specified	not specified	age, sex, SES, birth weight, maternal age, traffic, district, family history of cancer	42 ALL/AML cases (age<16) with Down syndrome from 4 (all) treating hospitals; 124 healthy controls with Down syndrome from 2 centers
Feizi & Arabi 2007	Iran (Tabriz)/1998-2004/Case-control	distance and calculated fields	n.a.	n.a.	age(m), sex(m), SES(m), race(m), district(m)	60 AL cases (83% of eligible) (age<15) and 59 hospital controls (79% of eligible)
Lowenthal et al. 2007	Tasmania/1972-1980/Case-control	distance from power line	n.a.	n.a.	age(m), sex(m)	783 adult and 71 childhood cases of MPD or LPD and matched controls

Study	Country/Period/Study Type	Exposure assessment	Interval diagnosis - measurement	Interval measurement cases-controls	Confounders considered & matching variables(m)	Case/control selection
Yang et al. 2008	Shanghai/2006-2007/Case-only	distance from transformer or power lines	n.a.	n.a.	age, gender, parental education, pesticides, television set etc. in children's room, chemical factory, telecom transmitter <500 m	123 AML cases (age<15) with or without XRCCI Ex9p16A
Abdul-Rahman et al. 2008	Malaysia/2001-2007/Case-control	distance from power lines and substations (GPS)	n.a.	n.a.	not specified	128 AL cases (age<15) and 128 hospital controls
Malagoli et al. 2010	Italy (Modena, Reggio Emilia)/1986-2007/	calculated fields from power lines ≥132 kV	n.a.	n.a.	age(m), sex(m), municipality(m), parent education, income	64 cases (age<14) of hematological malignancies and 256 controls
Kroll et al. 2010	England, Wales/1962-1995/Case-control	calculated fields from overhead power line (132kV, 275kV, 400kV) of residence at birth	n.a.	n.a.	age(m), sex(m), district(m)	28968 cancer cases (age<15)
Sohrabi et al. 2010	Iran (Teheran)/2007-2009/Case-control	distance to power lines (123, 230, 400 kV) using GPS	n.a.	n.a.	age(m), sex(m)	300 ALL cases (age<18) and 300 hospital controls

Study	Country/Period/Study Type	Exposure assessment	Interval diagnosis - measurement	Interval measurement cases-controls	Confounders considered & matching variables(m)	Case/control selection
Saito et al. 2010	Japan/1999-2002/Case-control	1-week measurement (EMDEX Lite) near bedside	Not specified	12.4 days	age(m), sex(m), region(m), population size(m), mother education	55 childhood brain tumor cases (age<15) and 99 controls
Does et al. 2011	California/2004-2007/Case-control	30 min measurement of contact current in the bathtub , indoor spot measurements (EMDEX Lite)	28 months	8 months	age, sex, race, income	245 leukemia cases (95% of eligible) (age<8) and 269 controls (92% of eligible)
Wünsch-Filho et al. 2011	Brazil (Sao Paulo)/2003-2009/Case-control	24 h measurements (EMDEX II) under the child's bed, distance to power lines	Not specified	Not specified	age(m), sex(m), city of birth(m),race, mobility,etc.	179 ALL cases (age<9) (90% of contacted) and 565 controls (88% of contacted)

RDD…Random Digit Dialing, n.a…not applicable, MF…magnetic field, SES…socio-economic status, ALL…acute lymphoblastic leukemia, AML…acute myeloid leukemia, AL…acute leukemia, LPD…lymphoproliferative disorders, MPD…myeloproliferative disorders

Table 11- 5: Synopsis of main results of childhood cancer studies (1979 – 2012)

Study	Endpoint	Exposure category	Outcome [95% CI]
Wertheimer & Leeper 1979[a]	Leukemia	LCC* (birth address)	
		HCC	OR 2.28 [1.34 – 3.91]
	Lymphoma	LCC*	
		HCC	OR 2.48 [0.73 – 8.37]
	Nervous system tumors	LCC*	
		HCC	OR 2.36 [1.03 – 5.41]
	Others	LCC*	
		HCC	OR 2.38 [0.93 – 6.06]
	All hematopoietic	LCC*	
		HCC	OR 2.31 [1.41 – 3.77]
	All cancers	LCC*	
		HCC	OR 2.33 [1.59 – 3.42]
Fulton et al. 1980	Leukemia	Very low*[c]	
		Low	OR 1.1 [0.5 – 2.4]
		High	OR 1.2 [0.6 – 2.6]
		Very high	OR 1.0 [0.5 – 2.3]
Tomenius 1986	Leukemia	no 200 kV-line*	
		200 kV-line<150m	OR 1.09 [0.29 – 4.12]
	Lymphoma	no 200 kV-line*	
		200 kV-line<150m	OR 1.48 [0.35 – 6.35]
	Nervous system tumors	no 200 kV-line*	
		200 kV-line<150m	OR 3.96 [0.85 – 18.52]
	Others	no 200 kV-line*	
		200 kV-line<150m	OR 2.59 [0.70 – 9.66]
	All hematopoietic	no 200 kV-line*	
		200 kV-line<150m	OR 1.26 [0.47 – 3.34]
	All cancers	no 200 kV-line*	
		200 kV-line<150m	OR 2.15 [1.12 – 4.11]

Study	Endpoint	Exposure category	Outcome [95% CI]
	All cancers	<3mG birth dwelling*	
		≥3mG	OR 2.67 [1.18 – 6.08]
	All cancers	<3mG diagn. dwelling*	
		≥3mG	OR 2.60 [1.20 – 5.67]
Savitz et al.1988	Leukemia	<2mG low power use*	
		2+ mG	OR 1.93 [0.67 – 5.56]
	Lymphoma	<2mG low power use*	
		2+ mG	OR 2.17 [0.46 – 10.31]
	Brain tumors	<2mG low power use*	
		2+ mG	OR 1.04 [0.22 – 4.82]
	Others	<2mG low power use*	
		2+ mG	OR 0.96 [0.31 – 2.98]
	All hematopoietic	<2mG low power use*	
		2+ mG	OR 1.99 [0.57 – 5.14]
	All cancers	<2mG low power use*	
		2+ mG	OR 1.35 [0.63 – 2.90]
	Leukemia	<2mG high power use*	
		2+ mG	OR 1.41 [0.57 – 3.50]
	Lymphoma	<2mG high power use*	
		2+ mG	OR 1.81 [0.48 – 6.88]
	Brain tumors	<2mG high power use*	
		2+ mG	OR 0.82 [0.23 – 2.93]
	Others	<2mG high power use*	
		2+ mG	OR 0.75 [0.30 – 1.92]
	All hematopoietic	<2mG high power use*	
		2+ mG	OR 1.51 [0.68 – 3.35]
	All cancers	<2mG high power use*	
		2+ mG	OR 1.04 [0.56 – 1.95]

Study	Endpoint	Exposure category	Outcome [95% CI]
	All cancers	0-0.64 mG low power use*	
		0.65-0.99 mG	OR 1.28 [0.67 – 2.42]
		1.0-2.49 mG	OR 1.25 [0.68 – 2.28]
		2.5+ mG	OR 1.49 [0.62 – 3.60]
	All cancers	0-0.64 mG high power use*	
		0.65-0.99 mG	OR 1.13 [0.61 – 2.11]
		1.0-2.49 mG	OR 0.96 [0.56 – 1.65]
		2.5+ mG	OR 1.17 [0.54 – 2.57]
	Leukemia	LCC*	
		HCC	OR 1.41 [0.57 – 3.50]
	Lymphoma	LCC*	
		HCC	OR 1.81 [0.48 – 6.88]
	Brain tumors	LCC*	
		HCC	OR 0.82 [0.23 – 2.93]
	Others	LCC*	
		HCC	OR 0.75 [0.30 – 1.92]
	All hematopoietic	LCC*	
		HCC	OR 1.51 [0.68 – 3.35]
	All cancers	LCC*	
		HCC	OR 1.04 [0.56 – 1.95]
	All cancers	UG 2y before diagnosis*	
		VLCC	OR 0.96 [0.39 – 2.34]
		OLCC	OR 1.17 [0.65 – 2.08]
		OHCC	OR 1.40 [0.71 – 2.75]
		VHCC	OR 5.22 [1.18 – 23-09]
	All cancers	VLCC/OLCC*[b]	
		UG	OR 0.89 [0.51 – 1.55]
		OHCC	OR 1.25 [0.67 – 2.31]
		VHCC	OR 4.66 [0.95 – 22.76]

Study	Endpoint	Exposure category	Outcome [95% CI]
Coleman et al. 1989	Leukemia	≥100 m nearest substation*	
		50-99 m	OR 0.75 [0.40 – 1.38]
		25-49 m	OR 1.49 [0.61 – 3.64]
		0-24 m	OR 1.63 [0.32 – 8.38]
Myers et al. 1990	All cancers	<0.1mG*	
		0.1-0.3mG	OR 0.96 [0.37 – 2.51]
		≥0.3mG	OR 1.73 [0.59 – 5.07]
London et al. 1991	Leukemia	<0.68mG* (24h.measurem.)	
		0.68-1.18mG	OR 0.68 [0.39 – 1.17]
		1.19-2.67mG	OR 0.89 [0.46 – 1.71]
		≥2.68mG	OR 1.48 [0.66 – 3.29]
		<0.32mG (spot bedroom)*	
		0.32-0.67mG	OR 1.01 [0.61 – 1.69]
		0.68-1.24mG	OR 1.37 [0.65 – 2.91]
		≥1.25mG	OR 1.22 [0.52 – 2.82]
		UG/VLCC*	
		OLCC	OR 0.95 [0.53 – 1.69]
		OHCC	OR 1.44 [0.81 – 2.56]
		VHCC	OR 2.15 [1.08 – 4.26]
Verkasalo et al. 1993	Leukemia	≥4mG any time	SIR 1.55 [0.32 - 4.54]
	Lymphoma	≥4mG any time	SIR [0.00 - 4.19]
	Nervous system tumors	≥4mG any time	SIR 2.31 [0.75 - 5.40]
	Others	≥4mG any time	SIR 1.24 [0.26 - 3.62]
	All hematopoietic	≥4mG any time	SIR 1.49 [0.74 - 2.66]
	All cancers	≥4mG any time	SIR 1.66 [0.34 - 4.84]
Feychting & Ahlbom 1993	Leukemia	<1mG* (calculated)	
		1-2mG	OR 2.1 [0.6 – 6.1]

Study	Endpoint	Exposure category	Outcome [95% CI]
		≥2mG	OR 2.7 [1.0 – 6.3]
	Lymphoma	<1mG* (calculated)	
		1-2mG	OR 0.9 [0.0 – 5.2]
		≥2mG	OR 1.3 [0.2 – 5.1]
	Nervous system tumors	<1mG* (calculated)	
		1-2mG	OR 1.0 [0.2 – 3.8]
		≥2mG	OR 0.7 [0.1 – 2.7]
	Others	<1mG* (calculated)	
		1-2mG	OR 1.6 [0.6 – 4.3]
		≥2mG	OR 0.2 [0.0 – 1.7]
	All hematopoietic	<1mG* (calculated)	
		1-2mG	OR 1.7 [0.6 – 4.5]
		≥2mG	OR 2.2 [1.0 – 4.7]
	All cancers	<1mG* (calculated)	
		1-2mG	OR 1.5 [0.7 – 2.9]
		≥2mG	OR 1.1 [0.5 – 2.1]
Olsen et al. 1993	Leukemia	<1mG* (calculated)	
		1-4mG	OR 0.3 [0 – 2.0]
		≥4mG	OR 6.0 [0.8 – 44]
	Lymphoma	<1mG* (calculated)	
		1-4mG	OR 5.0 [0.7 – 36]
		≥4mG	OR 5.0 [0.3 – 82]
	CNS tumors	<1mG* (calculated)	
		1-4mG	OR 0.4 [0.1 – 2.8]
		≥4mG	OR 6.0 [0.7 – 44]
	All three combined	<1mG* (calculated)	
		1-4mG	OR 0.7 [0.2 – 2.0]
		≥4mG	OR 5.6 [1.6 – 19]

Study	Endpoint	Exposure category	Outcome [95% CI]
Fajardo-Gutierrez et al. 1993	Leukemia	Transformer station[d]	OR 1.56 [0.73 – 3.30]
		High voltage power line	OR 2.63 [1.26 – 5.36]
		Electric substation	OR 1.67 [0.65 – 4.35]
		Transmission line	OR 2.50 [0.97 – 6.67]
Coghill et al. 1996	Leukemia	< 5 V/m E-field *	
		5-9 V/m	OR 1.49 [0.47 – 5.10]
		10-19 V/m	OR 2.40 [0.79 – 8.09]
		≥20 V/m	OR 4.69 [1.17 – 27.78]
Gurney et al.1996	Brain tumors	UG*	
		VLCC	OR 1.25 [0.74 – 2.13]
		OLCC	OR 0.74 [0.34 – 1.61]
		OHCC	OR 1.07 [0.55 – 2.06]
		VHCC	OR 0.51 [0.16 – 1.60]
		LCC*	
		HCC	OR 0.86 [0.50 – 1.48]
Preston-Martin et al. 1996	Brain tumors	0.09-0.51 mG Md 24h *	
		0.52-1.02 mG	OR 1.5 [0.7 – 3.2]
		1.03-2.03 mG	OR 1.8 [0.7 – 4.5]
		2.04-10.4 mG	OR 1.2 [0.4 – 3.2]
		VLCC/OLCC*	
		UG	OR 1.9 [1.0 – 3.6]
		OHCC	OR 0.8 [0.6 – 1.2]
		VHCC	OR 1.2 [0.6 – 2.1]
Tynes & Haldorsen 1997	Leukemia	<0.5mG (TWA birth-diagn)*	
		0.5-1.4mG	OR 1.8 [0.7 – 4.2]
		≥1.4mG	OR 0.3 [0.0 – 2.1]
	Lymphoma	<0.5mG (TWA birth-diagn)*	
		0.5-1.4mG	OR 1.0 [0.1 – 8.7]
		≥1.4mG	OR 2.5 [0.4 – 15.5]

Study	Endpoint	Exposure category	Outcome [95% CI]
	Nervous system tumors	<0.5mG (TWA birth-diagn)*	
		0.5-1.4mG	OR 1.9 [0.8 – 4.6]
		≥1.4mG	OR 0.7 [0.2 – 2.1]
	Others	<0.5mG (TWA birth-diagn)*	
		0.5-1.4mG	OR 2.9 [1.0 – 8.4]
		≥1.4mG	OR 1.9 [0.6 – 6.0]
	All hematopoietic	<0.5mG (TWA birth-diagn)*	
		0.5-1.4mG	OR 1.4 [0.7 – 3.1]
		≥1.4mG	OR 0.7 [0.2 – 2.4]
	All cancers	<0.5mG (TWA birth-diagn)*	
		0.5-1.4mG	OR 1.9 [1.2 – 3.3]
		≥1.4mG	OR 1.0 [0.5 – 1.8]
Petridou et al. 1997	Leukemia	Very Low*	
		Low	OR 0.99 [0.54–1.84]
		Medium	OR 1.84 [0.26–12.81]
		High	OR 4.26 [0.94–19.44]
		Very high	OR 1.56 [0.26–9.39]
Michaelis et al. 1997a	Leukemia	<2mG (Median 24h)*	
		≥2mG	OR 3.2 [0.7 – 14.9]
		<2mG (Median night)*	
		≥2mG	OR 3.9 [0.9 – 16.9]
Michaelis et al. 1997b (pooled with previous)	Leukemia	<2mG (Median 24h)*	
		≥2mG	OR 2.3 [0.8 – 6.7]
		<2mG (Median night)*	
		≥2mG	OR 3.8 [1.2 – 11.9]

Study	Endpoint	Exposure category	Outcome [95% CI]
Linet et al. 1997	ALL	<0.65mG (TWA)*	
		0.65-1mG	OR 0.96 [0.65 – 1.40]
		1-2mG	OR 1.15 [0.79 – 1.65]
		2-3mG	OR 1.31 [0.68 – 2.51]
		3-4mG	OR 1.46 [0.61 – 3.50]
		4-5mG	OR 6.41 [1.30 – 31.7]
		≥5mG	OR 1.01 [0.26 – 3.99]
Li et al.1998	Leukemia	≥100m from transm.line	
		<100m	SIR 2.43 [0.98 – 5.01]
		Total population<15y	
		≥100m from transm.line	SIR 1.05 [0.64 – 1.58]
		<100m	SIR 2.69 [1.08 – 5.55]
Dockerty et al. 1998	Leukemia	<1mG (24h bedroom AM)*	
		1-2mG	OR 1.4 [0.3 – 7.6]
		≥2mG	OR 15.5 [1.1 – 224]
		<1mG (24h daytime room)*	
		1-2mG	OR 3.7 [0.7 – 18.8]
		≥2mG	OR 5.2 [0.9 – 30.8]
UKCCS 1999	Leukemia	<1mG (estim.AM exp.)*	
		1-2mG	OR 0.78 [0.55 – 1.12]
		2-4mG	OR 0.78 [0.40 – 1.52]
		≥4mG	OR 1.68 [0.40 – 7.10]
	Central nervous system cancers	<1mG (estim.AM exp.)*	
		1-2mG	OR 2.44 [1.17 – 5.11]
		2-4mG	OR 0.70 [0.16 – 3.17]
		≥4mG	OR --
	Others	<1mG (estim.AM exp.)*	

Study	Endpoint	Exposure category	Outcome [95% CI]
		1-2mG	OR 0.81 [0.52 – 1.28]
		2-4mG	OR 1.08 [0.45 – 2.56]
		≥4mG	OR 0.71 [0.16 – 3.19]
	All cancers	<1mG (estim.AM exp.)*	
		1-2mG	OR 0.93 [0.72 – 1.19]
		2-4mG	OR 0.87 [0.53 – 1.42]
		≥4mG	OR 0.89 [0.34 – 2.32]
McBride et al. 1999	Leukemia	<0.8mG (lifetime predicted)*	
		0.8-1.5mG	OR 0.74 [0.48 – 1.13]
		1.5-2.7mG	OR 1.15 [0.70 – 1.88]
		≥2.7mG	OR 1.02 [0.56 – 1.86]
		Low (Kaune-Savitz)*	
		Medium	OR 1.12 [0.77 – 1.64]
		High	OR 1.17 [0.74 – 1.86]
Green et al. 1999a	Leukemia	<0.4mG (spot measurem.)*	
		0.4-0.9mG	OR 0.47 [0.12 – 1.89]
		0.9-1.5mG	OR 0.75 [0.19 – 3.02]
		≥1.5mG	OR 1.47 [0.44 – 4.85]
Green et al. 1999b	Leukemia	<0.3mG (48h measurem.)*	
		0.3-0.7mG	OR 2.0 [0.6 – 6.8]
		0.7-1.4mG	OR 4.0 [1.1 – 14.4]
		≥1.4mG	OR 4.5 [1.3 – 15.9]
		<0.4mG (spot measurem.)*	
		0.4-0.8mG	OR 1.8 [0.5 – 6.1]

Study	Endpoint	Exposure category	Outcome [95% CI]
		0.8-1.6mG	OR 2.8 [0.8 – 10.4]
		≥1.6mG	OR 4.0 [1.2 – 13.6]
Schüz et al. 2001a	Leukemia	<1mG (Md 24h)*	
		1-2mG	OR 1.15 [0.73 – 1.81]
		2-4mG	OR 1.16 [0.43 – 3.11]
		≥4mG	OR 5.81 [0.78 – 43.2]
		<1mG (Md night-time)*	
		1-2mG	OR 1.42 [0.90 – 2.23]
		2-4mG	OR 2.53 [0.86 – 7.46]
		≥4mG	OR 5.53 [1.15 – 26.6]
Schüz et al. 2001b	CNS tumors	<2mG (Md 24h)*	
		≥2mG	OR 1.67 [0.32 – 8.84]
		<2mG (Md night-time)*	
		≥2 mG	OR 2.60 [0.45 – 14.9]
Mizoue et al. 2004	All hematopoietic	0% area intersection*	
		<50%	IRR 1.6 [0.5 – 5.1]
		>50%	IRR 2.2 [0.5 – 9.0]
Draper et al.2005	Leukemia	≥600m (from power line)*	
		200-600m	RR 1.22 [1.01 – 1.47]
		<200m	RR 1.68 [1.12 – 2.52]
	Brain tumors	≥600m (from power line)*	
		200-600m	RR 1.18 [0.95 – 1.48]
		<200m	RR 0.74 [0.47 – 1.15]
	Others	≥600m (from power line)*	
		200-600m	RR 0.96 [0.82 – 1.12]
		<200m	RR 0.88 [0.62 – 1.25]
Perez et al. 2005	Leukemia	<1mG*	
		1 mG	OR 1.46

Study	Endpoint	Exposure category	Outcome [95% CI]
		5 mG	OR 6.72
		10 mG	OR 45.15
Kabuto et al. 2006	ALL+AML	<1mG (1wk TWA)*	
		1-2mG	OR 0.93 [0.51 – 1.71]
		2-4mG	OR 1.08 [0.51 – 2.31]
		≥4mG	OR 2.77 [0.80 – 9.57]
	ALL+AML	<1mG (1wk night-time)*	
		1-2mG	OR 0.97 [0.52 – 1.79]
		2-4mG	OR 1.08 [0.47 – 2.47]
		≥4mG	OR 2.87 [0.84 – 9.88]
	ALL	<1mG (1wk TWA)*	
		1-2mG	OR 0.87 [0.45 – 1.69]
		2-4mG	OR 1.03 [0.43 – 2.50]
		≥4mG	OR 4.67 [1.15 – 19.0]
Mejia-Arangure et al. 2007	ALL+AML	<1mG (spot)*	
		1-4mG	OR 0.94 [0.37 – 2.4]
		4-6mG	OR 0.88 [0.15 – 5.1]
		≥6mG	OR 3.7 [1.05 – 13]
		Low (Kaune-Savitz)*	
		Medium	OR 5.8 [0.92 – 37]
		High	OR 4.1 [0.66 – 25]
Feizi & Arabi 2007	Leukemia	≤4.5mG*	
		>4.5mG	OR 3.60 [1.11 – 12.39]
Lowenthal et al. 2007	LPD+MPD	>300 m from power line*	
		0-300 m (at age 0-15)	OR 3.23 [1.26 – 8.29]
Yang et al. 2008	AL with XRCC1 Ex9 + 16A allele	>500 m from power line*	

Study	Endpoint	Exposure category	Outcome [95% CI]
		0-500 m	OR 2.37 [0.94–5.97]
		>100 m from power line*	
		0-100 m	OR 4.31 [1.54–12.08]
		>50 m from power line*	
		0-50 m	OR 4.39 [1.42–13.54]
Abdul-Rahman et al. 2008	Leukemia	>200 m from power line*	
		0-200 m	OR 2.30 [1.18–4.49]
Malagoli et al. 2010	All hematological malignancies	<1mG*	
		≥1mG	OR 2.4 [0.4-15.0]
	Leukemia	<1mG*	
		≥1mG	OR 6.7 [0.6-78.3]
	ALL	<1mG*	
		≥1mG	OR 5.3 [0.7-43.5]
Kroll et al. 2010	Leukemia	<1mG*	
		1-2mG	OR 2.00 [0.50–7.99]
		2-4mG	0 case/ 2 controls
		≥4mG	OR 2.00 [0.18–22.04]
	CNS/brain tumors	<1mG*	
		1-2mG	OR 0.50 [0.09–2.73]
		2-4mG	1 case/ 0 control
		≥4mG	OR 0.33 [0.03–3.20]
	Other cancers	<1mG*	
		1-2mG	OR 0.33 [0.07–1.65]
		2-4mG	OR 1.00 [0.14–7.10]
		≥4mG	OR 5.00 [0.58–42.80]
Sohrabi et al. 2010	ALL	>400 m from power line*	
		0-400 m	OR 2.75 [1.59 – 4.76]
Saito et al. 2010	Brain tumors	<1mG bedroom*	
		1-2mG	OR 0.74 [0.17–3.18]
		2-4mG	OR 1.58 [0.25–9.83]

Study	Endpoint	Exposure category	Outcome [95% CI]
		≥4mG	OR 10.9 [1.05–113]
Does et al. 2011	Leukemia	<0.25mV contact current	
		0.25-1.5mV	OR 0.98 [0.63 – 1.53]
		≥1.5mV	OR 0.99 [0.65 – 1.52]
		<0.1mG*	
		0.1-0.2mG	OR 0.96 [0.57 – 1.62]
		0.2-0.5mG	OR 1.23 [0.74 – 2.04]
		≥0.5mG	OR 1.18 [0.71 – 1.96]
Wünsch-Filho et al. 2011	ALL	≥600 m from power line*	
		200-600 m	OR 0.69 [0.28–1.71]
		100-200 m	OR 1.67 [0.49–5.75]
		<100 m	OR 1.54 [0.26–9.12]
		≥600 m from power line*	
		200-600 m (never moved)	OR 0.91 [0.25–3.25]
		100-200 m	OR 3.68 [0.68–19.82]
		<100 m	OR 1.52 [0.11–21.24]

* Reference category

[a] Computed from table 5 of the original publication (could be biased due to not considering individual matching)

[b] Computed from table 5 of the original publication

[c] Quartiles of exposure distribution of controls (exposure calculated)

[d] Reference categories: Without the respective appliance near the residence

OR…odds-ratio, SIR…standardized incidence ratio, RR…relative risk, IRR…incidence rate ratio, LCC…low-current code, HCC…high-current code, UG…underground cable, VLCC…very low current code, OLCC…ordinary low current code, OHCC…ordinary high current code, VHCC…very high current code, Md…median, TWA…time weighted average, AM…arithmetic mean, ALL…acute lymphoblastic leukemia, AML…acute myeloid leukemia, LPD…lymphoproliferative disorders, MPD…myeloproliferative disorders