



SECTION 11

Evidence For Childhood Cancers (Leukemia)

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I. Introduction

Since the seminal work of Wertheimer and Leeper (1979) more than two dozen 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 controversy whether the observed relationships between exposure to power-frequency EMFs and childhood cancer (in particular leukemia) can be causally interpreted. Based on these 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 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; Greenland 2003) 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. As a consequence, the International Agency for Research on Cancer (IARC) concluded in 2001 that power-frequency EMFs are a possible human carcinogen (Group 2B). This classification was based on the evidence from epidemiological studies of childhood leukemia because the panel rated the evidence from all other types of cancer, from long-term animal experiments and mechanistic studies as inadequate.

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. glass wool, lead, styrene, Lindane, 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. 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.

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.

A. Epidemiological Studies of Power-Frequency EMF and Childhood Cancer

Table 11-2 gives a synopsis of studies on childhood cancer and exposure to power-frequency EMF, Table 11-3 presents the main findings of these investigations. Most often assessment of exposure was by measurements with 12 studies measuring for at least 24 hours up to 7 days, and 8 studies with spot measurements. Ten studies used distance from power lines as a proxy (some in combination with spot measurements) and 11 studies used wire codes classified according to the Wertheimer-Leeper or Kaune-Savitz methods. Several investigations covered more than one endpoint with hematopoietic cancers the most frequently included malignancies (overall 23 studies), followed by nervous system tumors (11 studies) and other cancers (8 studies). All childhood cancer cases were assessed by 8 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; Zaffanella, 1993; Zaffanella & Kalton, 1998).

Meta-analyses of wire-code studies (Greenland et al., 2000; 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

The only other endpoint except leukemia 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), whereas others have solely investigated CNS tumors (Gurney et al., 1996; Preston-Martin et al., 1996; Schüz et al., 2001a). 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.

II. Discussion

Power frequency EMFs are among the most comprehensively studied risk factors for childhood leukemia. 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 about these factors. Concerning power frequency EMFs few deny that the relationship is real and not due to chance, but still there is a controversy about the possibility that confounding, exposure misclassification, and selection bias is responsible for the observed relationship. 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.

A. 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):

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

(π_F is the prevalence of the confounder, Ψ_{DF} is the odds ratio for the confounder, 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. 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 in America, Europe, and Japan a confounder explaining this increased risk must not be quite strong and associated with magnetic fields of various sources but must also be present around 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.

B. 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. 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. It can easily be shown that in the case of rare exposures the greater effect on the risk estimate is

introduced by reduced specificity (hence by the presence of false positives). This may explain why longer measurement periods show a tendency to higher risk estimates. However, if the true exposure condition is actually not rare, sensitivity is more important and misclassification will result in a substantial underestimation of the true risk.

C. 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.

D. 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) were published, 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 comprehensive 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 up to now 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 convincing 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 events that lead to autonomous growth. Given this 100-fold 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.

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 assess their potential to facilitate transformation of already genetically damaged cells.

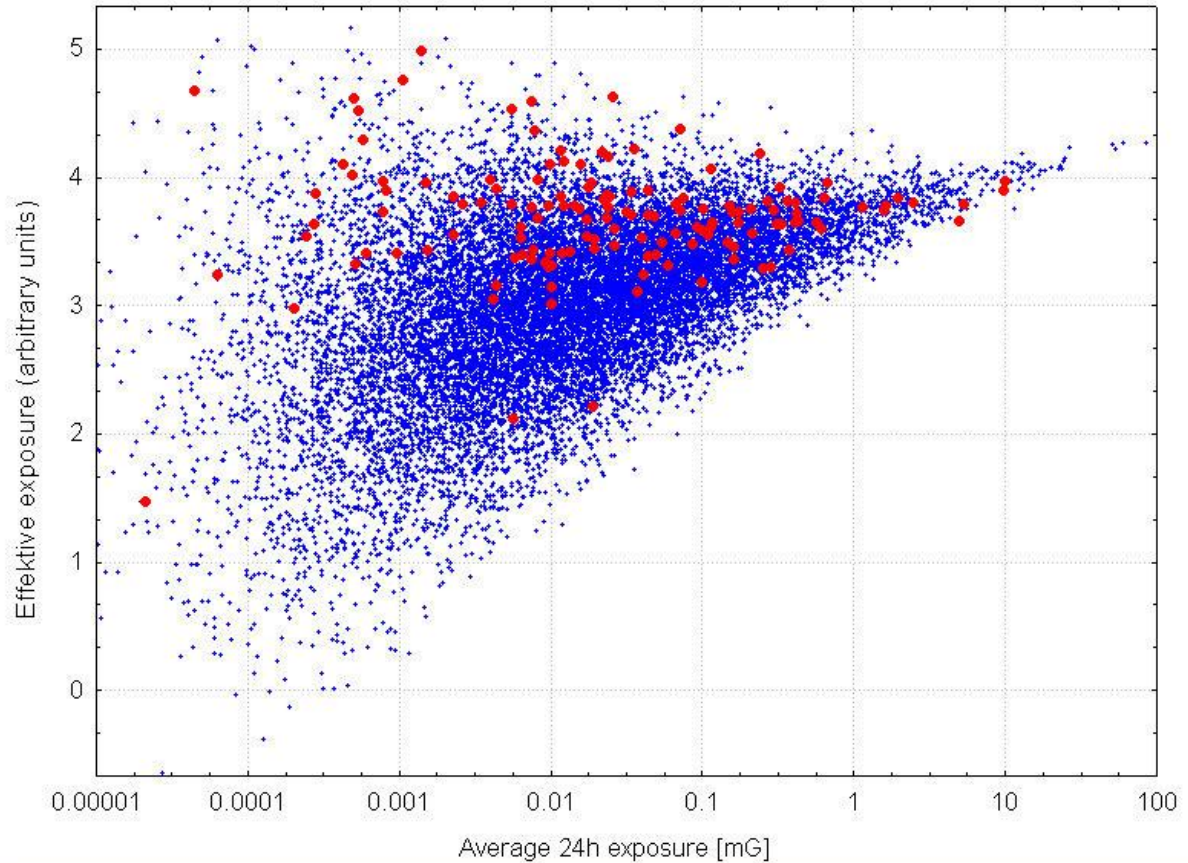


Fig. 1: Results of Monte Carlo simulation under the assumption of a log-normal distribution of average magnetic flux densities in the homes of children that are related to an assumed ,effective' exposure metric that follows the conditions a. and b. mentioned in the text. Blue are controls and red children 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.

III. 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.

Considering the possibility that aspects of exposure to power frequency EMFs that have not yet been detected may account for a great proportion of cases 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. 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.

- 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. Up to 80% of childhood leukemia may be caused by exposure to power frequency EMF.
- 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 are 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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