

# MINUTES

## Selection Bias in EMF–Childhood Leukemia

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### Participants

- Norman Breslow, *Department of Biostatistics, University of Washington*
- Raymond Greenberg, *Medical University of South Carolina*
- Sander Greenland, *Department of Epidemiology, University of California, Los Angeles School of Public Health*
- Robert Kavet, *Electric and Magnetic Fields Health Assessment Program, EPRI*
- Leeka Kheifets, *Radiation Studies Programme, World Health Organization*
- Mary McBride, *Cancer Control Research Programme, British Columbia Cancer Agency*
- Gabor Mezei, *Electric and Magnetic Fields Health Assessment Program, EPRI*
- Jörg Michaelis, *Institute of Medical Statistics and Documentation, University of Mainz*
- Charles Poole, *Department of Epidemiology, University of North Carolina School of Public Health*
- Susan Preston-Martin, *Department of Preventive Medicine, University of Southern California*
- Kenneth Rothman, *Boston University School of Public Health, School of Medicine*
- David Savitz, *Department of Epidemiology, University of North Carolina School of Public Health*

### Welcome and Introduction

Rob Kavet opened the workshop. In a brief introduction, Leeka Kheifets summarized recent evaluations by the National Institute of Environmental Health Sciences (NIEHS) and the International Agency for Research on Cancer (IARC). NIEHS concluded in its 1999 report to Congress that exposure to electric and magnetic fields (EMF) "cannot be recognized as entirely safe because of weak scientific evidence that exposure may pose a leukemia hazard." Earlier this year, IARC classified EMF as possibly carcinogenic. This classification was based largely on two pooled analyses of epidemiologic studies (Ahlbom et al. 2000, Greenland et al. 2000) that found a consistent association between childhood leukemia and exposure to EMF above 0.3–0.4 microtesla (m T). However, the association could result at least partially from chance, confounding, or, more likely, selection bias. Although data from the studies reviewed may be insufficient to determine whether selection bias—usually stemming from participation problems—is responsible, the design of future studies would help clarify this question. Further investigation remains important, particularly as the upcoming construction of new electricity transmission lines and generation plants will increase concerns about EMF.

### Survey Results

Gabor Mezei presented the results of a survey on the role of selection bias in individual childhood leukemia studies that was mailed to participants other than EPRI staff prior to the workshop. Eight participants completed and returned the survey. According to the respondents' judgments, there was no association between the probability of selection bias and the magnitude of effect estimates in the individual studies, and adjustment for selection bias was unlikely to substantially change the magnitude of effect estimates. Respondents thought that selection bias was more likely in studies using random-digit dialing (RDD) for control selection (mean probability in individual studies ranged between 57 and 81%), less likely in more recent studies (mean probabilities, 34–68%), and

unlikely in the Scandinavian studies (mean probabilities, 8–11%). Other types of bias were thought to be potentially important regardless of study design.

On average, respondents estimated the likelihood that EMF is causally related to childhood leukemia to be 35% (range, 5–50%). According to their judgment, the probability that the question of causality will be resolved through reanalysis of available data is 17% on average (range, 0–40%), and the probability that new methodology will resolve the question is

39% on average (range, 10–80%).

In the survey, respondents recommended that the workshop focus on available data on selection bias; hypotheses about patterns; further data to test hypotheses; measurement error; target populations; and alternative and improved methods of control selection. For new studies, they suggested investigating calculated fields; conducting a full risk analysis of all available data using explicit parameters for all sources of uncertainty; doing a combined analysis of nighttime exposure data; and waiting for determination of the relevant exposure metric. Other suggestions were determining the genetics of exposed cases; conducting registry-based studies with a higher prevalence of elevated exposure; and conducting cohort studies focusing on socioeconomic status (SES).

### **Summary of EMF–Childhood Leukemia Studies**

David Savitz reviewed major studies of EMF and childhood leukemia (Wertheimer and Leeper 1979, Savitz et al. 1988, London et al. 1991, Feychting and Ahlbom 1993, Olsen et al. 1993, Verkasalo et al. 1993, Linet et al. 1997, Michaelis et al. 1997, Schüz et al. 2001, Dockerty et al. 1998, 1999, McBride et al. 1999, Green et al. 1999, UK Childhood Cancer Study 1999, 2000), describing their progression with respect to control selection, exposure assessment, consideration of confounding, and focus on high fields.

Control selection, a concern in the Savitz and London studies, was less problematical in the Scandinavian studies by Feychting and Ahlbom, Verkasalo, and Olsen. The Linet study represented a marked expansion in study size, used concurrent control selection, and assessed exposure more completely than previous studies. Later studies tended to be larger, well-designed, and methodologically sound, relying primarily on measured fields. Scientific discussion shifted to fields as opposed to lines, and later concentrated on unusually high fields.

Exposure assessment in the initial Wertheimer and Leeper study consisted of wire coding to estimate magnetic fields from power lines. In the Savitz study, exposure assessment broadened to include spot measurements. The London study introduced limited 24-hour measurements; the Scandinavian studies used historical reconstruction to estimate fields; and the McBride study added personal exposure monitors. In the more recent studies, measurements have been of longer duration, with the opportunity to focus on specific periods of time.

The wire-code paradox first arose in the London study, which found an association between childhood leukemia and wire codes (relative risk,  $RR = 2$ ), but not measured fields. However, measurements in the London study were limited. No association with wire codes has been observed in recent studies. The possibility remains that wire codes may have a proxy value for high fields.

In the early studies, confounding was a major concern; high fields correspond to adverse conditions generally. However, adjustment for the few known risk factors or for correlates of high fields, such as traffic density or type of housing (rented or owned), made little difference.

High fields have increasingly been a focus in childhood leukemia studies, particularly in the pooled analyses. Even the earliest studies indicated stronger associations with cutpoints

$> 0.3$  m T. The Olsen study first suggested that magnetic field effects might be limited to higher fields; the Linet study supported this suggestion. A reexamination of how fields

$> 0.3$  or  $0.4$  m T arise is needed. High measured fields could be a marker for other aspects of exposure.

Savitz concluded that repeating any previous studies would be inefficient, and suggested designing a new, large study free of selection bias, with a greater prevalence of high-exposure homes.

## **Beyond Sensitivity Analysis for Bias in EMF Studies**

Sander Greenland discussed the limitations of sensitivity analysis in epidemiologic studies and the advantages of using a Bayesian alternative. Used to address the problem of unidentified parameters governing bias, sensitivity analysis can be misleading in that the range of parameter variation may be under- or over-encompassing. Sensitivity analysis is usually based on a sparse and nonrandom selection of parameter values. Additionally, it must be carried out for each aspect of bias, followed by synthesis of the results. Sensitivity analysis can also be Bayesianly misleading when inferences are drawn regarding plausibility.

A Bayesian alternative would involve taking note of any prior expectations, translating them into distributions for parameters, and performing an update based on new observations. Background judgments about what is likely could thus be employed without overstating any prior certainty about what is possible.

In conclusion, Greenland stated that a Bayesian analysis is an advance over a conventional analysis when the model underlying the former subsumes the model underlying the latter.

### **Evidence concerning Selection Bias in the Canadian EMF–Childhood Leukemia Study**

Mary McBride explored evidence for selection bias in her 1999 study of EMF and childhood leukemia among Canadian children who were resident in one of five provinces. Cases were children aged 0–14 years diagnosed with all leukemias between January 1990 and December 1994 or (in two provinces) in June 1995. Cases were ascertained through pediatric oncology centers and cancer registries. Controls, matched 1:1 to cases for sex, birth date, and province of residence, were randomly selected from population-based provincial medical insurance rolls.

EMF exposure assessment included 48-hour personal monitoring, front-door and perimeter spot measurements, and 24-hour bedroom measurements, as well as wire coding. Interviews with parents assessed appliance use. A complete residential history and interviews using a questionnaire on other potential risk factors provided further data.

Of 445 eligible cases, 399 (90%) responded. Of 525 eligible controls, 399 (76%) responded. All participants were interviewed. For exposure assessment, 79% wore personal monitors. Wire coding was done for 74% of residences and perimeter measurements, for 63%.

A possible source of selection bias is case and control identification. In this study, the sources used to identify both cases and controls represented the same base population. However, the provincial medical insurance rolls used for control selection would have missed illegal immigrants, anyone not resident in a province for at least three months, and anyone who did not enroll owing to inability to pay the insurance premium.

Another potential source of selection bias is differential response among cases and controls. Of 675 potential controls, 149 could not be contacted, 399 consented to participate, and 127 refused to participate. The main reason for inability to contact potential controls was that their addresses were incorrect.

Participating controls were more residentially stable than cases and generally had a higher socioeconomic status. Potential controls refusing to participate, however, had a lower median income than participating controls. They also had a significantly higher proportion of very high wire code configuration (VHCC) homes, and significantly more of them lived in apartments. The SES of first-choice controls was not different from that of cases. An SES bias could be present that could be explained by identification and response bias. However, study results, which provided little support for an association between EMF and childhood leukemia, did not change much after adjustment for residential mobility and SES (adjusted odds ratio, OR = 0.95 for personal magnetic fields). Selection bias thus does not seem to have been an influence.

### **Evidence concerning Selection Bias in the German EMF–Childhood Leukemia Study**

Jörg Michaelis discussed the study of EMF and childhood leukemia published in 2001 by Schüz et al. This study investigated the risk of acute leukemia among children exposed to magnetic fields

above 0.2 m T and sought to confirm or refute the findings of two smaller studies by the same group (Michaelis et al. 1997, 1998) indicating an increased risk with exposure to stronger fields at night. The Schüz study, part of a previous population-based case-control study of childhood cancers, included children under age 15 living in West Germany who were diagnosed with acute leukemia between 1990 and 1994. Cases were identified from the German Childhood Cancer Registry and matched for gender, date of birth, and community with controls identified from local resident registration files.

EMF exposure was assessed using 24-hour measurements in children's bedrooms and in the living rooms of their homes. The home where a child lived longest before the reference date (date of diagnosis for cases or corresponding time for controls) was used for measurements. Because some subjects had more than one relevant residence, a total of 2935 residences were considered for the study. Measurements were made in 1815 residences (62%) of 514 cases and 1301 controls. The study reported an odds ratio of 1.55 for median 24-hour magnetic field measurements  $\geq 0.2$  m T (9 cases and 18 controls). For nighttime measurements  $\geq 0.2$  m T, the OR was 3.21 (12 cases and 12 controls).

Of eligible leukemia cases, 73% were contacted and 48% participated in the study. Of controls, 64% were contacted and 42% participated. The main reasons for nonparticipation were refusals (19%), inability to trace residences (14%), and renovation of residences (4%).

To explore the possibility of selection bias, study participants were compared with "partial participants" who took part in interviews but not in EMF exposure measurements. Partial participants were more likely than participants to be urbanized and less likely to have high SES. They were more likely to have mothers who were younger than 20 years old at delivery and to have mothers who smoked during pregnancy. Partial participants also tended to be more residentially mobile and to live in apartments.

Evidence for differential selection bias was found for SES, family income, and maternal age at delivery. Non-differential selection bias was observed for degree of urbanization, maternal smoking, residential mobility, and housing type. Differential selection bias could be partially responsible for elevated ORs; however, the observed association between acute leukemia and EMF exposure is probably not due to selection bias.

### **Evidence concerning Selection Bias in the NCI Study**

Gabor Mezei summarized a reanalysis by Hatch et al. (2000) of confounding and selection bias in the National Cancer Institute (NCI) study (Linnet et al. 1997). The reanalysis compared the relation between childhood acute lymphoblastic leukemia (ALL) and wire codes or magnetic field measurements among study participants and partial participants. Partial participants were those who refused in-person interviews and indoor measurements but allowed telephone interviews and front-door measurements.

Excluding partial participants increased the OR for ALL by 23% among those living in VHCC homes. Smaller increases in odds ratios occurred when partial participants were excluded from comparisons using direct measurements. Because partial participants generally had lower SES, selection bias is a possibility in the NCI study.

Adjustment for individual confounding variables changed the OR for ALL in the NCI study by less than 8%, while multivariate adjustment lowered the OR by 15%. The authors concluded that confounding alone is not likely to explain the results of previous studies and that selection bias is more of a concern.

### **Control Selection Issues**

Charles Poole offered some thoughts on possible sources of selection bias in EMF-childhood leukemia studies and their direction and magnitude. He observed that selection bias may arise from a biased sampling frame; for example, all of the controls in a study may have telephones, while some of the cases may not. A biased sample may be chosen from such a frame; for example, there would

likely be a lower sampling probability for low-SES controls who have phones. Selection bias may also stem from nonparticipation or from missing data. It may involve wire codes, interviews, or field measurements. In the Savitz study (1988), for instance, the OR for leukemia for all participants living in high current configuration homes compared with those living in low current configuration homes was 1.5. An increased OR of 1.7 was observed for participants who were interviewed, and the OR was 1.8 for those with measurements.

Adjustment for SES-related bias may not be sufficient if measures of SES do not accurately reflect the underlying characteristics related to exposure and selection, or if specification of measured variables is poor. Whether mobility needs to be adjusted for in estimating the SES-leukemia association needs to be considered.

Nonconcurrent case and control selection and enrollment is another issue. The lag time between case enrollment and diagnosis increases missing data for cases. Similarly, control selection and enrollment after case diagnosis increases missing data for controls and can reduce the sampling frame for each control to a subset of the case's risk set. These issues are complex and differ in each study.

Poole pointed out that early studies of childhood leukemia (beginning with Sacks 1947) almost all showed a positive association between SES and risk of leukemia. In contrast, later studies showed a negative association. This difference may result from changes in methodology. An alternative explanation is that the difference is real. This explanation may be congruent with Greaves's hypothesis, which suggests a viral etiology for leukemia, so that in the early studies, children with lower SES and thus lower levels of hygiene with more exposure to viruses may have acquired immunity.

### **Contact Current, EMF, and Childhood Leukemia**

As an alternative to selection bias, Rob Kavet proposed the hypothesis that exposure to contact current may explain the association between EMF and childhood leukemia observed in epidemiologic studies. Contact current typically flows from one hand to the other or from a hand through the feet when a person simultaneously touches two conductive surfaces—a water faucet and a refrigerator, for example—with different electrical potentials, or voltages.

In the United States, many residences are wired and grounded such that contact voltages are generated when conductive surfaces are in physical contact with the grounding system. This system consists of neutral and grounding wires along which electric current from a residence returns to the transformer and substation.

Using computer modeling of a hypothetical neighborhood, Kavet et al. (2000) have reported a correlation between contact voltage and residential magnetic fields. Dawson et al. (2000) reported that dosimetry modeling indicates that, unlike magnetic field exposure, contact current can produce a tissue dose that could plausibly lead to biological effects. A current of only 10 microamperes (mA) flowing into a child's hand exposes approximately 5% of the bone marrow of the arm to an electric field of about 130 millivolts per meter (mV/m). According to NIEHS, a tissue dose of 1 mV/m is biologically significant. The tissue dose produced by a 1-m T magnetic field is about one order of magnitude less than this dose.

Kavet and Zaffanella's just-completed pilot study (submitted) investigated contact voltages in 36 single-family and duplex residences in Pittsfield, Massachusetts. The study found that the voltage between the earth and the main water pipe to which the neutral return wire for a residence is grounded could serve as a source of contact voltage from the faucet to the drain of a bathtub. Children could thus be exposed to contact current whenever they touch a bathtub faucet while bathing; being wet would facilitate an electrical bond. However, exposure can occur only if a residence has conductive (metal) plumbing and a conductive drain without a metal drain lever. The pilot study found a correlation between water-pipe-to-earth voltage and spot-measured magnetic fields. Neither voltage nor fields were related to wire codes. Both magnetic fields and water-pipe-to-

earth voltage were higher in residences located near high-voltage transmission lines, most likely due to magnetic field induction.

The study also examined voltage, generated by current in the grounding wire, between appliances and the water pipe. This voltage appears between conductive appliance frames and water fixtures. Study results indicated no relation to either wire code or line type. Children are not likely to be exposed, and dry skin and footwear would impede a large body dose. In contrast, a large dose is possible for children exposed to contact current in bathtubs.

## **Discussion**

Workshop participants concluded that differential participation of cases and controls based on their socioeconomic status is the most likely source of selection bias in EMF–childhood leukemia studies, usually increasing the apparent strength of an association. However, they deemed exposure misclassification as important a source of error as selection bias.

The discussion focused on research to clarify the role of selection bias in epidemiologic studies and minimize its occurrence in future studies. Reanalyses of existing data, new cohort studies, and novel control selection methods were suggested and ranked according to scientific merit. The following summary lists recommendations for each of these areas in order of importance. Research topics are marked with one to three asterisks according to merit.

### **Reanalysis of existing data**

- \*\*\* Conduct an uncertainty analysis incorporating other sources of error (bias, confounding, and misclassification).
- \*\*\* Revisit homes with high magnetic field measurements. Also, look at the relation between magnetic field exposure and contact current.
- \*\*\* To study selection bias, examine socioeconomic factors most closely associated with participation, as well as random-digit dialing bias factors and the issue of nonconcurrency.
- \*\* Reexamine nighttime magnetic field measurements, especially for younger children, in previous studies.
- \* Look at selection bias in studies of childhood brain tumors and exposure to EMF.
- \* Reexamine wire codes and type of housing for eligible subjects who refused to participate in previous studies. Attempt to gain permission to enter the residences of nonparticipants by offering money as compensation (\$50 was the suggested amount).

### **Pilot work for new cohort studies**

- \*\*\* Revisit the SES association with the incidence of childhood leukemia.
- \*\* Determine the feasibility of a Web-based cohort study in which in elementary- or middle-school science teachers would enroll children's newborn siblings. A nested case-control study could then be conducted using mailed-in exposure meters.
- \*\* Conduct a cohort study of children enrolled from prenatal clinics.
- \*\* Conduct a cohort study of children enrolled from health maintenance organizations.
- \*\* Conduct a cohort study of children enrolled from pediatric care offices.

### **Pilot work on novel control-selection methods**

- \*\*\* Recruit cousins of cases living in the same geographical area to serve as controls in a case-control study, since cousins would likely have similar SES.
- \*\*\* Conduct a pilot case-control study to be followed by a cohort study in China (where pregnant women are required to register).
- \* Select cases and controls for a new study from high-SES strata only.
- \* Use hospitals or multiple sources or both for control selection.