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CHILDHOOD LEUKAEMIA

AND EXPOSURE TO ELECTRIC AND MAGNETIC FIELDS

by

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A thesis submitted in conformity with the requirements
for the degree of Doctor of Philosophy
Graduate Department of Community Health
University of Toronto

CHILDHOOD LEUKAEMIA

AND EXPOSURE TO ELECTRIC AND MAGNETIC FIELDS

Lois Margaret Green - Doctor of Philosophy, 1998

Graduate Department of Community Health, University of Toronto

A population-based case control study was conducted in southern Ontario to assess the relationship between paediatric leukaemia and a number of environmental factors, of which exposure to electric and magnetic fields (EMF) was of primary interest. Children diagnosed with leukaemia during the period 1985-1993 who were less than 15 years of age at the time of diagnosis were ascertained from the records of the Hospital for Sick Children (Toronto). Controls were randomly selected from a data base created using teledirect marketing lists applicable to the defined study catchment area and were individually matched to the cases on year of birth and sex.

A total of 201 cases and 406 controls were identified. Information relating to demographic and potential risk factors for leukaemia was collected through detailed personal interviews. For current and previous residences occupied by the child within the catchment area during the defined period of inquiry, point-in-time measurements of magnetic fields both inside and outside the home were made. Residences were categorized according to three different wire code classifications. If the residence in which the child was living at the time of interview was relevant to the period of inquiry, the child wore a personal monitor for approximately 48 hours.

The findings reported in this thesis are based on the subset of 338 children (108 cases and 230 controls) with EMF measurements derived from personal monitoring. The child's residence accounted for almost 80% of the total average exposure for most children. There was evidence of an association between exposure to magnetic fields measured by monitoring the child's usual activities at home and increased risk of developing leukaemia. The risk was more pronounced for children who were diagnosed at less than six years of age and those children with acute lymphoblastic leukaemia. After

adjustment for potential confounders, residential magnetic field exposures of 0.18μT or more were associated with an odds ratio of 4.79 (95% confidence interval 1.66-13.88). When magnetic field exposures in the home were corrected for power consumption, the resulting odds ratios for all exposure levels above the referent (exposures of 0.04μT or greater) were significantly elevated.

Point-in-time measurements of magnetic fields within the child's residence (child's bedroom and two other rooms frequently occupied by the child) were associated with elevated but non-significant odds ratios. No relationship was observed with electric fields as measured by personal monitoring nor with wire configuration.

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It is my hope that the efforts of all those who have contributed will advance our understanding of the causes of leukaemia in young children.

TABLE OF CONTENTS

LIST OF TABLES

APPENDICES

Chapter 1

INTRODUCTION

Background

In 1979 Wertheimer and Leeper reported an association between childhood cancer and close residential proximity to power line configurations associated with high electrical currents and attendant magnetic fields. This study had methodological limitations which caused some to question whether the findings had a valid scientific basis. Nevertheless, their work has come to be regarded as a sentinel study upon which almost two decades of research have followed in the attempt to better understand the relationship which was proposed by the authors.

Extensive research since that time has not resolved the question of whether electric and magnetic fields (EMF) increase the risk of cancer. The issue is controversial not only in the scientific domain but also politically, since the putative exposure (as presently envisioned) is ubiquitous and its mitigation could have profound cost implications.

The research has spanned many scientific avenues from laboratory studies focusing on carcinogenicity and toxicology, to epidemiology. There are proponents both for and against the proposed etiologic association between exposure to electric and magnetic fields at the generating frequency (60 Hertz) in the electric power distribution system and the risk of childhood cancer. Doll (1996) has recently suggested that there is "some good quality epidemiological evidence that residence near high-power electricity cables producing magnetic fields in houses of the order of 0.2μT and above may approximately double the risk of childhood leukaemia". The National Academy of Sciences issued a statement in October 1996 claiming that their evaluation of the current body of evidence does not show that exposure to power-frequency electric and magnetic fields presents a human health hazard (Committee on the Possible Effects of Electromagnetic Fields on Biological Systems, 1996). Such disparate views have contributed to the public concern and have furthered interest in continuing scientific research to help resolve the uncertainties.

The literature relating to whether electric and magnetic fields cause cancer has been subjected to many reviews using such approaches as statistical meta-analyses and the more qualitative application of the causality criteria proposed by Bradford Hill (Hill, 1965). To a large extent the EMF issue has been driven by the epidemiological research and the primary reason for this is the consistency with which some of the associations have been observed.

While not all studies have shown uniform risk estimates, depending upon the health outcome, the character of the study population and the type of EMF measurement, some consistency has been observed in spite of methodologic and geographic differences between studies. The greatest consistency of findings relates to studies of children, specifically those with leukaemia, and EMF exposure as defined by wiring configuration.

However, to date there has been a notable failure to identify a biologic mechanism by which exposure to electric and magnetic fields might cause adverse health effects in humans: it is this fact which strengthens the possibility that EMF is not causally related to cancer.

There is also the question of 'dose response'. With the absence of an established, or even suspected, biologic mechanism, it is difficult to determine what, if any, is the biologically relevant metric for the exposure. Many surrogates of EMF exposure have been applied. Increasing risks with residential proximity to power lines with high current capacity "high wire configurations" have been observed, but the extent to which the wire code is an accurate index of exposure and, indeed long-term exposure, has not been demonstrated and remains the subject of ongoing research.

Objectives

This thesis describes a study designed to investigate the association between paediatric leukaemia and a number of environmental factors of which exposure to electric and magnetic fields is of primary interest.

The risk of leukaemia in children will be evaluated according to more accurate measures of personal exposure than those used in previous research. Electric and magnetic field exposures as measured by personal monitors will be used to examine the relationship with paediatric leukaemia. This represents the first study to report electric and magnetic field exposures as recorded by personal monitors actually worn by children at home, in school and in other locations.

Chapter 2

OVERVIEW OF THE LITERATURE

Descriptive Epidemiology of Childhood Leukaemia

Leukaemia is the most common malignancy of childhood and is the second most frequent cause of death in children, second only to mortality due to accidents. Despite its importance in terms of morbidity and mortality in childhood where potential years of life lost can be considerable, childhood leukaemia is not common.

The significant progress which has been made in the treatment of paediatric leukaemia and the recent work which has helped to establish possible leukaemogenic mechanisms have not been paralleled by advancement of understanding of the etiology of this malignancy. Much research has been done and some causal factors clearly identified, but the extent to which these account for the current incidence of paediatric leukaemia is thought to be small.

Descriptive epidemiology studies have been limited in their contribution of etiologic clues because of artifactual aspects relating to diagnosis, reporting and classification. Diagnostic accuracy depends entirely upon the availability of medical expertise and technology and as a result there are wide variations in the quality of case ascertainment in the world. There is considerable variation in reporting and registration of childhood leukaemia incidence and mortality both between and within countries which has made meaningful international comparisons difficult (Devesa et al., 1984; Draper et al., 1994).

The specificity of leukaemia classification has been greatly aided by the progress in clinical and laboratory techniques which have contributed to changes in the criteria for diagnosis and the methods of classification (Birch and Marsden, 1987). The leukaemia rubrics of the International Classification of Diseases reflect these advances and accordingly have changed substantially over the 'decade' revisions. In the sixth revision (adopted in 1948) there was no distinction between acute and chronic leukaemia but with

each subsequent revision, there has been refinement of the categories such that in the ninth revision there are five broad categories by which to classify leukaemia and several more at the fourth digit level. As a result, descriptive epidemiology according to specific diagnostic subgroups of childhood leukaemia has only been possible since the 1950's.

Secular trends both nationally and internationally in childhood leukaemia incidence are very difficult to interpret because of changes relating to diagnosis, reporting and histopathologic classification, although Draper et al. (1994) have concluded from a comprehensive review of childhood cancer rates around the world that there is "some limited evidence for a small increase in the incidence of ALL".

The available vital statistics information has suggested that since about 1911 there has been a steady increase in the incidence and mortality of childhood leukaemia. The increase was particularly dramatic in the 1950's and then showed a leveling off. Today some reports claim that a slight increase in incidence is still evident while others suggest there may be a slight decline. Recently reported amendments to the annually released cancer statistics by the National Cancer Institute (US) showed an increase in childhood cancers overall for the period 1973-1990 and, particularly, for acute lymphoblastic leukaemia (Desch and Bleyer, 1994). There has been controversy as to whether the early pronounced increase was in fact real or artefactual. Although the secular increase is generally thought to be real, the magnitude of the apparent increase is clouded by the complexities cited previously.

Ontario cancer statistics for the period 1964 to 1991 show an average of 96 paediatric leukaemias diagnosed each year among children 0-14 years resident in Ontario. This reflects an overall incidence of 4.7/100,000 in children aged 0-14 years, 5.2/100,000 for males and 4.2/100,000 for females. Incidence was highest among children 0-4 years (7.9/100,000) at time of diagnosis and lowest for those 10-14 years (2.5/100,000) (Ontario Cancer Registry, 1996). In Ontario, there has been a very slight, but non-

significant, increase in the incidence of childhood leukaemia over the period of cancer registration.

Relative to adult leukaemia, childhood leukaemias are histologically more homogeneous. In developed countries, approximately 85% of paediatric leukaemias are acute lymphoblastic, but this proportion varies according to age at diagnosis. Acute lymphoblastic leukaemia (ALL) is more common at younger ages and there is a dramatic peak at two to four years of age that is not present for other histologic types and is sometimes absent for ALL in developing countries (Robison and Ross, 1995).

Males are slightly more affected than females with the exception of leukaemias in those less than one year of age where the incidence for females is higher.

Descriptive epidemiology studies have indicated with some consistency that higher socioeconomic status is associated with an increased risk of leukaemia. However, socioeconomic factors are defined by many aspects of lifestyle which can confuse and create difficulties in disentangling these factors from true etiologic agents.

Leukaemia incidence shows some urban/rural differences with an apparent higher incidence of childhood leukaemia in urban populations compared to rural. The reason for this is clouded by the fact that urban residence is closely tied with other measures such as socioeconomic status and occupation.

Although occupation may not seem directly relevant to children, it may be indirectly relevant through parental occupation. Occupational exposures of both the father and mother, in the pre-conception, pre-natal and post-natal periods are increasingly the subject of research.

Studies of Cancer and Exposure to Electric and Magnetic Fields

At power frequencies (60 Hertz), there is no constant quantitative relationship between electric field strength and magnetic flux density, and therefore it is necessary to measure these components separately. Electric field strength is measured in volts/meter and depends upon the voltage in the circuit. Electric fields are easily perturbed and therefore, stable and reliable measures of personal exposures to electric fields are difficult to obtain. The attenuation of electric fields is so dominant that penetration of the body is minimal, however, these fields do induce currents in the body. Magnetic flux density is a measure of magnetic field strength per unit area and is quantified by units of tesla or gauss. In contrast to electric fields, power frequency magnetic fields easily penetrate the body and in general are not easily shielded. Current thinking is that the magnetic fields are the most biologically active.

In residential settings, the electric and magnetic fields vary temporally and spatially, making the measurement of human exposure difficult and complex.

The ability of epidemiologic research to assess the relationship between cancer risk and exposure to electric and magnetic fields (EMF) is very dependent upon the quality of the exposure assessment. The literature is reviewed by exposure circumstance, residential or occupational, and by subject, children or adults, with attention paid to the way in which EMF measurements were made.

Residential Studies

In 1979, Wertheimer and Leeper reported a statistically significant two- to threefold increase in leukaemia mortality in Denver, Colorado among children in residential proximity to wiring of high-current configuration (Wertheimer and Leeper, 1979). Exposure to EMF was assessed indirectly according to what has come to be known as the "Wertheimer/Leeper wire code". This code refers to a categorization of electrical wiring of power lines close to residences according to the number of conductors

and their diameters, location of transformers and service drops as well as the distance of the conductors from the home. A 'dose response' relationship was observed for homes with higher current configurations. Factors such as social class, traffic density, type of neighbourhood (urban versus rural) which the authors thought might be related to either the risk of leukaemia or magnetic field exposure were also taken into account. Fulton et al. (1980) attempted to replicate the study by Wertheimer and Leeper in Rhode Island with respect to only childhood leukaemia. No association was found but there was some indication that the replication of measurement methodology was not as close as originally claimed.

Subsequent studies accomplished some refinement of the wire code by including more comprehensive measures of the distance from the power lines or electrical installations and taking into account line loading. Power lines must be within approximately 100 metres for their effects to predominate over those generated in the homes by household wiring and appliances. Unfortunately these studies did not use identical 'sources' of electric and magnetic fields from which distances were measured making direct comparisons difficult.

Myers et al. (1990) studied childhood cancers in Yorkshire, England (1970-1979). No association between childhood cancer and proximity to overhead power lines for a child's residence at birth or for exposure to magnetic fields as calculated on the basis of line-network maps and load records was observed. The authors acknowledged the study's limited ability to detect an excess risk should one exist in those exposed to high levels of 'exposure' as few addresses, for cases or controls, had background levels of calculated magnetic fields exceeding 0.01μT.

In a case control study of childhood cancers in Sweden all cancers and cancers of the nervous system were found to be associated with proximity to 200 kVolt transmission lines and with measured residential magnetic field measurements >0.3μT (Tomenius et

al., 1986). No excess risk was observed for childhood leukaemia but a statistically significant excess of brain cancer was found. EMF exposure was considered for both birth residence and residence at the time of diagnosis. Controls appeared to be more residentially stable than the cases in this study but it was not possible to assess how this might have biased the results, if at all. Exposures to magnetic fields were assessed according to distance to electrical conductors and from calculations of magnetic fields from the source. Potential confounders were not considered in the analysis of this association.

Savitz et al. (1988) introduced further improvements in exposure assessment of magnetic fields by carrying out point-in-time measurements as well as wire code information in a case control study of incident childhood cancers among children in Denver, Colorado. Cases were those children diagnosed at 0-14 years and controls matched by age and sex were selected through random digit dialing to achieve further matching in terms of residence in the same telephone exchange area at the time the case was diagnosed. Of the 70% eligible cases, only 36% had measures of magnetic fields, whereas measurements were available for a substantially greater proportions of controls. Wire codes denoting high current configurations were correlated with higher measured magnetic fields within the home. However, wire codes associated with higher magnetic fields were more common among case than control homes. Odds ratios for total cancers, leukaemia and brain cancer, showed an association with wire code but not with the measured magnetic field exposures. The authors suggested that this might be due to the imprecise manner by which a current and point-in-time measurement predicts past exposure which is potentially the relevant etiologic exposure sought. They reasoned that wire codes are more stable over time and thus might "better approximate historical field levels". Savitz concluded that the data was "more supportive of a positive gradient relating to residential magnetic field exposures to childhood cancer risk than the absence of such a relationship". Although Savitz' conclusion related to all cancers, he further claimed that any trends or excesses observed showed a clearer pattern for leukaemia.

London et al. (1991) also tried to improve upon the measurement of EMF in their case control study of childhood leukaemia carried out in Los Angeles County, California. Three exposure measures were used: 24-hour magnetic field measurements in the child's bedroom, spot measurements of electric and magnetic fields and wiring configuration as defined by Wertheimer and Leeper. A non-significant association was observed between direct measures of magnetic fields and leukaemia (OR=1.69, 95% CI 0.71-4.00) and a statistically significant association (OR=2.15, 95% CI 1.08-4.28) for leukaemia risk and exposure according to the Wertheimer-Leeper high current configuration. As with some previous studies, this study was compromised by its ability to obtain EMF measurements for only half of the eligible cases and by other possible biases such as residential stability and housing characteristics which were not taken into account. Although the association of leukaemia risk with wire code was similar to that reported by Savitz et al. (1988) the mean magnetic field measurements associated with wire code in Los Angeles were lower than those observed in Denver. This, together with the unexplained seemingly wide discrepancy between 24-hour and spot measurements in the London et al. (1991) study furthers the question of what wire codes actually mean. Recommendations for further work were made which would clarify the possible effect of selection bias by assessing all eligible subjects, not just those who participated, and which would help determine whether the lack of association with direct measurements was due to measurement error.

Three Scandinavian studies relating magnetic field exposures and childhood cancer were published in 1993. The important distinction of the study in Sweden by Feychting and Ahlbom (1993) was their attempt to improve estimates of historical magnetic field exposures at the time of diagnosis using power line load data. With this calculated estimate of magnetic field exposure, significant associations with leukaemia risk were observed with the highest level (0.3μT) of exposure (OR=3.8, 95% CI 1.4-9.3). However, no associations were observed with contemporary exposures whether measured or calculated, findings consistent with those of Savitz et al. (1988) and London et al. (1991). The authors have suggested that calculated historical fields were reasonably good

predictors of past exposure and reasoned that the "lack of an association with spot measurements is consistent with the assumption that fields assessed through contemporary, short-term measurements are poor predictors of past exposure". In Denmark, Olsen et al. (1993) reported significant associations of all "major types of childhood cancer combined and exposure to magnetic fields from high voltage installations of $\geq 0.4\mu T$.". A pooled analysis of these two studies confirmed the findings of the components, showing an increased risk of childhood leukaemia (OR=5.1, 95% CI 2.1-12.6) in relation to magnetic field levels of $\geq 0.5\mu T$ (Feychting et al., 1995). In a Finnish cohort study investigating cancer risk, Verkasalo et al. (1993) found no evidence of an increased risk for leukaemia, or for all cancers, in children living close to overhead power lines. An elevated odds ratio for nervous system tumours for boys was observed with magnetic fields $\geq 0.2\mu T$. However, the small numbers and the fact that one boy had three primary tumours of the nervous system necessitates that the results be qualified.

A case control study of childhood leukaemia in Germany designed to test several etiologic hypotheses indicated an elevated but non-significant association between high-level exposure ($0.2\mu T$) and an increased risk of developing leukaemia based on 24-hour measurements of electric and magnetic fields in the bedroom of residence where the child had lived the longest and spot measurements in residences in which the child had been living for more than one year before diagnosis. The increased risk was based on only four leukaemia cases. This along with the fact that only 1.5% of the study population was exposed to magnetic fields $> 0.2\mu T$ weigh against the claim of a definitive association (Michaelis et al., 1997).

A nested case control study assessing cancer risk among children and proximity to high voltage power lines in Norway found no association with leukaemia or brain cancer but did find an excess risk for "other cancer sites" in relation to residences ≤ 50 metres from these lines. However, the numbers were small and firm conclusions were not possible (Tynes and Haldorsen, 1997).

The most recently published case control study evaluated acute lymphoblastic leukaemia in relation to wiring configuration and 24-hour measurements of magnetic fields in the child's bedroom, and magnetic field point-in-time measures in three to four other rooms and just outside the front door in the child's residence (Linet et al., 1997). Measurements covered a substantial proportion (95%) of defined reference period for 77% of the subjects. Slightly over 200 cases were eligible for the analyses of summary time weighted averages of magnetic fields in the home, although the study enrolled substantially more. Quartiles of exposure to magnetic fields were defined *a priori*. When applied to those subjects eligible for the summary averages of magnetic fields in the home, a substantial proportion of subjects (45%) were exposed to magnetic field levels of less than 0.065μT. The authors concluded that their findings provided little support for an association between leukaemia and the measured magnetic field exposure in the child's home(s). However, further subdivisions of the upper exposure quartile showed that one level of exposure (0.40-0.49μT) was associated with a significant increased risk in both the unmatched (OR=3.28, 95% CI 1.15-9.89) and matched (OR=6.41, 95% CI 1.30-31.73) analyses. For the highest level of exposure (≥ 0.5μT), similar elevations were not observed either for the unmatched (OR=1.41, 95% CI 0.49-4.09) or the matched (OR=1.01, 95% CI 0.26-3.99) analyses. While the stated conclusion cited lack of support for a relationship with measured magnetic field exposures and the risk of leukaemia, it would seem that insufficient numbers were available in the exposed category to demonstrate a risk should one exist. Linet et al. (1997) also found no evidence of increased risk of leukaemia with increasing wire code. Random digit dialing was used for the selection of controls according to the first eight digits of the telephone number. Depending upon how telephone numbers are assigned within the areas studied, it is possible that this has introduced some matching by neighbourhood and hence by wire code. This may partially explain why there was no evidence of an association with wire code.

There are fewer studies relating to adults. Wertheimer and Leeper (1982) attempted to replicate and to improve upon the methodology used in their original study of childhood cancers in an adult population in Denver, Colorado. They found statistically significant associations for all cancer mortality, cancers of the nervous system, uterus and breast and for lymphomas with increased exposure to electric and magnetic fields assessed by wiring configuration. A major problem with this study related to the fact that those carrying out the exposure assessment were not blind to the case control status of the subject and hence might have biased the results.

Coleman et al. (1989) used distance between residence and overhead power lines and electrical installations as well as a measure of the calculated magnetic field over a three-year period to evaluate adult leukaemia incidence in southeast England. A non-significant elevation in risk due to leukaemia in relation to residential exposure to EMF from power lines and transformer substations was found. However, the authors cautioned that the study had limited statistical power (less than 80%) to detect even a threefold excess in risk in relation to proximity to overhead power lines.

A retrospective population cohort based study was undertaken by McDowall et al. (1986) in East Anglia, England, examining cancer mortality for all ages in relation to distance from overhead power lines (30 metres) and from electrical installations (50 metres). The only statistically significant finding was an approximately twofold increase in risk of lung cancer for females with a dose response relationship evident for distance from electrical installations.

Youngson et al. (1991) studied haematological malignancies in Northwest England and Yorkshire using controls who were discharged from hospital. Exposures were assessed according to distance from overhead power lines and calculated measured magnetic fields based on current load. No statistically significant associations were observed although excess risk was seen for myeloid leukaemia.

Severson et al. (1988) investigated population-based, registry-based incidence of acute non-lymphoblastic leukaemia (ANLL) in adults in western Washington State in relation to wire codes comparable to those defined by Wertheimer and Leeper in the residence closest to the reference date and the longest residence three to ten years before the reference date. Spot measurements of magnetic fields were also made in several rooms in the home. There was no evidence of significant increased risk with any EMF measurement. High wiring configuration was in fact associated with a decreased risk of ANLL.

The reported findings by Feychting and Ahlbom (1994) supported an excess risk of myeloid leukaemia in adults in relation to residential magnetic fields assessed according to distance from power lines and by calculating fields generated by power lines and using archival information on line current to make historical corrections. Excess leukaemia risk was observed for cumulative exposure of 2.0μT-years or more during the 15 years preceding diagnosis and distance of 50 metres or less from the lines.

A retrospective cohort study design was used to compare observed and expected deaths among residents who had lived five years or more in a section of Maastricht, Holland which had two 150 kV power lines and one transformer substation (Schreiber et al., 1993). Exposure was defined according to distance from power lines or substation, greater than 100 metres with associated measured magnetic fields of 0.1 - 1.1μT. The referent was defined as less than 100 metres with magnetic field exposures of 0.02 - 0.15μT. The standardized mortality ratios showed no associations between exposure as defined and those cancers with previously reported relationships with EMF.

A study of residential exposure and adult cancers (leukaemia, brain and female breast cancer) in Taiwan (Li et al., 1997) showed a statistically significant increased risk of leukaemia with measured magnetic fields greater than 0.2μT (OR=1.4, 95% CI 1.0-1.9) and with residential proximity (at time of diagnosis) of less than 50 metres to the

nearest transmission line (OR=2.0, 95% CI 1.4-2.9). No evidence of risk was observed for the other two cancers studied.

A reported study from Finland related to adults and found no evidence of increased risk of leukaemia although an excess of multiple myeloma in men and colon cancer in women was observed (Verkasalo et al., 1996). Exposure was based on calculations of the average annual magnetic fields similar to that used for the childhood study (Verkasalo et al., 1993).

Electrical Appliances

Electric and magnetic field exposures associated with household appliances can be high because of the close personal proximity with use. As an example, the magnetic flux density of a hair dryer is 6-2000μT at a distance of three centimetres from the hair dryer whereas at a distance of 30 centimetres this range is <.01 to 7μT (National Radiological Protection Board, 1992; Mader and Peralta, 1992). Because magnetic fields are greatly attenuated with distance, electric blankets, electric razors, hair dryers, and water beds are candidate 'appliances' for evaluation of potential risk because they are so close to the body during use (Preston-Martin et al., 1988; Savitz et al.,1990; London et al., 1991; Severson et al.,1988). Overall the evidence from studies to date is inconclusive because the numbers of subjects associated with any increased risk are very small. Savitz et al. (1990) found a non-significant association (OR=1.7) for leukaemia risk and a significant risk for brain cancer (OR=2.5) associated with prenatal electric blanket use. A non-significant leukaemia risk was found with postnatal exposure to bedside electric clocks. The authors cautioned against over-interpretation of these results in light of the small numbers and non-response rate. In the study by London et al. (1991) examining childhood leukaemia, significant risk (OR=2.82) at the 95% level was found with the regular (at least once a week) use of electric hair dryers and (OR=1.49) with black and white television use. These are the only two studies examining appliance use by children.

Occupational Studies

The early reports of associations between cancer risk and electric and magnetic fields were based primarily on proportional mortality studies using job titles as surrogate indices of exposure to electric and magnetic fields. Collectively, these "electrical occupations" were associated with increased risks of leukaemia and/or brain cancer (Milham, 1982; Milham, 1985; Calle and Savitz, 1985; Savitz and Calle, 1987). In addition to the imprecision and potential for misclassification associated with the use of job title as a surrogate for exposure, the job title was frequently that derived from the death certificate and hence gave no information about the individual's work history. Death certificate based studies were further limited by the lack of specific diagnostic information about the malignancy. In general, elevated risks have been seen more consistently with acute myelogenous leukaemia than for all leukaemias, but histologic type is often not reported on the death certificate and thereby undermines the specificity of such studies.

Numerous occupational studies followed, each showing general improvement in study design but still restricted in exposure assessment by the use of job titles to infer exposures to electric and magnetic fields. More recent studies have shown further methodological improvements in terms of exposure assessment and case ascertainment (Floderus et al., 1993; Theriault et al., 1994; Miller et al., 1996).

Floderus et al. (1993) carried out a population-based case control study of leukaemia incidence and brain cancer in Sweden. Measurements of magnetic fields derived from a personal monitor worn for a representative day in the work environment with a focus on those jobs or tasks held the longest during the ten year period before diagnosis. Adjustments were made for potential confounders such as benzene, ionizing radiation, pesticides, solvents, smoking. A dose response relationship was observed for all leukaemia and for chronic lymphocytic leukaemia with statistical significance attained at the highest exposure levels. There was no association with acute myelogenous

leukaemia. Elevated risks were also found for brain cancer with statistical significance attained, but not necessarily in the highest exposure level.

Sahl et al. (1993) examined leukaemia, brain cancer and lymphoma mortality among workers in a US electric power utility in relation to measured magnetic field exposures and also to employment in electrical occupations defined as "exposed" *a priori*. Using both a cohort and case control approach, no excess risk of any cancer site under study was observed. However, the study was limited by its size and statistical power and, in spite of the improved exposure assessment, opportunities for exposure misclassification remained.

It was not until the studies by Theriault et al. (1994) and Savitz et al. (1995) of electric power utility workers that significant advances were made in exposure assessment. Cancer incidence was investigated for a study of electric utility workers from Canada and France for the period 1970-1988 using a nested case control study design. Current workers, selected according to job title, wore personal monitors which measured electric and magnetic fields. Using these measurements and a work history, a job-exposure matrix was created and applied to cases and controls in each of the participating utilities. The investigators also attempted to control for possible occupational confounders, a deficiency noted in most of the earlier studies. For two of the utilities, case ascertainment was based on cancer registration in the province and this contributed importantly to the completeness of ascertainment and to the acquisition of histologic information. An effort was also made to apply historical corrections where there was information to suggest that the exposures in the respective companies changed over the time period of study. A statistically significant association was observed for acute non-lymphocytic leukaemia and specifically for acute myelogenous leukaemia: the excess risk was most pronounced in the Ontario Hydro cohort but also apparent in the Hydro Quebec cohort as all cases of acute myeloid leukaemia (n=6) were confined to the exposed group and as a result the reported odds ratio was undefined.

In 1995 Savitz et al. reported on the mortality experience of five US utilities. Personal monitors were worn but unlike the Canada/France study, yielded only one measurement of the magnetic field per worker, a time-weighted average exposure. An association was observed with leukaemia for electricians (OR=2.5, 95% CI 1.08-5.76) having 20 or more years of employment and a statistically significant excess of brain cancer mortality (OR=2.3, 95% CI 1.15-4.56) was associated with magnetic field levels of ≥4.3μT years. The findings relating to brain cancer showed a significant trend of increasing risk with increasing exposure to magnetic fields.

Until recently, magnetic fields have been the primary focus of the occupational studies, indeed all epidemiologic studies. However, never has the effect of electric fields been systematically demonstrated and dismissed as noncontributory. Rather, it has been assumed that because electric fields generated naturally within the body exceed those from external sources, the latter could not be potential contributors to the associations which have been observed in epidemiological studies. Notwithstanding this claim, in a study of Ontario Hydro workers, Miller et al. (1996) raised the possibility that electric fields might be more important than magnetic fields with respect to occupational exposures and leukaemia risk. An odds ratio for all leukaemia of 4.5 (95% CI 1.01-19.7) was reported for electric field levels ≥345 volts/metre-years. Further, the authors also reported evidence of an interaction between electric and magnetic fields (OR=11.3, 95% CI 1.52-84.3) for electric field exposure ≥345 v/m-years and magnetic field exposure ≥7.1μT-years, with the electric field component being dominant in the contribution of excess risk. Whether this statistical interaction is relevant biologically is not known at this time and needs to be explored in laboratory studies and further tested in epidemiological studies.

Guenel et al. (1996) also reported findings which pointed to occupational exposures to electric fields. Among French electric utility workers increased odds ratios for brain tumours which were statistically significant at the highest exposure level

(OR=3.08, 95% CI 1.08-8.74) and for those with employment of 25 years or more were observed. There was no evidence of increased risk of leukaemia with electric field exposure. The authors cautioned that the unexpectedly elevated odds ratios for colon cancer, not previously associated with electric and magnetic fields, needed to be confirmed by other research.

"Overall, the most recent studies have increased rather than diminished the likelihood of an association between occupational exposure to electric and magnetic fields and cancer, but they have failed to establish an association with a high degree of certainty" (Committee on the Possible Effects of Electromagnetic Fields on Biological Systems, 1996). Failure to reach certainty may be due to the fact that the biologically relevant exposure is not being measured. The early studies were likely undermined by both exposure and disease misclassification (Delpizzo, 1992; Savitz et al., 1993). Cumulative exposure may not be the appropriate metric and more effort is required to estimate past exposures and to explore other exposures and time above a threshold. It is possible that one summary metric is insufficient and exposure needs to be evaluated in several ways.

To date only one study has considered both occupational and residential exposures to electric and magnetic fields (Feychting et al., 1997). For adults especially, who spend a large proportion of their time away from home and can be exposed to high EMF in their work environment, and for whom the etiologic relevant period is potentially more extensive than for children, it is important to attempt to estimate exposure from a totality of sources. The authors brought together in this study of leukaemia and central nervous system tumours the exposure assessment methodologies from each of their previously reported studies (Feychting and Ahlbom, 1994; Floderus et al., 1993). Modest increases in risk were observed for leukaemia and exposure (0.2μT) in the residential (OR=1.7, 95% CI 1.1-2.7) and occupational environments (OR=1.3, 95% CI 0.8-2.2). The odds ratios were higher for myeloid leukaemia which is consistent with some studies

of occupational exposures. Exposure to magnetic fields of 0.2μT or more in both the residential and occupational environments were associated with risk estimates for acute myeloid leukaemia of 3.7 (95% CI 1.5-9.4). Central nervous system tumours showed no association with magnetic field exposure.

Summary of EMF Studies

In spite of extensive efforts over a period of 20 years, no consensus has been reached regarding the carcinogenic effects of electric and magnetic fields. While there have been notable improvements in epidemiologic methods relating to case ascertainment, exposure assessment needs further refinement and the relevant exposure metric is as yet undefined.

Studies to date have suffered from lack of specificity with respect to exposure. It is by no means certain that these epidemiology studies are measuring the right parameters for EMF exposures. While consistency of reported risks by certain metrics of EMF is the most compelling argument suggesting a causal role for EMF, biologic plausibility is the weakest and a critical argument against the existence of a causal relationship. Without detailing the cellular and animal studies to date, the point of significance is that laboratory work has failed to clearly demonstrate a biologic mechanism which might explain the epidemiologic findings. As a result there have been few clues about the relevant exposure metric, if any, to apply to epidemiologic investigations. Nevertheless, by citing the contributions of the early studies of lung cancer and smoking carried out long before the specific toxicological effects of cigarette smoke were known and characterized, Stevens (1993) has reminded us that "epidemiology can be conducted fruitfully in the absence of a biologic rationale".

The studies of children present the enigmatic, but consistent, association between leukaemia and brain cancer risk and wire code. This association should not be confused with causality in light of the studies which have shown no risk, or an acutely attenuated

risk, with "measured" magnetic fields. There are, however, sufficient reasons to question whether the fields as measured are appropriate indices of the relevant etiologic exposure as they fail to account for changes over time, peak exposures or time varying fields.

While several studies have shown measured magnetic fields do increase with higher wire configuration, the disparate associations of these two 'measures' observed with leukaemia risk have led to the speculation that wire code may be a surrogate for the 'true etiologic' agent. Research directed at a better understanding of the correlates with wire code such as traffic density, housing density is underway (Wachtel et al., 1996). Many of these potential correlates are related to socioeconomic status. Wire codes have been tested in relatively few urban environments and there is a need to gather more information to determine if the 'presumed' meaning of wire code changes with the city.

It has also been proposed that wire configuration is more stable and as such may be a superior indicator of integrated exposure over time to point-in-time measurements (Savitz et al., 1993). Wire code has been the source of comparability between many studies and indeed will remain so for this investigation.

Measures of exposure as distance from electrical installations have not been particularly helpful in clarifying the relationship between electric and magnetic fields and cancer. The Scandinavian studies of children and adults attempted to incorporate historical corrections with distance to better estimate lifetime exposures but recent work has suggested that these are at best predictive of exposure within the last five years (Kaune et al., 1996). This recent work demonstrated that a significant increase in leukaemia risk is seen with calculated exposure using historical line load data and that the effect is not seen using any 'current' measurement that was tried. The authors found that the correlation between the current measured value of magnetic field and the calculated magnetic field using historical line loading data diminished to zero as the historical data

extended back more than five years. This argues that studies using contemporary measurements of magnetic fields may not capture the relevant exposure of the child if the etiologic period extends back many years.

In addition to the difficulties in interpretation posed by the different methods of EMF exposure assessment, potential selection and information biases may exist in several of the published childhood cancer residential studies and it is not possible to determine how this might have influenced the results. Jones et al. (1993) have suggested that the association between wire codes and childhood cancer might be explained by selection bias by imposing a criterion relating to residential stability for the controls (Savitz et al., 1988). By studying defined areas of Columbus, Ohio, they found that "high wire codes were associated with homes in which the residents were mobile and low wire codes were associated with homes occupied by stable residents".

Differential non-participation of controls as function of socioeconomic status was proposed by Gurney et al. (1995) as a possible explanation of the association between wire codes and childhood cancer. Their study in Washington State found that non-participants were more likely to have lower income which was in turn found to be associated with very high wire configuration. The studies by Savitz et al. (1988) and London et al. (1991) have the potential for this non-response bias.

The studies of residential exposures and cancer in adults generally suggest no effect. However, in most studies measurements have been confined to one residence (current) for which representativeness of lifetime exposure cannot be assumed. While this issue of studying only one residence is also applicable to children, it would seem to be even more important with respect to adults who have many more years for exposure opportunities to electric and magnetic fields and to known or suspected carcinogens both occupationally and residentially. In a recent review of adult cancers, Li et al. (1996) calculated the statistical power of these studies to detect a doubling of risk with 'high'

levels of residential exposure. That only four studies (Coleman et al., 1989; Youngson et al., 1991; Feychting and Ahlbom, 1993; McDowall, 1986) had power over 80% to detect such levels of risk led the authors to conclude that "inadequate statistical power is more of a concern than bias in explaining the inconsistencies across studies". The studies where no leukaemia was demonstrated had a very small proportion of the population exposed to magnetic field levels of 0.2μT or more, however that measurement was derived.

The studies of electric and magnetic field exposures and cancer risk in workers present the generic advantages of studying occupationally exposed groups. The exposures of workers often can be more accurately measured without bias as a result of records collected and retained for independent purposes and prior to the onset of disease. However, exposures with respect to electric and magnetic fields in the work environment are very different from exposures usually found in residential settings. Occupational exposures are typically higher and reflect wider ranges than those found in homes and generalization from occupational to residential environments is not appropriate given the current state of knowledge. Moreover exposures in a residential setting are comparatively uniform, whereas workers may move in and out of high fields throughout their workday or week. It is possible that measuring exposures in the workplace allows for better distinction between exposure ranges and as a result high exposures are more accurately characterized and an association detected. However in particular, the results associated with high exposures in the workplace cannot be generalized to the public.

Occupational studies have tended to show an effect with exposure when a distinction was possible by histologic type with acute myelogenous leukaemia showing stronger associations. Higher risks have also been observed with cancer incidence than with cancer mortality.

Particularly, but not exclusively, for adults, historical corrections may be important. Most occupational studies have used current exposures applied to current job titles. Recent studies have attempted to apply a correction factor to account for changes over time, however, there is no way by which the validity of the correction can be assessed and as a result current measurements are used to estimate exposures as much as 50 years ago.

Delpizzo (1992) highlighted the susceptibility to misclassification by the use of job titles as a surrogate of exposure. Miller et al. (1996) alluded to the possibility that failure to consider work location in addition to job title and *a priori* selection of job titles according to 'presumed' exposure to magnetic fields can attenuate risk estimates.

Given the ubiquity of electric and magnetic fields, continued research efforts are justified to clarify the carcinogenic or leukaemogenic potential of such exposures. While recognizing that children may be differentially susceptible and that paediatric cancers are generally regarded as very different from adult cancers, studying cancer in children offers the advantage of a shorter opportunity for exposure to electric and magnetic fields as well as other exposures and therefore it may be possible that EMF exposures may be more accurately measured. There is also a need to contribute further to the understanding of other possible risk factors for childhood leukaemia and to evaluate their possible contribution to the overall etiology of this malignancy.

Studies of Other Known and Suspected Risk Factors for Childhood Leukaemia

The extensive study of paediatric leukaemia has confirmed few etiologies but has suggested several worthy of further investigation, of which exposure to electric and magnetic fields is but one. For the most part, all of the following have shown either weak or inconsistent associations with childhood leukaemia.

Genetics and Family History

Perhaps because of the comparatively limited opportunities for environmental exposures among young children, childhood cancer research has contributed more to our understanding of the genetic basis for cancer causation. Genetics appears to play an important etiologic role in childhood leukaemia. The evidence for this is based on the observed associations between childhood leukaemia and family history and with chromosomal abnormalities.

There are a number of genetic syndromes, such as Down syndrome, Bloom syndrome, neurofibromatosis, Fanconi syndrome, ataxia telangiectasia, Shwachman syndrome, and Klinefelter syndrome, where childhood leukaemia, particularly acute myelogenous leukaemia, is well documented (Robison and Neglia, 1987, Shaw et al., 1992). It is widely recognized that Down syndrome is associated with a 10-20-fold increase in childhood leukaemia risk. The tendency for leukaemia to aggregate in families who have a history of excess cancers suggests a genetic etiologic component but does not rule out environmental exposures which are more likely to be similar within families (Maklin,1960; Farwell and Flannery 1984; Heath and Molone 1965; Draper et al., 1977).

Infectious Disease and Immunology

Certain infectious agents that the mother may be exposed to during pregnancy, such as influenza and chicken pox (Austin et al.,1975), and that the child directly encounters after birth have been implicated as etiological. Viral infections at a very early age have been suggested as a causal criterion for the early age peak of childhood leukaemia but the theorized mechanisms are divergent in direction. Some studies have suggested that infection at an early age increases the risk of childhood leukaemia, whereas others have proposed that early exposures to childhood infections might reduce the risk (vanSteensel-Moll et al., 1986). The latter relates to theories by Greaves and Chan (1986) and Kinlen et al. (1991).

Greaves postulated that two separate events, the first being a mutation *in utero* to pre-B cells and the second being postnatal exposure to an infectious agent, are required for the leukaemia to develop. A delay in this second event might lead to overstimulation of B-cells and increased probability of leukaemia. Translated to non-medical or family circumstances, this has been offered as an explanation of why firstborn children, those without younger siblings to contribute to the 'infectious disease burden in the household' and confer protection might be at increased risk of leukaemia, and those who attend daycare at an early age and thereby are exposed to many antigenic challenges are at decreased risk (Greaves, 1988; Petridou et al., 1993; Greaves and Chan, 1986; MacMahon, 1992).

Kinlen's hypothesis, although circumstantially different, is similar in its underlying premise. Kinlen proposed that the rapid migration into previously unpopulated isolated areas might bring the migrants into contact with infectious agents for which the population has no immunity. This was suggested as a possible explanation of some excesses of leukaemia around nuclear power plants for which radiation exposure does not seem to be biologically plausible (Kinlen, 1988; Kinlen et al., 1991) although the hypothesis remains inadequately tested (MacMahon, 1992).

Compromised or deficient immunologic status has been associated with increased cancer risk in children. Rare immunodeficiency diseases such as ataxia telangiectasia and agammaglobulinemia are thought to increase risk of leukaemia (Kersey et al., 1973). Of more general significance is immunologic status which has been assessed indirectly according to vaccination status. Children with up-to-date immunizations have been found to be at decreased risk of childhood cancer (Hartley et al., 1988). Breast feeding is advocated as providing immunologic benefits to the child and in considering this possibility, Davis et al. (1988) have reported a protective effect of breast feeding with respect to leukaemia risk but other studies have shown no evidence of a protective effect (Magnami et al., 1988; McKinney et al., 1987).

Ionizing Radiation

Radiation-induced leukaemia has been well documented for high levels of exposure, such as those seen in the study of the atomic bomb survivors and patients treated with radiotherapy. The effects of low level radiation however, have not been well defined and controversy remains regarding the nature and magnitude of the radiation effect derived by extrapolations from high radiation dose levels. Radiosensitivity is known to vary with age, with those at younger ages being at greater cancer risk than those at older ages. *In utero* exposures to x-rays for diagnostic and therapeutic purposes, particularly in the first trimester, seems to be an established leukaemogen but such exposures are thought to be responsible for very few cases of childhood leukaemia. Preconceptional exposure to ionizing radiation in the father has also been implicated as a possible cause of childhood leukaemia (Gardner et al., 1990) but not substantiated. Residential proximity to nuclear power plants thought to be associated with elevated radiation exposure have been extensively studied with respect to childhood leukaemia with no resulting consensus. From population surveillance of those exposed to radiation as a result of the Chernobyl nuclear power accident in 1986, childhood leukaemia cases (and childhood thyroid carcinoma), particularly in Belarus, are being detected, although firm estimates of risk have not been established and are the focus of ongoing research efforts (Kadhim et al., 1992).

Parental Exposures

For young children, indirect exposures may occur coincidentally by proximity to their parents or other caregivers. Maternal exposures to alcohol and cigarette smoke have been inconsistently associated with childhood leukaemia (Severson et al.,1993; vanSteensel-Moll et al., 1985; Buckley et al., 1989).

Fabia and Thuy (1974) first reported an association between occupational exposures to hydrocarbons in the father and cancer in young children. Since then numerous studies have hypothesized different paternal occupational exposures, either

preconceptionally or postnatally. Implicated exposures for both fathers and mothers include solvents, paints, methylethylketone, dyes and pigments, petroleum products, pesticides, ionizing radiation (Vianna et al., 1984; Shaw et al., 1984; McKinney et al., 1991).

Much work remains to identify actual etiologic exposures as studies to date have been limited by their evaluation according to only job titles which are highly non-specific.

Factors related to the mother's reproductive history and circumstances relating to birth have been studied extensively. The reproductive history of the mother, notably spontaneous abortions, stillbirths and history of infertility, have been associated with an increased risk of acute lymphoblastic leukaemia (van Steensel-Moll et al., 1985; Kaye et al., 1991). The research is inconclusive but if the effect is real, both environmental and genetic factors might be responsible. Advanced maternal age, while taking into account risks associated with Down syndrome, has also been observed not only for leukaemia but also for other childhood cancers.

Elevated weight at birth (>4000 grams) has been observed with more consistency than other hypothesized agents or circumstances in leukaemic children with the effect being more pronounced with diagnosis at a very early age (Robison et al., 1987; Kaye et al., 1991; Zack et al., 1991).

Zack et al. (1991) found a relationship between leukaemia and the administration of nitrous oxide for anaesthesia during delivery and also of oxygen to the newborn.

Other Childhood Exposures

As children grow older and assume more independence, the opportunities for personal exposures which are distinct from their parents increase.

Savitz and Feingold (1989) investigated traffic density as a possible surrogate of exposure to motor vehicle exhaust and found a non-significant leukaemia risk. The hypothesis may also have relevance to the reported associations between leukaemia and wire code as first defined by Wertheimer and Leeper (1979).

A number of studies have investigated medication use but demonstrated associations have been limited. Chloramphenicol and growth hormone (Shu et al; 1987) are among the few medications which have been related to leukaemia risk.

Several studies have shown pesticides to be associated with leukaemia in young children. As for ionizing radiation, it has been suggested that young children might be particularly susceptible to such chemical agents (Fenske et al., 1990). Increased risk of childhood leukaemia has been associated with household pesticide exposures by Lowengart et al., 1987; Buckley et al., 1989; Infante et al., 1978; Leiss and Savitz, 1995. However, the non-specific epidemiologic inquiry of such exposures together with the potential for recall bias justifies cautious interpretation of the findings which have been reported with moderate consistency.

Chapter 3

METHODS

Study Design

This is a population-based case control study design with cases ascertained through the Hospital for Sick Children in Toronto and controls randomly selected from the general population of the defined exclusive catchment area for the hospital.

Definition of Study Catchment Area

The Hospital for Sick Children is the major children's hospital in southern Ontario and is a medical institution of international renown. Approximately 65% of the newly diagnosed childhood cancers in the province of Ontario are diagnosed at this hospital (Paediatric Oncology Group of Ontario, 1992). That the cases may be considered population-based for the defined catchment area and that they have been completely ascertained are reinforced by the characteristics relating to the referral patterns for the hospital which reflect its diagnostic expertise.

The geographic profile of leukaemia diagnoses made at this hospital extend to residents province-wide and even across provincial and national boundaries. As the Hospital for Sick Children was the source of cases, it was necessary to define, for the purpose of this study, a geographic area which would equally represent the source population for cases and controls.

The Paediatric Oncology Group of Ontario (POGO) maintains a registry of all new paediatric patients seen at the five children's hospitals in Ontario who were less than 18 years of age at the time of diagnosis. The registry covers the years 1985 to present and contains information relating to age and date at diagnosis, sex, race, cancer site, stage, histology, tumour behaviour (malignant, benign and unspecified), physician, treating institution and geographic area defined for Ontario by District Health Council boundaries and separately for those who are not Ontario residents. The POGO registry has undergone cross-checks with the Ontario Cancer Registry for a two-year period (1990

to 1991) to compare and reconcile the completeness and accuracy of reporting for the two data bases. The results of this reconciliation confirm that the reporting of leukaemia diagnoses in the POGO registry for the age group under study was comprehensive and accurate (Greenberg, 1997). The registry was used as the starting point for the delineation of the catchment area for this study.

Leukaemia cases were identified from the POGO registry using district health council information and the first three digits of the postal code. From this information plots of leukaemia diagnoses according to the hospital at which the diagnosis was made and district health council were available. District health councils coincide with census county boundaries. Those district health council areas where the leukaemia cases were diagnosed exclusively at the Hospital for Sick Children and which were geographically adjacent to Metropolitan Toronto comprised the catchment area for the study. District health council areas where cancer diagnoses originated from more than one paediatric hospital, of which the Hospital for Sick Children was one, were not included because a corresponding area for control selection could not be identified. For example, Halton County was not included because some leukaemia diagnoses were made at the Hospital for Sick Children and some at the McMaster University Medical Centre and therefore it was not possible to define a geographic area which would exclusively represent a source of controls for the respective hospitals. Also excluded were northern Ontario areas where diagnoses were made exclusively from the Hospital for Sick Children because the geographic distance precluded exposure measurements. Thus, the catchment area was defined as Metropolitan Toronto and the counties of York, Durham and Peel. All leukaemia diagnoses in these areas were made at the Hospital for Sick Children.

Case Ascertainment

Cases were of either sex, alive or deceased, and diagnosed between birth and 14 years, the traditional delineation of the paediatric period. Cases were ascertained over a nine-year period, January 1985 to December 1993 inclusive. Cases under the age of 12

months were only included for the period March 1, 1988 to December 31, 1993, as the cases diagnosed prior to this time period were the subject of another study and the treating physicians felt that it was inappropriate to approach the family again regarding another study. Cases were resident in the catchment area at the time of diagnosis. All types of leukaemias were included. Even though there are differences in survival factors and potential etiologic factors, all histologic sub-types of leukaemias were studied to guard against the exclusion of a subgroup for which an association with a certain exposure might be considered. The inclusion criteria are summarized as follows:

Age at diagnosis	0 - 14 years
Sex	Males and females
Source	Hospital for Sick Children
Catchment Area	Must have resided at the time of diagnosis in: Metropolitan Toronto York County Durham County Peel County
Year of Diagnosis	1985 - 1987 (ages 1-14) 1988 - 1993 (ages 0 -14)

There were no exclusion criteria.

Approach to Cases

Children diagnosed with leukaemia were ascertained initially from the POGO registry in accordance with the inclusion criteria for the time period of study. After identification of the relevant cases from this source, the POGO registry and hospital records were reviewed for current address information. Some cases had moved out of the catchment area since diagnosis. If the relocation introduced geographic distance which prevented contact with the family (eg. family moved to England, Malaysia, etc.), these individuals were not approached.

In accordance with the protocol approved by the Department of Public Health Sciences (formerly the Department of Preventive Medicine and Biostatistics), the Scientific Review Committee of the Hospital for Sick Children and the Office of Research Administration of the University of Toronto, the first contact with the case parent(s) or the case was with the treating (or alternate) physician at the Hospital for Sick Children. This approach was considered appropriate in order to reinforce the hospital's involvement with the study, to ensure continuing contact with the treating physician for those cases for whom deferral was requested and to avail the study investigators of the treating physician's and clinic nurse's knowledge of family and/or patient circumstances which might influence participation in this study.

Lists of cases for each treating physician were distributed to that physician for his/her approval to approach the case family regarding participation in the study. Physician responses consisted of three possibilities: not to approach, delay approach or proceed with approach.

If the approval to proceed was indicated, a letter was sent to the case family from the physician explaining the nature of the research and asking if they would permit their name to be given to the research staff at the University of Toronto so that they may be contacted directly about the study. It was explicitly stated that their participation was entirely voluntary and their child's care would not be affected in any way if they chose not to participate. A consent card was enclosed together with a self-addressed envelope for reply. There were some cases who were approached directly in the hospital clinic and who provided verbal consent.

To overcome potential language barriers, the letter from the physician was translated as required into three languages, Cantonese, Portuguese and Spanish.

Follow-up letters were sent by the treating physician to those case families who had not previously responded and in some instances the data manager/coordinator at the hospital approached the families directly when they came to the clinic to confirm willingness to be contacted by the University about the study.

Each case where deferral was requested, was re-considered for approach throughout the study, until such time when the study was deemed 'closed'. Hence, for some cases, time constraints prohibited re-approach. The request for "deferred approach" was reversed in some cases during the course of the study.

There are some cases who initially agreed to be approached by the research team at the University of Toronto and for whom contact could not be made. The hospital had also lost contact with these families.

Control Selection

The aim in the selection of controls was the identification of a population representative of that from which the cases arose (Wacholder et al., 1992a; Miettenen, 1985). Identification of a population of children in the ages 0-14 years was a major challenge given the avenues available within the province of Ontario. In Ontario, no means exists by which to identify a fully enumerated group of children comparable to those in the age group of this study. As such, it was necessary to design a means by which children could be randomly selected from the population. A stepwise/layered approach commencing with Teledirect Marketing Lists was adopted.

Teledirect Marketing Lists which consist of published residential telephone numbers are available for purchase from Bell Canada. The lists do not include unlisted telephone numbers and are intended to exclude business numbers and residential numbers where a written request has been received from the subscriber for his/her telephone details to be removed from these lists. Lists are updated monthly.

Although telephone-dependent, these lists are superior to random digit dialing because they contain address information in addition to name which will allow for a more personalized approach while also providing a means by which to better assess the characteristics of potential non-respondents (Greenberg, 1990). As the lists do not include unlisted numbers, which are estimated to comprise 10% of all urban residential telephone numbers, there is a need to evaluate comparability of the cases and controls with respect to their eligibility for inclusion (Wacholder et al., 1992b). Accordingly, all study participants were asked during the interview whether or not their telephone number was unlisted and whether they had ever requested that their name be removed from a teledirect marketing list.

Postal codes which corresponded with census districts or district health council boundaries were identified. It was necessary to include some postal codes where there was overlap with areas outside the catchment, but these were few in number. When a telephone number belonging to a residence which was out of the catchment area was identified through the control selection process, it was removed from the sampling frame for controls.

In February 1992 a list was purchased containing 10,000 names representing residential households selected at random from the Bell Canada Teledirect Marketing Lists. Six thousand names were from the Metropolitan Toronto area as designated by postal codes commencing with "M" and the remaining 4,000 names were selected from specified postal codes which corresponded with census/district health council boundaries in the defined catchment area. The proportion of numbers sampled for Metropolitan Toronto and non-Metropolitan Toronto in the catchment area was based on the known populations less than 14 years of age derived from published census statistics. The lists contained name, address and telephone number.

Telephone numbers were selected at random from these lists and calls were made for the sole purpose of inquiring whether the resident had children born in the years 1970 to 1993 and if so, the sex of those children. It was explained to the respondent that this information would be entered into a data base, and that if at a later date, their child was randomly selected to match with a case child, they would be approached regarding participation in the study. Inquiry was therefore made of the respondent's willingness to be contacted again. Using this approach, the information relating to date of birth and sex was entered into a data base thereby creating a "mini-census" of children of ages relevant for the study. When a child with a particular birth year was needed, the data base was accessed in a random manner to obtain the name and address and a letter was sent describing the study. Approximately one week later, telephone contact was made. Only one control per family or residence was selected.

Over a 24-month period a total of 4,180 contacts were made using telephone numbers randomly selected from the Teledirect Marketing Lists. For those numbers where contact could not be made on the first attempt, a pre-determined algorithm for re-approach was followed. A minimum of 10 attempts were made at different times of the day and different days of the week. Of the 3,299 for whom a response was directly obtained, 34.6% (n=1,142) had children in the eligible age range for the study. Of this total 96.4% agreed to be contacted again and to be part of the "mini-census" which they understood would comprise the list from which the controls for the study were to be selected.

Two hundred and three refused to provide the requested information and it was therefore not clear whether or not the household had children of eligible age. In addition to these direct refusals, information could not be obtained for 368 telephone numbers for a variety of reasons which included, no response (after following prescribed algorithm), answering machine only, language barrier, wrong number, written request needed. If the telephone number no longer belonged to the name identified in the teledirect lists, the

current resident was asked the same questions or attempts were made through directory assistance to find the new telephone number and make contact.

It could be assumed that those numbers for which contact was not successful in addition to the telephone numbers where there were direct refusals did not differ proportionately from those who did directly respond with respect to eligible children. Using this assumption and in the absence of a clearly enumerated denominator or study base, a total of 198 eligible children might have been omitted from the "mini-census". If those for whom contact could not be made were less likely to have children, this number would be an overestimate. There were reasons to suggest that this might be so as some of the incorrect numbers belonged to businesses and/or were fax numbers.

Apart from respecting the boundaries of the catchment area there was no attempt to match according to any geographic variable as this could constitute overmatching with respect to the exposure of primary interest. Cases were individually matched to the controls according to birth year and sex. In all instances a control child of the same sex was located. Birth year was matched within 12 months. Two controls were selected for each case.

Previous population-based case control studies of childhood leukaemia and exposure to electric and magnetic fields (Savitz et al., 1988) have been criticized (Poole and Trichopoulos, 1991; Jones et al., 1993) because of the imposed criteria for the selection of controls and the related opportunity for differential mobility between cases and controls which might have introduced bias. To avoid such potential bias, controls should be selected according to comparable eligibility criteria from sampling frames which reflect the dates of diagnosis of the cases. As previously explained, no means exists in Ontario by which this comparability could be readily achieved. The teledirect marketing lists were approximately current to the time of purchase and did not necessarily reflect the dates of diagnosis. It was thought *a priori*, however, that the

inability to select contemporaneous controls would not be a problem in terms of differential mobility and potential selection bias because those individuals no longer resident in the catchment area at the time of sampling, but who would have been eligible for inclusion and present for sampling in an earlier year of the ascertainment period, have been 'replaced' by individuals for whom there is no reason to assume their potential for mobility is different from those who have left. In other words, the assumption is, although those who moved out of the catchment area are not included, their replacements do not differ with respect to residential mobility (Wacholder et al., 1992a).

As cases must have been resident in the catchment area at the time of diagnosis, so must have the controls. No minimum requirement on the length of residence in the catchment area was imposed even though it was recognized that this would lead to some loss of information with respect to actual measurements of electric and magnetic fields, if the case and/or control had not been resident in the catchment area for at least some time prior to the relevant period of inquiry.

The criterion of residence in the catchment area was more readily imposed for the cases through the check with hospital records, but was not as easily accomplished for the controls because controls were contacted on the basis of eligibility only according to age and sex. To confirm that controls were resident in the catchment area at the time of diagnosis of the case, all data gathered through the interview process were scrutinized and those who were not eligible excluded. This ensured that eligibility for the selection of cases and controls is comparable in the final data set.

Vital status was not a criterion for matching: no effort was made to seek deceased controls for deceased cases. The epidemiologic literature on the subject of matching by vital status suggests this is neither necessary nor appropriate. Death cannot confound a possible etiologic relationship because, by definition, it occurs after the diagnosis and it has been pointed out that the "use of dead controls, will in fact, be likely to make the

controls less representative of the non-diseased population than if death had not been used as a matching variable" (Gordis, 1982). The consensus would seem to be that in terms of comparability and consistency of data, it is appropriate to use live controls with dead cases (Wacholder et al., 1992b; Walker et al., 1988).

Period of Inquiry

The etiologic period defined for inquiry depended upon the exposure of interest and the biologically relevant time and varied according to the age of the child at diagnosis. The period of inquiry dictated the type and number of measurements taken of electric and magnetic fields (Figure 1).

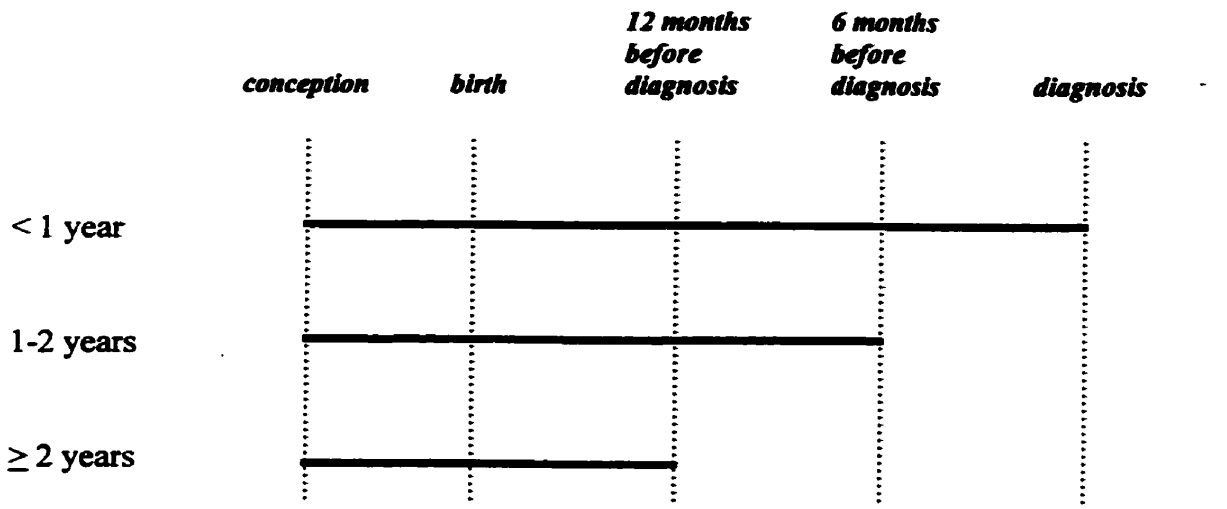
Age at Diagnosis	Prior to Birth	Prior to Reference Date
< 1 year	9 - 12 months	0 months
1-2 years	9 - 12 months	6 months
≥ 2 years	9 - 12 months	12 months

The intervals correspond to the latency periods as defined in the study by London et al. (1991). For controls, a 'reference date' was derived which corresponded to either the case's age or date of diagnosis. For controls matched to cases who were less than four years of age at the time of diagnosis, the reference date was equal to that date at which the control was exactly the same age as the case at diagnosis. For controls matched to cases who were four years of age or older at the time of diagnosis, the reference date was equal to the case's calendar date of diagnosis, as it was felt that for older children, very close matching on exposure opportunity was not required.

Sample Size and Power Calculations

At the time the study protocol was being developed, there was little information to suggest a reasonable estimate of expected exposure in the population to electric and magnetic fields. No information was available relating to measurements from personal

Figure 1


Period of Inquiry
Age at Diagnosis
conception
birth
12 months before diagnosis
6 months before diagnosis
diagnosis
< 1 year
1-2 years
≥ 2 years

monitoring of EMF exposures. Furthermore, what constitutes a biologically relevant 'exposure' was not defined. The research to date still does not clearly characterize the exposure which is most appropriate for inclusion in sample size calculations. The available estimates of residential exposures which were used for calculating sample size were limited to point-in-time measurements of magnetic fields (Savitz et al., 1988; Severson et al., 1988; London et al., 1991). Spot measurements in the Savitz study showed that about 14% of the controls were exposed to fields of 0.2μT or more under high power use conditions. Thus, power calculations based on power of 80% (β=0.2), level of significance (α) equal to 0.05 and the magnitude of the effect judged worthy of detection set at 2.0, suggested that the appropriate number of cases and controls with a 1:2 ratio was about 160 cases and 320 controls or with a 1:1 ratio, 300 each cases and controls. Either ratio was compatible with the anticipated available cases for selection at the Hospital for Sick Children over the defined time period.

Data Collection

Interview

Information relating demographics, medical history of child and family, residential and school characteristics, socioeconomic characteristics, parental occupational history, medications, appliance use, and specific exposures was ascertained by personal interview in the home of the child's parents. Exceptions to this included a few instances where case parents were interviewed in hospital, and other situations where older children provided answers directly, rather than their parents. The interview was structured and was pre-tested as part of a feasibility study carried out in 1990 (Watson, 1990).

Residential history was also collected as part of the interview process. This information was essential for identification of addresses of current and previous residences relevant to the etiologic period of inquiry and subsequent assessment of

electric and magnetic field exposures in these residences. The interviewer also inquired about the location of the child's bedroom in previous residences.

The interviewer inquired of schools and/or daycares which the child attended during the period of inquiry. Specific information was collected on the address and duration of attendance in terms of both times and days per week and calendar time period. This information was required for the exposure assessment of electric and magnetic fields in schools and daycares.

Four interviewers having been selected for their ability to engender rapport conducive to the acquisition of complete and accurate information from the parents and in particular, for their sensitivity to the situation and their capacity to demonstrate the necessary tact and diplomacy, administered the questionnaire. Where necessary, a translator accompanied the English-speaking interviewer. This allowed for the questionnaire to be administered in the language with which the respondent was most comfortable while retaining the presence of the interviewer who was familiar with the questions and their intent should immediate clarification be required. The interviewer was also able to carry out measurements of electric and magnetic fields as appropriate thereby obviating the need to instruct the translator in this regard.

Interviews were carried out over a 35-month period, June 1992 to April 1995.

Interviewers were instructed to focus on the period of inquiry specific to the respondent and to ensure that information was as complete as possible for this time period. Inevitably for some questions, information was provided for times proximal to the period of inquiry.

Measurements of Electric and Magnetic Fields

General

In 1990, a pilot study (Donnelly and Agnew, 1991) was undertaken to determine the feasibility of a number of methods by which exposure to electric and magnetic fields might be assessed. This was considered necessary as some methods had not previously been used with children and/or had not been designed for the situations in which their use was planned. The information from this feasibility study provided an objective basis for the selection of exposure methods and parameters which will improve upon those measures used in previous epidemiologic investigations.

Exposure to electric and magnetic fields was measured according to several different methods, as dictated in part by the cooperation and availability of the child and his/her family. Direct assessment of electric and magnetic field exposures was carried out according to a protocol defined by Agnew and Donnelly (1992). Depending upon the relevance of the residence to the period of inquiry, electric and magnetic field exposure assessment consisted of the following:

- personal monitoring of electric and magnetic fields using the Positron™ monitor
- magnetic field measurements inside the home with a specific focus on the child's bedroom and two other rooms in which the child spent most of his/her time; in some instances, measurements were also taken in a sibling's bedroom if the family indicated the index child had previously used that room
- magnetic field measurements outside the home
- wiring configuration

Electric and magnetic field measurements were also made in schools and daycares within the catchment area attended by the child during the period of inquiry.

Current Residences

If the residence in which the interview took place was relevant to the period of inquiry, it was considered "current". Electric and magnetic field measurements were made by both interviewers and technicians as subsequently described.

Previous Residences

From the questionnaire, all residences within the catchment area and relevant to the period of inquiry were identified. Although every effort was made to ensure the address was complete, there were a few instances where the address information provided was so vague that the residence could not be located. The address information was abstracted from the questionnaire and sent to the technician coded only as to the number of previous residences eligible for measurement for a particular subject. No identification was provided about case control status.

Prior to the technician making an appointment, a letter was sent to the resident of those homes in which the case or control child had lived during the etiologic period. To personalize the approach and to enable telephone follow-up, the name of the current resident was ascertained from the relevant Municipal offices. It was necessary to know the name of the resident so that a telephone number could be obtained and an appointment made to visit the home. The letter explained the purpose of the study and requested permission to take measurements inside and outside the home.

The letter did not yield a good response in terms of the addressee calling as requested to set up an appointment. Therefore, after an appropriate time interval, and in an effort to increase the efficiency of the measurements made over a wide geographic area, technicians approached the address directly offering a letter from the Hospital for Sick Children and the University of Toronto as introduction and asked for permission to take the necessary measurements. Even if contact with the resident was not made it was

still possible in some instances to carry out limited EMF measurements, sometimes with a perimeter assessment, or "front door measurement" or a curb visit.

Schools

Approval to approach the public schools attended by the subject child during the period of inquiry and within the geographic catchment area was first sought through the relevant Boards of Education and then through the school principal. Private schools were approached directly.

Through the interview process, the years in attendance and the associated grades were determined. This information was passed to the technician without the name or case control status of the child.

Before visiting the school, the technician asked the principal to fax a school floor plan and this was received most of the time. Upon visiting the school, the technician met a designated contact to obtain information about the classrooms on the location of specific grades for specific calendar years. It was not uncommon that there was more than one grade attended by the index child and more than one classroom per grade. Frequently the existing school staff did not know which classrooms were occupied by which grades in a specific year. The exception to this was the kindergarten classroom(s) which tend not to change from year to year. As a result, in many instances several classrooms were measured and the average of all rooms taken.

Information was obtained about the number of classrooms and age of the school building.

Measurement of magnetic fields was taken inside the appropriate classrooms with nine measurements made in each classroom.

Daycares/Nurseries

For licensed registered daycare and nursery schools, letters similar to those used for schools were sent. For private home child care centres, a technician approached the home directly with a letter of introduction and explanation about the study from the Hospital for Sick Children and the University of Toronto.

Measurements of magnetic fields inside the buildings followed the procedure described for schools.

Personal Monitoring

If the residence in which the interview took place was relevant to the period of inquiry, the child was asked to wear the Positron™ monitor for at least two days. Several options were offered by which the monitor could readily be kept close to the body. For infants not able to carry the device, the mother was asked to keep the monitor by the child in the crib or play area at all times and/or it was placed in a stuffed toy animal with a pocket which the child could "cuddle". Young children who were mobile were offered a backpack designed to specially appeal to a child. The backpack was padded with foam to enclose the monitor and prevent the child from injury in the event of a fall. Older children were given a "sport-type" waist pouch that similarly contained foam to protect the child. Some children elected to wear the monitor simply attached to their waist through a belt loop. The preferred carrying method was selected by the family in consultation with the interviewer. Once the carrying case was selected, the interviewer inserted the monitor and sealed the case.

The parent and/or child was asked to keep a log sheet on which information was recorded relating to the location of the child's activities (home, school or other), the type of activities and the associated times spent. Parents were instructed to log time of more than 15 minutes spent outside the home. If the child removed the monitor to bathe, to play sports, or when going to bed, this information was recorded. They were instructed to

also record the time when the monitor was not worn, but was in close proximity. Integration of the information from these log sheets was used to categorize the child's time according to home, school/daycare or 'other' and to produce time-weighted averages of exposure.

The parent or child was instructed to place the monitor close to the bed during sleep hours, at a location prescribed by the interviewer. The location was selected so as to avoid electrical appliances and such that the magnetic field was similar to that measured on the child's bed.

At one-minute intervals, the Positron™ monitor measured the 60 Hz electric field and three orthogonal axes of the 60 Hz magnetic field. Each measurement is 'assigned' to one of 16 bins spread across a logarithmic scale. The bin classification scheme was chosen to cover, as much as possible, the environmental values of everyday life as well as those of workplace exposure (Deadman et al., 1988). The threshold of detection for 60 Hz electric field is 0.6 volt/metre and 12.2 nanoTesla for the 60 Hz magnetic fields.

The readings from the Positron™ were then integrated with the times and locations recorded on the log sheet to derive the following variables with day defined as 07:00 to 21:59 hours and night defined as 22:00 to 06:59 hours. The averages take into account a time element which reflects the duration the child was in each environment and time over which the measurement was taken. Measurements were not recorded for time periods when the monitor was neither worn nor kept close by.

Duration Positron™ worn or kept close by

- home (day and night)
- school
- other.

Average electric field strength (volts/metre) only while Positron™ worn

- home (day and night)
- school
- other.

Average magnetic field flux density (μTesla) while Positron™ worn and/or kept close by

- home (day and night)
- school
- other.

Measurements Inside the Home

Inside measurements of 60 Hz magnetic fields in three rooms were made under "as is" or typical power conditions of electrical usage. In the child's bedroom point-in-time measurements were made approximately 12 inches over the centre of the child's bed and in other rooms, at the room centre at waist height and away from electrical appliances. The other two rooms represented those used most frequently by the child.

Static DC geomagnetic fields were measured at locations in current and previous residences (to which access was obtained) where the child spent most of his/her time - in bed, in the bedroom and in the family room. Measurements were taken using a Walker Scientific Flux-Gate Magnetometer (digital) to take readings in three orthogonal directions. Three measures were taken along the diagonal of the child's bed and in the centre of the relevant room.

For current residences, these measurements were made by the interviewer at the time of interview. When the technician subsequently visited the house to take outside measurements, permission was sought to re-enter the house to repeat 60 Hz and DC magnetic fields measurements taken by the interviewer.

Technicians made all these measurements for previous residences.

Measurements Outside the Home

Measurements of magnetic fields outside the home were taken by a technician blind to case control status. These measurements provided an index of magnetic field exposure which was common to both current and previous residences, while also serving as estimates of exposure inside the home where access was not possible and as a check for personal monitoring results and measurements taken inside the home.

Evidence from the previously completed pilot study (Donnelly and Agnew, 1991) indicated that magnetic fields just originating outside the house are generally important contributors to the magnetic field within the house and therefore it was thought that an outside perimeter measurement of magnetic fields would provide a reliable estimate of the fields inside the home.

A "perimeter measurement" was defined as measurements taken at uniform intervals of five metres around the perimeter of the home, commencing at one corner and restricting measures to only obvious living areas (e.g. garages were excluded unless there was living space above). All measurements were taken one metre from the house if possible and one metre above the ground. An average of these measures was calculated, after elimination of highly perturbed readings defined as one which was three times higher than the average of the two adjacent readings. The purpose of eliminating high readings was to avoid including fields from sources close to the point of measurement which are unlikely to have a significant influence inside the home, such as local conductors carrying current into or out of the house.

If a reading appeared to be high and apparently localized, additional measurements one metre before and after that point and two metres from the wall were taken. If the high field persisted in these additional readings, the value was retained in the perimeter average, as the field disturbance likely extended into the house.

The extent to which the perimeter measurement could be carried out was dictated by the willingness of the respondent to grant access to the property, the accessibility to the outside perimeter of the living area of the house and the type of housing structure. For example, only three walls of a semi-detached house are accessible for measurement. If the garage was attached to the home, measurements were not taken around the garage unless the interior wall of the garage adjacent to the living area of the house was accessible.

For each residence, a sketch was prepared which included information on the location of the service drop, electrical meter and entrance of electrical supply to the house, distance from the street and lot dimensions.

Measurements of net current on the drop to the house were also taken. A direct measurement of the net electric current on the electrical conductors entering the house were made outside the house by the technician. If a direct measurement could not be made, an estimate of the net current was obtained by measuring the magnetic field at a fixed distance from the same electrical conductors.

Wiring Configuration

Wiring configuration was determined according to criteria developed by Wertheimer and Leeper (Wertheimer and Leeper, 1979). The "Wertheimer and Leeper" wire code uses the type and number of distribution circuits and the distance of the residence to conductors (Appendix A).

- VHCC Very High Current Configuration,
- OHCC Ordinary High Current Configuration,
- OLCC Ordinary Low Current Configuration,
- VLCC Very Low Current Configuration and Underground.

A modified Wertheimer and Leeper code was also used which made special accommodation of underground wiring rather than assign this to VLCC. This modified

approach was based on Barnes et al., (1989) and denotes a house with underground service and no overhead wires within 150 feet. The categories are the same as listed above for the Wertheimer/Leeper codes with addition of UG which designates underground service.

Kaune and Savitz (1994) proposed and tested a simplified version of the wiring configuration which eliminated many of the ambiguities and inconsistencies inherent in the Wertheimer and Leeper code while enhancing the ability to predict magnetic fields (Appendix A). The "Kaune code" was also determined and consists of three categories:

. High
. Medium
. Low.

"Residency"/Attendance Requirements

Economy of resources dictated some modifications to the comprehensiveness of the measurements of electric and magnetic fields made in previous residences, schools and daycares/nurseries.

If the residence in which the child was living at the time of interview was relevant to the defined period of inquiry, the residence was labeled as "current". All current residences were eligible for measurement regardless of residence duration.

If the child was less than two years of age at diagnosis, all previous residences applicable to the defined period of inquiry and within the geographic catchment area were eligible for measurement. If the child was two years or more at the age of diagnosis, he/she must have resided at this residence for at least six months for the home to be eligible for measurement. Up to 10 previous residences were eligible for measurement. If there were more than 10 residences, the 10 of longest duration were identified for measurement.

For a school in the catchment area to be eligible for measurement, the child must have attended for a period of at least six months and for at least two hours per day. A few exceptions were made when the school was the only one for the child even though attendance was for less than six months.

All daycares and nurseries in the catchment area attended, regardless of duration, by children who were diagnosed at less than two years of age were eligible for measurement. If the child was two or more years of age and but less than six years at the time of diagnosis, daycares/nurseries attended for six months or more at least two hours per day were eligible. With few exceptions, no daycares/nurseries were designated as eligible if attended by a child who was six or more years of age at time of diagnosis.

	Age at Diagnosis or Reference Age/Date	
Residence in Catchment Area	**Less Than Two Years**	**Greater Than Two Years**
Current	All Eligible	All Eligible
Previous Residences	All Eligible	Residence Duration ≥ Six Months
Schools	N/A	Attendance ≥ Six Months ≥ Two Hours/Day
Daycares/Nurseries*	All Eligible	Attendance ≥ Six Months ≥ Two Hours/Day

- If child was ≥ six years at diagnosis, no daycares/nurseries were eligible for measurement, although there were a few exceptions.

Data Processing

Questionnaire data were coded by only two individuals. All diseases or medical conditions were coded using ICD-9 (International Classification of Diseases). Parents' occupations were coded using standard Canadian occupational and industry classifications (Statistics Canada, 1980a and 1980b). Information relating to medications was verified with a compendium of pharmaceuticals (Canadian Pharmaceutical

Association, 1991) which specified both the product and generic names and was then categorized according to broad therapeutic indications, e.g. analgesics, antibiotics, etc.

Information for previous residences, essential for exposure assessment, was sometimes incomplete. As far as possible each address was completed with respect to full street name, postal code, city/town. Address information pertaining to previous residences within the period of inquiry was extracted from the questionnaire and given to personnel responsible for the exposure assessment.

Information derived from the questionnaire was coded and entered by two data entry clerks into a total of 32 relational data bases created in FoxPro. The data was also converted to SAS version 6.04 to facilitate manipulation and to prepare the data for analysis.

Quality Assessment

The coded questionnaires were randomly checked by an individual (blind to case control status) who did not originally code it to ensure consistency of interpretation. Also, each question was checked to ensure that information relating to the period of inquiry for that child was included.

A series of data logic checks which focused primarily on the consistency dates with respect to the period of inquiry were carried out. For example, dates of reported exposures must be prior to date of diagnosis or reference date and within the period of inquiry. All discrepancies were resolved. Missing data were also checked: if possible, where information from related questions was available to complete that which was missing, this was done.

Verification of data entry was carried out by entering a sample of questionnaires twice. A random sample of 16% of the questionnaires was entered a second time by a

person different from the person who originally entered the data. Any discrepancies were resolved after consultation with at least two members of the research staff. There was minimal data entry error. There were over 350 variables per questionnaire, of which the sample showed data entry error of less than 1.3%.

Calibration checks of all monitors were performed after each use and of survey meters at regular intervals of approximately one month.

All field measurements performed by interviewers and technicians were entered into a database. Every measurement entered was then checked against the value recorded on the field data collection forms. The information recorded on the log sheet by the parent or child in conjunction with the wearing of the Positron™ monitor was occasionally ambiguous. Therefore, the personal monitoring data was re-examined for all study participants having an average electric field exposure greater than 20 volts per metre and magnetic field exposure greater than 1μT for any time period. The electric and magnetic field data was examined graphically and compared with the log sheet for consistency. Typically the wearing of a monitor is associated with changes in the electric field strength and magnetic flux density with time. If the electric field or magnetic flux density reading was constant at elevated levels for a period greater than 30 minutes and the log sheet indicated that the child was active, the electric field data was flagged for further scrutiny. Such examination was extended to all time periods for that subject to determine if there were similar incompatibilities of the reading and log sheet. If information did not support there being a high electric field and magnetic field present in the environment occupied during the time period in question, this time period was not used in the assessment of electric or magnetic field exposures. Fifty-nine from a total of 4460 time periods were removed from further analyses due to such incompatibilities.

Over 75% of the measurements made in the current residence by the interviewer, were checked by the technician at a subsequent visit. These duplicate measurements

were considered for consistency and changes in home conditions which might contribute to possible differences. No significant differences were found between the measurements made by the interviewer and the technician.

Data Analysis Methods

The data were initially explored with SAS (SAS Institute, 1985) and STATA (Stata Corporation, 1997) to produce frequency distributions and descriptive statistics which were used to evaluate potential differences between cases and controls. Differences between cases and controls for categorical variables were based on the chi-square statistic. For continuous variables, differences were evaluated using the mean and standard deviation using a t-test with $p<0.05$. Given the inconsistencies in the literature, all statistical tests were two-sided.

For logistic regression analyses, continuous variables, in particular those relating to measurements of electric and magnetic fields, were categorized into quartiles with the cut-points based on the distribution of the exposures for the controls. Because the relationship between electric and magnetic field exposure and childhood leukaemia, in particular that defined by personal monitoring, is neither well characterized nor well understood, the decision was taken to not analyze electric and magnetic field exposures as continuous variables. There is no evidence to date which suggests these exposures are linearly related to the risk of childhood leukaemia and the categorical approach was expected to facilitate interpretability and allow for the detection of relationships which might not fit the linear association. The categorical approach also helped avoid undue influence of 'outliers'.

To assess possible differences between cases and controls with respect to missing information, where appropriate, a category denoting missing data was included in the analyses.

Standard methods were used for the analysis of case control studies as described by Breslow and Day (1980). The study was a matched design and accordingly the matching was retained in the analysis to ensure the least biased estimate of risk (Schlesselman, 1982; Kleinbaum et al., 1982). Univariate conditional logistic regression was used to estimate odds ratios for those potential confounders or known risk factors derived from the questionnaire and for measures of electric and magnetic field exposure.

Maximum likelihood estimates of leukaemia risk were obtained using multivariate methods to describe the relationship with electric and magnetic field exposures based on the total monitored time, on residential monitoring and wiring configuration, while controlling for confounders. Univariate analyses using information derived from the questionnaire were the basis for determining potential confounding variables to be included in the multivariate model. A criterion of $p<0.20$ was used to identify those parameters for inclusion in the multivariate model. This applied to binary variables and to categorical variables (any category) attaining this level of significance. This significance level was regarded as 'conservative' and was chosen to minimize the chance of missing some important confounders which might not be apparent from univariate analyses but rather only in combination with other factors (Mickey and Greenland, 1989; Hosmer and Lemeshow, 1989).

Previous research has not suggested any potentially important factors related to electric and magnetic fields and childhood leukaemia risk, although socioeconomic characteristics and residential mobility were possible candidates for inclusion in a multivariate model. In the absence of any compelling information in this regard, explanatory variables were identified according to statistical criteria. Stepwise backward regression was used to estimate leukaemia risk with the full model containing all explanatory variables or potential confounders meeting the $p<0.20$ criterion (Hosmer and Lemeshow, 1989). A significance level of 0.15 was specified for the removal of a term from the model and a p-value of 0.10 for re-introduction of terms. The stepwise

backward approach was selected because it allowed all potential confounding variables to be tested in relation to the other variables and the exposure of primary interest. The main effect was retained in all models.

The likelihood ratio test was used to evaluate the significance of each explanatory variable to the fully adjusted model.

Odds ratios and corresponding confidence intervals were computed using STATA for all analyses using EMF information and all multivariate modelling or SAS for interview derived variables.

Chapter 4

RESULTS

Case Control Participation

A total of 256 children with leukaemia were approached to participate in this study. Consent to be interviewed was received from a total of 212 (Table 1). One of these cases could not be located when an attempt was made to schedule the interview and eight subsequently declined. The main reasons for this change in willingness to participate were that the child had relapsed or there had been an alteration in family or medical circumstances which were not conducive to the interview process.

Not surprisingly, given the retrospective nature of the study, several families could not be traced and/or were known to have moved out of the catchment area since the date of diagnosis. The vital status of some of these cases is unknown as there had been no ongoing contact but many are known to be deceased. No attempt was made to contact these families.

As previously described, the approach to the cases first required the physician's approval. At the end of the study, there were 22 potentially eligible cases where the physician requested deferral or did not wish the family to be approached at all. In some instances, the child had recently relapsed or died or the prognosis was known to be poor. There were other situations when it was judged inappropriate to approach the family about the study due to social and/or other family health problems. The majority of these cases where physician consent was not given were deceased and it is therefore possible that, even if consent had been provided, the family might have relocated outside the catchment area. Throughout the study the treating physicians who requested that some patients not be contacted or that contact be deferred were periodically asked if they would reconsider this decision until such time when the study was deemed "closed". As the end of the period of case recruitment approached, for some cases sufficient 'compassionate' time had not elapsed and these deferred cases became synonymous with physician refusal. Necessarily time constraints prohibited re-approach for the cases recruited near the end of the study period.

TABLE 1

Case Control Participation

	Case	Control
Eligible	298	1133*
Physician Refusal	22**	n/a
Unable to contact	22**	n/a
Approached	256	645
No response: untraceable, communications problems	36**	45
Refused	17	168
Interviewed	203	419
Discarded***	2	13
Final	201	406

* Number indicating eligibility and agreeing to be contacted at a later date regarding participation in the study

** Several known to have moved out of the catchment area

*** Post-interview determination that the child was not resident in the catchment area at the date of diagnosis or reference date and therefore ineligible

After receiving the letter from the treating physician regarding the study and seeking agreement from the family to be contacted by the University of Toronto, eight families declined.

There were 36 cases approached by the treating physician who did not respond and six for whom the letter was returned undelivered. Attempts were made to ascertain a current address but several remained untraceable. Most of those who were untraceable were known to be deceased but it was also possible that some had moved out of the catchment area.

Of the 645 control names randomly selected from the constructed 'census' of potential controls, 25 could not be contacted to inquire if they would participate, 168 refused participation in the study, and 20 could not communicate in English and it was not possible to determine the language needed to make appropriate inquiries. Thirteen were considered "unevaluable": although these respondents agreed to participate they did not have knowledge about the child which would be sought in the interview process, such as the child's medical history, residential history, etc. In such instances, the child may have been in foster care. The resulting number of controls interviewed was 419.

Characteristics of the Cases and Controls

The distribution of participating children with leukaemia according to histologic diagnoses (Birch and Marsden, 1987) is presented in Table 2. All cases of leukaemia were confirmed by appropriate histopathological review. The majority (84.1%) of the cases were acute lymphoblastic which is consistent with childhood leukaemia patterns observed in developed countries.

Leukaemia cases by year of diagnosis and vital status at the time the physician was asked to provide consent to approach the family or child regarding participation in the study are presented in Table 3.

TABLE 2

Histologic Subtypes of Leukaemia

Type of Leukaemia	Frequency *(n)*	%
Acute Lymphoblastic Leukaemia	169	84.1
Acute Myeloid Leukaemia	9	4.5
Acute Myelomonocytic Leukaemia	4	2.0
Acute Erythrocytic Leukaemia	2	1.0
Acute Promyelocytic Leukaemia	3	1.5
Acute Megakaryoblastic Leukaemia	5	2.5
Chronic Myeloid Leukaemia	4	2.0
Juvenile Chronic Myeloid Leukaemia	2	1.0
Acute Leukaemia NOS, e.g., mixed lineage, myeloid dysplastic syndrome, biphenotypic	3	1.5

• According to Manchester Classification (Birch & Marsden, 1987)

TABLE 3

Year of Diagnosis and Vital Status of Participating Cases at Time of Approach

Calendar Year of Diagnosis	*n*	Alive	Deceased
1985	12	9	3
1986	16	15	1
1987	23	21	2
1988	19	19	-
1989	20	18	2
1990	32	29	3
1991	29	28	1
1992	29	29	-
1993	21	20	1
	201	**188**	**13**

The demographic and family characteristics of the cases and controls are summarized in Table 4. The distribution by age and sex confirms the success of the matching process. Fifty-one percent (51%) of the leukaemia cases were less than five years of age at the time of diagnosis and slightly more were male, a distribution representative of that for age and sex for childhood leukaemia in Ontario (Ontario Cancer Registry, 1996). The characteristic peak in the age at diagnosis of two to four years was observed in this study population and is compatible with the descriptive epidemiologic features of childhood leukaemia.

The majority of participants were Canadian-born but with a wide representation of racial and ethnic backgrounds, reflective of the cultural diversity of the defined catchment area. There were more cases reporting Asian ancestry and/or Oriental race than controls. There were proportionately fewer Caucasian cases than controls. Cases and controls did not differ significantly with respect to whether or not they had siblings, nor whether they were the biologic child of either parent interviewed. Affiliation with a religious group was not appreciably different between cases and controls. Cases were more residentially mobile than controls. More cases than controls reported living in excess of three residences during the defined period of inquiry. There were significant differences in reported family income between cases and controls with controls on average having higher incomes.

It was not possible to select controls concurrently with the time of diagnosis of the cases. To ensure that this had not compromised comparability, both cases and controls were scrutinized after data collection with respect to residence in the catchment area at the date diagnosis. This led to the removal of two cases and 13 controls and introduced some disruption to the 1:2 matching ratio. Necessarily there was a random reassignment of controls to cases which took into account the year of birth, child's gender and dates relating to the period of inquiry. This resulted in the following number of matched sets:

TABLE 4

Number and Percent Distribution of Study Subjects by Demographic and Family Characteristics

	Cases		Controls	
	n	%	*n*	%
Age at Diagnosis or Reference Date				
< 2 years	22	11.0	44	10.8
2 - 3	58	28.9	128	31.5
4 - 5	42	20.9	68	16.8
6 - 9	38	18.9	81	19.9
10+	41	20.4	85	20.9
Sex				
Male	114	56.7	225	55.4
Female	87	43.3	181	44.6
Country of Birth				
Canada	183	91.0	379	93.4
Other	18	9.0	27	6.6
Racial Group				
Caucasian	160	79.6	352	86.5*
Oriental	15	7.5	13	3.2
Black	10	4.9	13	3.2
East Indian	7	3.5	19	4.7
Other	9	4.5	9	2.2
Father's Ancestry				
British Isles	67	33.3	146	35.9
European	41	20.4	86	21.1
Eastern European	16	8.0	37	9.1
Scandinavian/Baltic	3	1.5	4	1.0
Middle East	2	1.0	7	2.2
Far East/Asia	19	9.4	20	4.9
India/Pakistan	11	5.5	19	4.7
Latin/South American/Caribbean	14	7.0	21	5.2
Russian	4	2.0	17	4.2
Canadian/American	12	6.0	16	3.9
Other	5	2.5	5	1.2
Unknown	7	3.5	28	6.9

* $p < 0.05$ difference between cases and controls

TABLE 4 (continued)

Mother's Ancestry				
British Isles	67	33.3	147	36.1
European	42	20.9	85	20.9
Eastern European	14	7.0	33	8.1
Scandinavian/Baltic	3	1.5	4	1.0
Middle East	2	1.0	8	2.0
Far East/Asia	18	8.9	20	4.9
India/Pakistan	10	5.0	19	4.7
Latin/South American/Caribbean	15	7.5	20	4.9
Russian	7	3.5	14	3.4
Canadian/American	14	7.0	25	6.2
Other	2	1.0	7	1.7
Unknown	7	3.5	24	5.9
Religion				
Catholic	69	34.3	143	35.1
Protestant	54	26.9	115	28.3
Jewish	11	5.5	23	5.6
Greek Orthodox	3	1.5	8	2.0
Hindu	1	0.5	4	1.0
Buddhist	5	2.5	1	0.3
Islam	7	3.5	11	2.7
Other	2	1.0	9	3.0
No Religion	48	23.9	88	21.6
Unknown	1	0.5	4	1.0
Siblings				
Only Child	15	7.5	44	10.8
Has Siblings	185	92.0	361	88.9
Unknown	1	0.5	1	0.3
Adopted Child				
Yes	3	1.5	8	2.0
No	198	98.5	398	98.0
Number of Residences				
1	68	33.8	157	38.7
2	65	32.3	136	33.5
3	25	12.4	60	14.8
4	23	11.4	28	6.9
5+	20	10.0	25	6.2
Family Income				
< $20,000	20	9.9	15	3.7
≥ $20,000-39,000	33	16.4	59	14.5
$40,000-59,000	61	30.4	103	25.3
$60,000	76	37.8	208	51.2*
Refused	5	2.5	11	2.7
Don't Know	6	3.0	10	2.5

* $p < 0.05$ difference between cases and controls

Case control ratio	Number of matched sets
1:1	14
1:2	173*
1:3	12
1:4	1
1:6	1

- disruption of matching for one case control set - male case matched to one male control and one female control

Characteristics of Non-Participants

For cases and controls who did not participate there was some information which permitted a limited assessment of comparability of participants with non-participants.

Table 5 shows the histologic subtypes of leukaemia for non-participants. Acute myelogenous leukaemia was more common among non-participating cases. This cell type is associated with a poorer prognosis than the more common acute lymphoblastic leukaemia and is compatible with the observation that for several cases who did not respond regarding study participation, the hospital had lost contact and had no forwarding address. The distribution of age at diagnosis was not significantly different for non-participating cases, although there were slightly more younger cases among the non-participants. In the final year (1993) of case ascertainment which was essentially prospective, there were proportionately more cases who did not participate than those who did. It is possible that sufficient time had not elapsed for the recently diagnosed case to have achieved remission.

Wire code was determined for those identified controls who volunteered that they had an eligible child but who did not participate either because of direct refusal, language barriers, or inability to re-contact. From the teledirect marketing lists address information was available for controls and therefore an attempt was made to determine the wire code for the non-participant addresses. The address information was current to the date of the telephone lists.

TABLE 5

Non-Participating Cases - Histology and Age at Diagnosis

	Frequency *(n)*	%
Histologic Subtypes of Leukaemia*		
Acute Lymphoblastic Leukaemia	44	74.6
Acute Myeloid Leukaemia	5	8.5
Acute Myelomonocytic Leukaemia	1	1.7
Acute Erythrocytic Leukaemia	2	3.4
Acute Promyelocytic Leukaemia	2	3.4
Chronic Myeloid Leukaemia	1	1.7
Juvenile Chronic Myeloid Leukaemia	2	3.4
Acute Leukaemia NOS, e.g., mixed lineage, myeloid dysplastic syndrome, biphenyltypic	2	3.4
Age at Diagnosis		
< 2 years	10	17.0
2 - 3 years	12	20.3
4 - 5 years	11	18.6
6 - 9 years	13	22.0
≥ 10 years	13	22.0

* According to Manchester Classification (Birch and Marsden, 1987)

Limited resources allowed for visits to be made to only a sample of addresses (n=116) for non-participating controls. Three of these residences could not be located. Of those remaining, wire codes were assigned according to the coding scheme initially proposed by Wertheimer and Leeper (1979) and to that proposed by Kaune and Savitz (1994).

Similarly a comparison was made between cases who participated and those who did not either because of direct refusal or inability to contact. For case non-participants residential information was abstracted from hospital records.

Table 6 presents wire code information for case and control non-participants. With the exception of residences coded to VLCC, the distribution of wire codes for current residences did not differ between participants and non-participants. Generally participants had a greater proportion of very low current configuration homes, compared to those of non-participants but no differences existed between cases and controls with respect to participant status.

A component of wire code is distance from the line. This is relevant for single family dwellings but not for apartments. Apartments differ importantly from single unit dwellings as EMF fields are more influenced by wiring within the apartment complex itself than by proximity to power lines. It is therefore not meaningful to assign wire codes to apartments. That being so, case and control non-participants were compared with respect to residence type. However, the residence designation of "apartment" showed statistically significant ($p<.05$) differences between participants and non-participants for both cases and controls. For participating subjects, cases and controls, where information was available for current residence, 7.0% (25/358) were living in an apartment while for non-participating cases and controls the corresponding percentage living in an apartment at the time of diagnosis of the case or the time of first contact for the controls was 28.5 % (59/207).

TABLE 6

Comparison of Wire Codes for Case and Control Non-Participants

	Participants				Non-Participants			
	Cases		Controls		Cases		Controls	
Wire Code	n	%	n	%	n	%	n	%
Wertheimer Leeper Code								
VLCC	63	59.4	129	56.3	34	47.2	47	58.0
OLCC	24	22.6	49	21.4	18	25.0	13	16.0
OHCC	17	16.0	39	17.0	15	20.8	15	18.5
VHCC	2	1.9	10	4.4	3	4.2	3	3.7
Missing	-	-	2	0.9	2	2.8	3†	3.7
Kaune Code								
Low	74	69.8	154	67.7	47	65.3	54	66.7
Medium	27	25.5	46	20.1	15	20.8	18	22.2
High	5	4.7	27	11.8	8	11.1	6	7.4
Missing	-	-	2	0.9	2	2.7	3†	3.7
Apartment*	11	9.4	14	5.8	25	25.8	34	29.6

Notes:

Participants' information based only on current residence
Non-participant information for controls based on residence in teledirect marketing lists (1992)
Non-participant information for cases based on residence at date of diagnosis

† Residence could not be located
• Residence in 'Apartment' different between cases and controls ($p<0.05$)

Interview

Information relating to the mother was obtained primarily from the mother herself, with 92.5% of the cases and 97.8% of the control mothers providing responses directly. For 6.0% of the cases and 1.3% of the controls the spouse provided the information about the mother. Information relating to the father was obtained directly from the father for 56.2 % of the cases and 36.4% of the controls. The spouse provided the information about the father for 41.8% of the cases and for 61.6% of controls.

At the end of each interview, the interviewer made a subjective judgement concerning the reliability of the information about the mother and the father which had just been collected. The mother's information was judged to be more reliable than the father's, probably due in part to the fact for a large percentage of the fathers the information was not gathered directly. Nevertheless, the judged reliability did not differ significantly between cases and controls.

Univariate Analyses of Risk Factors and Potential Confounders

Comparisons of cases and controls for demographic characteristics, risk factors and potential confounders derived from the questionnaire were evaluated using univariate conditional logistic regression.

Univariate analyses showed consistent excess leukaemia risks for children of Asian ancestry or Oriental race (Table 7). The collinearity between these characteristics was the basis for the decision to select only race for inclusion in the multivariate model.

Having no siblings was associated with a non-significant decreased risk of leukaemia (OR=0.66, 95% CI 0.36-1.21).

Cases had higher residential mobility than controls. Increasing number of changes of residence ($\geq$ four residences) was associated with a significant increased risk of leukaemia (OR=2.19, 95% CI 1.31-3.65).

TABLE 7

Childhood Leukaemia Risk in Relation to Demographic and Family Characteristics

	Odds Ratio	95% Confidence Interval
Country of Birth		
Canadian Born	1.00	-
Other	1.46	0.76 - 2.82
Father's Ancestry		
British Isles/Canadian/American	1.00	-
European/Eastern European	0.97	0.63 - 1.49
Far East/Asia	1.96	0.99 - 3.87
Other	1.20	0.73 - 1.96
Unknown	0.50	0.20 - 1.29
Mother's Ancestry		
British Isles/Canadian/American	1.00	-
European/Eastern European	1.01	0.67 - 1.55
Far East/Asia	1.90	0.97 - 3.75
Other	1.25	0.77 - 2.03
Unknown	0.66	0.27 - 1.59
Siblings		
Siblings	1.00	-
No siblings	0.66	0.36 - 1.21
Religion		
No religion	1.00	-
Catholic	0.87	0.55 - 1.40
Protestant	0.86	0.54 - 1.38
Jewish	0.90	0.40 - 2.02
Other	1.03	0.53 - 2.00
Racial Group		
Caucasian	1.00	-
Oriental/Asia	2.22	1.20 - 4.10
Other	1.30	0.72 - 2.35
Number of Residences		
Categorical		-
1 - 3	1.00	
≥ 4	2.19	1.31 - 3.65
Continuous	1.20	1.04 - 1.37
Day Care Attendance		
No	1.00	-
Yes	0.88	0.63 - 1.25

Education at the high school level or lower for both fathers and mothers was associated with elevated risk for leukaemia in their children (Table 8). For mothers with incomplete high school education, the risk was statistically significant (OR=2.26, 95%CI 1.22-4.22).

Childhood leukaemia risk was inversely related to family income with each annual income level.

Estimates of leukaemia risk for selected characteristics relating to the child's medical history, with a focus on common childhood diseases, are presented in Table 9. Birth defects, including Downs syndrome which is known to be associated with an increased risk of childhood leukaemia, showed an elevated but non-significant odds ratio (OR=1.42, 95% CI 0.91-2.23). A history of measles, tonsillitis and otitis media was associated with a decreased but non-significant leukaemia risk but reported influenza was associated with a slightly elevated risk.

Infant feeding practices were evaluated (Table 10). Duration of breast feeding was associated with a significant decreased risk of leukaemia (OR=0.19, 95% CI 0.04-0.85) for those fed for six months or more compared to bottle fed children.

TABLE 10

Childhood Leukaemia Risk in Relation to Infant Feeding

	Odds Ratio	95% Confidence Interval
Formula only or Breastfeeding with Formula Supplementation	1.00	-
Breast Feeding only for -		
First 3 months after birth	1.10	0.75 - 1.60
4 - 5 months after birth	0.89	0.53 - 1.49
≥ 6 months after birth	0.19	0.04 - 0.85

TABLE 8

Childhood Leukaemia Risk and Characteristics of Parents

	Odds Ratio	95% Confidence Interval
Mother's Education		
University	1.00	-
Some post-secondary education	1.17	0.71 - 1.91
Grade 12/13 complete	1.62	1.00 - 2.62
Less than Grade 12	2.26	1.22 - 4.22
Unknown (n=4)	-	-
Father's Education		
University	1.00	-
Some post-secondary education	1.38	0.87 - 2.18
Grade 12/13 complete	1.38	0.86 - 2.21
Less than Grade 12	1.59	0.91 - 2.78
Unknown (n=17)	1.07	0.36 - 3.17
Family Income		
≥ $60,000	1.00	-
$30,000 - $59,000	1.52	1.03 - 2.23
< $30,000	2.90	1.67 - 5.05
Unknown/Refused	1.60	0.73 - 3.52

TABLE 9

Childhood Leukaemia Risk and Selected Factors Related to Delivery and Child's Medical History

	Odds Ratio*	95% Confidence Intervals
Birth Weight		
≥ 2500 gm	1.00	-
< 2500 gm	0.97	0.43 - 2.19
Gestational Age		
38 - 41 weeks	1.00	-
28 - 37 weeks	0.83	0.43 - 1.60
≥ 42 weeks	0.93	0.52 - 1.67
Type of Delivery		
Vaginal	1.00	-
Cesarean	0.98	0.65 - 1.49
Birth Defects		
No	1.00	-
Yes	1.42	0.91 - 2.23
History of Specific Childhood Diseases		
No	1.00	-
Yes	0.65	0.39 - 1.06
Chickenpox		
No	1.00	-
Yes	1.07	0.72 - 1.60
Measles		
No	1.00	-
Yes	0.57	0.25 - 1.29
Tonsillitis		
No	1.00	-
Yes	0.70	0.43 - 1.13
Jaundice		
No	1.00	-
Yes	0.95	0.61 - 1.48
Influenza		
No	1.00	-
Yes	1.33	0.91 - 1.95
Otitis Media		
No	1.00	-
Yes	0.73	0.52 - 1.03

* Matched pairs analysis using conditional logistic regression

Odds ratios for leukaemia risk relative to selected environmental risk factors and household products are presented in Table 11. All exposures related only to the defined period of inquiry. Associations were observed with the child's exposure to glues, fumes, gases or solvents (OR=1.52, 95% CI 1.00-2.29), garden or agricultural sprays (OR=1.37, 95% CI 0.87-2.18) and exposure to insecticides (OR=2.22, 95% CI 1.44-3.43). Exposure to household products such as turpentine showed an increased risk with leukaemia of borderline statistical significance (OR=1.64, 95% CI 0.99-2.72). Reported exposures of the child to household bleach were associated with decreased leukaemia risk (OR=0.67, 95% CI 0.45-0.99).

Selected characteristics relating to the mother were evaluated during or just prior to pregnancy of the index child (Table 12). A significant association was observed between the risk of leukaemia and reported diseases in the mother either immediately prior to or during pregnancy (OR=2.37, 95% CI 1.37-4.11). Medication use (OR=1.37, 95% CI 0.95-1.99) and x-rays (OR=1.40, 95% CI 0.97-2.01) prior to or during pregnancy were also related to increased, but non-significant, risks. Detailed inquiry was made of smoking habits of the mother. Although not statistically significant, risks were more pronounced for mothers who smoked during pregnancy (OR=1.36, 95% CI 0.89-2.08).

As for children, mothers were similarly questioned regarding environmental exposures and common household products such as cleaning agents, bleach, paint removers (Table 13). Exposure just prior to or during pregnancy to pesticides in general (OR=1.53, 95% CI 1.08-2.18) and specifically to garden insecticides (OR=1.99, 95% CI 1.12-3.55) showed a significant relationship with childhood leukaemia.

Specific inquiry was made regarding the use of those appliances previously reported to be related to leukaemia (London et al., 1991). In this study, no associations were observed with reported use of electric hair dryers, electric blankets or having a bedside clock (Table 14). Very few children reported no exposure to television. Of those who did watch television, there was a relationship between increased risk with increasing

TABLE 11

Childhood Leukaemia Risk and Child's Exposure* to Selected Environmental Factors and Household Products

	Odds Ratio**	95% Confidence Interval
Exposure to Glues, Fumes, Gases or Solvents		
Never	1.00	-
Ever	1.52	1.003 - 2.29
Exposure to Garden or Agricultural Sprays		
Never	1.00	-
Ever	1.37	0.87 - 2.18
Exposure to Insect Exterminator Treatment		
Never	1.00	-
Ever	2.22	1.44 - 4.08
Exposure to any Household Products		
No	1.00	-
Yes	1.04	0.73 - 1.48
Exposure to Paint Removers		
No	1.00	-
Yes	1.33	0.72 - 2.45
Exposure to Turpentine Products		
No	1.00	-
Yes	1.64	0.99 - 2.72
Exposure to Household Bleaches		
No	1.00	-
Yes	0.67	0.45 - 0.99

* Relevant to the period of inquiry
** Univariate analysis, conditional logistic regression

TABLE 12

Childhood Leukaemia Risk in Relation to Mother's Pregnancy Events

	Odds Ratio*	95% Confidence Interval
Diseases of Mother Immediately Prior to and/or During Pregnancy		
No	1.00	-
Yes	2.37	1.37 - 4.11
Medications Taken by Mother Immediately Prior to and/or During Pregnancy		
No	1.00	-
Yes	1.37	0.95 - 1.99
Don't Know	1.11	0.41 - 2.98
Maternal X-rays Two Years Prior to and/or During Pregnancy		
No	1.00	-
Yes	1.40	0.97 - 2.01
Don't Know	1.31	0.79 - 2.17
Smoking During Pregnancy		
Non-smoker	1.00	-
Smoked During Pregnancy	1.25	0.76 - 2.05
Non-smoker or Previous Smoker	1.00	-
Smoked During Pregnancy	1.36	0.89 - 2.08

* Matched pairs analysis using conditional logistic regression

TABLE 13

Childhood Leukaemia Risk in Relation to Mother's Exposure to Environmental Factors and Household Products Just Prior to or During Pregnancy

	Odds Ratio*	95% Confidence Interval
Exposure to Pesticides		
No	1.00	-
Yes	1.53	1.08 - 2.18
Unknown	0.62	0.23 - 1.70
Exposure to Garden Insecticides		
No	1.00	-
Yes	1.99	1.12 - 3.55
Exposure to Agricultural Sprays		
No	1.00	-
Yes	1.28	0.55 - 2.98
Exposure to Insect Exterminators		
No	1.00	-
Yes	1.03	0.54 - 1.97
Unknown	1.56	0.94 - 2.60
Cleaning Exposure to Household Products		
No	1.00	-
Yes	1.61	0.86 - 3.02
Unknown	1.52	0.41 - 5.62
Exposure to Paint Removers		
No	1.00	-
Yes	1.11	0.63 - 1.95
Exposure to Household Bleaches		
No	1.00	-
Yes	1.24	0.84 - 1.84
Exposure to Hair Colouring Products		
No	1.00	-
Yes	0.72	0.47 - 1.13

* Matched pairs univariate analysis using conditional logistic regression

TABLE 14

Childhood Leukaemia Risk in Relation to Child's Direct Exposure* to Specific Electrical Appliances

	Odds Ratio**	95% Confidence Interval
Electric Hair Dryer Used		
No	1.00	-
Yes	1.16	0.80 - 1.68
Age Hair Dryer First Used		
<1 Year	1.00	-
2 - 3 Years	1.09	0.29 - 4.09
4+ Years	0.56	0.13 - 2.48
Electric Blanket Used		
No	1.00	-
Yes	1.04	0.26 - 4.18
Heating Pad Used		
No	1.00	-
Yes	1.18	0.52 - 2.69
T.V. Hours (hours per week)		
≤7 hours	1.00	-
8 - 14	1.21	0.71 - 2.04
15 - 21	1.75	1.01 - 3.04
22 - 28	1.25	0.65 - 2.38
> 28	1.67	0.96 - 2.90
Bedside Clock		
No	1.00	-
Yes	1.17	0.69 - 1.99

* During period of inquiry
** Matched analysis using conditional logistic regression

hours of television viewing. However, if the Positron monitor was worn when watching television, EMF exposures would be measured more directly in this manner and therefore, this variable was excluded from the multivariate model.

Measurement of Electric and Magnetic Field Exposures in Current Residences

Personal Monitoring

For 571 of the 607 subjects either point-in-time measurements of magnetic field or wire code were available. Collectively the percentage of the total etiologic period represented by these residences, current and previous, was 77% and 87% for cases and controls respectively.

For 58.7% (n=118) of the cases and 62.8% of the controls (n= 255), the residence in which they were currently residing was relevant to the period of inquiry and therefore these children were eligible to wear the Positron monitor (Table 15). It is these subjects who are the focus of the following analyses.

TABLE 15

Personal Monitoring According to Case Control Status

	Case		Control	
	n	%	*n*	%
Eligible to Wear Monitor	118		255	
Wore Monitor	108	91.5	230	90.2
Refused	3	2.5	8	3.1
Failed	2	1.7	3	1.1
Other	5	4.2	14	5.5

Some studies have imposed a residency requirement on the controls (Savitz et al., 1988; Tomenius, 1986). This has led to the criticism that the controls might be more residentially stable than cases which in turn might be associated with other lifestyle or socioeconomic characteristics which are confounding the relationship between leukaemia risk and electric and magnetic field exposures (Jones et al., 1993). In this study, no such restrictions were imposed and therefore, both cases and controls might have resided only a short time in the catchment area. The shortest residence duration (excluding the prenatal period) in the current home was just over 1.5 months, a control, and the longest duration was over 14 years, also a control. Cases and controls had lived in their current residence, excluding the prenatal period, approximately the same period of time, mean duration in the current residence for cases was 4.2 ± 3.2 years and for controls, 3.63 ± 2.7 years. For 65 cases and 158 controls, the current residence was also relevant to the prenatal period.

Overall, compliance in wearing the monitor was excellent, with 92% of cases and controls agreeing to wear the dosimeter. For 35 study participants, Positron information was not available for the following reasons: there were five instances (two cases and three controls) where the monitor malfunctioned and the readings were lost; three cases and eight controls refused to wear the dosimeter; there were two controls for whom the interviewer judged it inappropriate for the monitor to be left; and five cases and 12 controls were missed.

Unlike the questionnaire data, for electric and magnetic field exposures, there were many different types of measurements and not all were available and/or applicable to all study participants. Personal monitoring was appropriate for only those participants whose current residence was relevant to the period of inquiry. Although overall the proportion of cases and controls eligible to wear the monitor was not significantly different, eligibility or relevance of current residence to the period of inquiry was not necessarily the same for matched cases and controls. The number of matched sets where both the case and control wore the Positron monitor were substantially reduced:

Case control ratio	Number of matched sets
1:1	45
1:2	41
1:3	2

Point-in-Time Measurements

Other magnetic field measurements of the current residence, both inside and outside, consisted of those previously described: measurements in the child's bedroom and two other rooms most commonly used by the child, outside perimeter measurement if appropriate and feasible and measurements at the housefront if applicable (Table 16). Consideration of these measurements by themselves and in relation to those from personal monitoring will be used as the basis to derive an estimate of exposure for previous residences where personal monitoring was not possible but are not the focus of these analyses.

TABLE 16

Types of Magnetic Field Measurements (μT) for Eligible Current Residences

	Cases			Controls		
	Number	Mean	(S.D.)	Number	Mean	(S.D.)
Child's Bedroom	111	0.11	(0.14)	234	0.11	(0.15)
Room 1	111	0.14	(0.17)	235	0.12	(0.15)
Room 2	107	0.12	(0.13)	219	0.13	(0.20)
Outside Residence	111	0.12	(0.16)	237	0.12	(0.15)
Housefront*	102	0.16	(0.20)	226	0.15	(0.18)

* Excludes apartments

Wiring Configuration

Wiring configuration for the current residence was classified according to the coding schemes of Wertheimer and Leeper and Kaune. Mean magnetic field

measurements derived from wearing the Positron monitor inside the home and measurements taken outside (perimeter) according to wire code classification are presented in Table 17. Measured levels of magnetic fields increased for wire code categories denoting higher wire configuration. Unless the residence is in close proximity to a high voltage transmission line, it is unlikely that the electric field strength within the home would be influenced and this was confirmed by examining the personal monitoring data for electric fields within the home (data not shown). Depending upon the classification of wiring configuration, homes with VHCC accounted for 4% (Wertheimer and Leeper) and 9% (Kaune) of the current residences (excluding apartments), a percentage less than that observed by London et al. (1991) in Los Angeles (16%) but slightly more than that observed in Denver (3%) by Savitz et al. (1988).

Duration of Personal Monitoring

For a total of 338 subjects, the Positron monitor was worn or kept nearby for approximately two days with no differences observed between cases and controls. The family and/or child kept log information according to time spent at home, at school and "other" (Table 18). More than 98% of the cases and 94% of the controls wore the monitor at home. The child's residence represented the greatest proportion of the total monitoring time for both cases (78%) and controls (76%) which might be expected given the young age of the subjects. Cases wore the monitor at home significantly ($p<0.05$) longer (14.5 hours) than did controls (12.6 hours).

The Positron monitor was worn or taken to school for a total of slightly more than eight hours. While the monitoring time did not differ between cases and controls, fewer cases (46%) than controls (60%) actually took the monitor to school.

Slightly more cases (92%) than controls (89%) wore the monitor in locations "other" than school or home but monitoring time in these locations did not differ between cases and controls, with average time being approximately eight hours.

TABLE 17

Wire Codes and Measured Magnetic Flux Density (μT)

Wiring Configuration	Cases		Controls	
Wertheimer and Leeper				
	Measurements Taken Outside the Residence			
	n	**mean (± S.D.)**	***n***	**mean (± S.D.)**
VLCC	60	0.08 (0.07)	124	0.08 (0.13)
OLCC	21	0.15 (0.09)	47	0.15 (0.13)
OHCC	14	0.15 (0.12)	36	0.16 (0.15)
VHCC	2	0.88 (0.50)	10	0.24 (0.10)
	Personal Monitoring Inside the Residence			
	n	**mean (± S.D.)**	***n***	**mean (± S.D.)**
VLCC	60	0.08 (0.07)	124	0.08 (0.07)
OLCC	21	0.18 (0.10)	47	0.18 (0.14)
OHCC	15	0.20 (0.19)	36	0.19 (0.16)
VHCC	2	0.63 (0.38)	10	0.38 (0.23)
Kaune Wire Code				
	Measurements Taken Outside the Residence			
	n	**mean (± S.D.)**	***n***	**mean (± S.D.)**
Low	70	0.08 (0.08)	149	0.08 (0.12)
Medium	22	0.15 (0.11)	43	0.17 (0.14)
High	5	0.49 (0.45)	25	0.21 (0.15)
	Personal Monitoring Inside the Residence			
	n	**mean (± S.D.)**	***n***	**mean (± S.D.)**
Low	70	0.09 (0.08)	149	0.10 (0.14)
Medium	23	0.20 (0.15)	43	0.21 (0.15)
High	5	0.43 (0.23)	25	0.28 (0.20)

TABLE 18

Duration of Personal Monitoring (Hours) According to Case Control Status

	Cases			Controls		
	n	Mean	(S.D.)	*n*	Mean	(S.D.)
Duration Positron™ Worn						
At Home*	105	14.53	(8.61)	216	12.54	(7.29)
At School	50	8.04	(5.19)	138	9.21	(4.74)
Other	99	7.78	(6.19)	204	6.96	(5.22)
Total	106	25.45	(10.31)	216	24.99	(9.60)
Duration Positron™ Worn and/or In Close Proximity						
At Home	108	41.42	(14.18)	230	38.75	(15.89)
At School	50	8.08	(5.17)	138	9.28	(4.75)
Other	99	8.45	(8.01)	204	7.55	(6.51)
Total	108	52.91	(16.43)	230	51.01	(16.11)
Duration Positron Worn™ and/or In Close Proximity by Age* (Home, School, Other)						
<4 Years	13	52.14	(19.02)	26	48.46	(12.75)
4 - 9	55	55.74	(16.68)	99	52.49	(16.10)
10 - 14	28	54.34	(13.66)	70	51.75	(16.63)
15+	12	37.45	(10.08)	35	47.27	(17.16)
Duration Worn™ and/or In Close Proximity by Sex (Home, School, Other)						
Male	60	53.81	(16.99)	124	49.22	(15.30)
Female	48	51.78	(15.81)	106	53.12	(16.85)

* Cases and controls significantly different, P<0.05

** Age at date Positron™ was worn

For both cases and controls, older children, in particular those 15 years of age or older at the time of monitoring wore the Positron for a shorter period of time than younger children. Controls who were 15 years of age or older wore the monitor longer ($p=0.02$) than the cases of corresponding age.

Descriptive Statistics of Electric and Magnetic Field Exposures

The distribution of electric and magnetic field exposures by case control status and location of exposure are presented in Tables 19 and 20. Average electric and magnetic field exposures in the child's residence according to time of day (day versus night) and whether the monitor was worn or kept close by are shown in Table 21. No differences existed between cases and controls with respect to mean electric and magnetic field exposures. On average, residential exposures to electric fields were higher than those found in schools or elsewhere and magnetic field exposures were highest in "other" locations (Table 22).

As expected average daytime residential magnetic field exposures, whether the monitor was worn or kept close by, were higher than nighttime exposures.

Table 23 presents both electric and magnetic field exposures received in the school environment. Only 46% of cases and 60% of controls wore the monitor to school and as a result the mean values are based on comparatively small numbers. The school attended by the child at the time she/he was wearing the monitor was relevant to the period of inquiry for only 21 subjects, 7 cases and 14 controls, which is not surprising since the time between the end of the period of inquiry and the time the monitor was worn was on average four years. Both electric and magnetic field exposures in schools are on average lower than those typical of residential environments.

TABLE 19

Distribution of Magnetic Field (μT) Exposures Measured by Personal Monitoring According to Location

Levels	Cases		Controls	
	n	%	n	%
Home[1]				
<.02	6	5.56	21	9.13
.02 - .039	18	16.67	37	16.09
.04 - .59	12	11.11	31	13.48
.06 - .079	10	9.26	24	10.43
.08 - .099	15	13.89	14	6.09
.10 - .19	23	21.30	51	22.17
.20 - .39	20	18.52	35	15.22
.40 - .79	4	3.70	13	5.65
≥ .80	-	-	4	1.74
School[2]				
< 02	5	4.63	17	7.39
.02 - .039	9	8.83	24	10.43
.04 - .059	7	6.48	22	9.57
.06 - .079	1	0.93	12	5.22
.08 - .099	5	4.63	12	5.22
.10 - .19	17	15.74	26	11.30
.20 - .39	3	2.78	20	8.70
.40 - .79	2	1.85	3	1.30
≥ .80	1	0.93	2	0.87
missing	58	53.70	92	40.00
Other[3]				
< .02	2	1.85	2	0.87
.02 - .039	2	1.85	9	3.91
.04 - .059	5	4.63	17	7.39
.06 - .079	6	5.56	30	13.04
.08 - .099	8	7.41	11	4.78
.10 - .19	45	41.67	74	32.17
.20 - .39	23	21.30	45	19.57
.40 - .79	8	7.41	13	5.65
≥ .80	-	-	3	1.30
missing	9	8.33	26	11.30

[1] Time weighted average of magnetic field density while Positron™ worn and/or kept close by in the home
[2] Time weighted average of magnetic field density while Positron™ worn and/or kept close at school
[3] Time weighted average of magnetic field density while Positron™ worn and/or kept close in location designated as "other"

TABLE 20

Distribution of Electric Field (V/m) Exposures Measured by Personal Monitoring According to Location

Levels	Cases		Controls	
	n	%	n	%
		Home[1]		
<2.0	2	1.85	6	2.61
2.0 - 3.9	15	13.89	20	8.70
4.0 - 5.9	25	23.15	43	18.70
6.0 - 7.9	22	20.37	47	20.43
8.0 - 9.9	11	10.19	27	11.74
10.0 - 11.9	10	9.26	24	10.43
12.0 - 13.9	4	3.70	14	6.09
14.0 - 15.9	5	4.63	16	6.96
≥ 16.0	11	10.19	19	8.26
missing	3	2.78	14	6.09
		School[2]		
< 2.0	22	20.37	48	20.78
2.0 - 3.9	12	11.11	40	17.39
4.0 - 5.9	7	6.48	18	7.83
6.0 - 7.9	4	3.70	12	5.22
8.0 - 9.9	2	1.85	6	2.61
10.0 - 11.9	2	1.85	6	2.61
12.0 - 13.9	-	-	1	0.43
14.0 - 15.9	-	-	2	0.87
≥ 16.0	1	0.93	5	2.17
missing	58	53.70	92	40.00
		Other[3]		
< 2.0	14	12.96	20	8.70
2.0 - 3.9	36	33.33	41	17.83
4.0 - 5.9	14	12.96	36	15.65
6.0 - 7.9	13	12.04	29	12.61
8.0 - 9.9	8	7.41	20	8.70
10.0 - 11.9	1	0.93	20	8.70
12.0 - 13.9	4	3.70	15	6.52
14.0 - 15.9	3	2.78	3	1.30
≥ 16.0	6	5.56	20	8.70
missing	9	8.33	26	11.30

[1] Average electric field strength while Positron™ worn in the home
[2] Average electric field strength while Positron™ worn at school
[3] Average electric field strength while Positron™ worn in location designated as "other"

TABLE 21

Comparison of Mean Electric and Magnetic Field Measurements - Child's Residence

	Cases			Controls		
	Number	**Mean**	**S.D.**	**Number**	**Mean**	**S.D.**
Electric Fields (V/m)						
Day (worn)	105	8.35	5.33	216	9.29	6.85
Night (worn)	48	8.34	8.69	102	9.53	8.75
Total (worn)	**105**	**8.24**	**5.07**	**216**	**9.33**	**6.84**
Magnetic Fields (μT)						
Day (worn)	105	0.18	0.16	216	0.18	0.21
(proximal)	104	0.13	0.16	226	0.16	0.24
Day Total (worn + proximal)	**108**	**0.16**	**0.15**	**227**	**0.17**	**0.21**
Night (worn)	48	0.18	0.17	102	0.16	0.33
(proximal)	108	0.11	0.13	230	0.12	0.18
Night Total (worn + proximal)	**108**	**0.11**	**0.13**	**230**	**0.12**	**0.19**

Worn = measurement taken while monitor worn on body
Proximal = measurement taken while monitor in close proximity to body
Total (worn + proximal) = mean weighted by time worn/close proximity

TABLE 22

Comparison of Mean Electric and Magnetic Field Measurements - "Other"

	Cases			Controls		
	Number	**Mean**	**S.D.**	**Number**	**Mean**	**S.D.**
Electric Fields (V/m)						
Worn	99	6.44	7.78	204	8.02	6.69
Magnetic Fields (μT)						
Worn	99	0.19	0.13	204	0.20	0.36
Proximal	7	0.26	0.35	15	0.09	0.10
Total (worn + proximal)	**99**	**0.19**	**0.14**	**204**	**0.20**	**0.36**

Worn = measurement taken while monitor worn on body
Proximal = measurement taken while monitor in close proximity to body
Total (worn + proximal) = mean weighted by time worn/close proximity

TABLE 23

Comparison of Mean Electric and Magnetic Field Measurements - School

	Cases			Controls		
	Number	**Mean**	**S.D.**	**Number**	**Mean**	**S.D.**
Electric Fields (V/m)						
Worn	50	3.65	3.43	138	4.92	7.53
Magnetic Fields (μT)						
Worn	50	0.12	0.15	138	0.12	0.14
Proximal	1	0.15	-	4	0.13	0.02
Total (worn + proximal)	**50**	**0.12**	**0.15**	**138**	**0.12**	**0.14**

Worn = measurement taken while monitor worn on body
Proximal = measurement taken while monitor in close proximity to body
Total (worn + proximal) = mean weighted by time worn/close proximity

Univariate Analyses of Electric and Magnetic Field Exposures

Personal Monitoring

The unadjusted odds ratios for time and location specific exposures of electric and magnetic fields as measured by the Positron monitor are presented in Tables 24 to 27. The risk estimates are based on arithmetic means weighted by the time the personal monitor was worn or kept close by for magnetic fields and by time worn for electric fields. Because electric fields are so readily attenuated by the body, only those electric field strength measures when the monitor was worn were considered to be reliable.

Quartiles of exposure were defined according to the exposure distribution of the controls with no missing information.

All reported odds ratios were derived by conditional logistic regression.

Home Daytime average magnetic field exposures measured only while the monitor was worn showed a non-significant association with increasing risk and increasing exposure. These estimates of leukaemia risk are based on an average of 12 hours wearing time from 7:00 to 21:59 hours and are assumed to reflect 'usual' power conditions in the home. Daytime average magnetic field exposures weighted by the time the monitor was worn and kept close by in the home showed no significant association with leukaemia risk.

In contrast to magnetic field exposures, electric field exposures in the home were consistently associated with a risk of leukaemia less than unity. Because the monitor was generally not worn during the night, electric field strength is referring primarily to daytime levels of exposure in usual power conditions.

During the nighttime, defined as 22:00 hours to 06:59 hours, few children wore the monitor, but all kept it close by while sleeping. The assumption that low power conditions prevailed in the home at this time was confirmed by the lower values of the

TABLE 24

Childhood Leukaemia Risk in Relation to Magnetic Flux Density (μT) in the Child's Residence as Measured by the Positron ™ Monitor

Quartiles* of Exposure	Odds Ratio**	95% Confidence Interval
Daytime Average Magnetic Field While Positron Worn		
< 0.06	1.00	-
0.06 -	1.07	0.47 - 2.43
0.11 -	1.41	0.64 - 3.12
≥ 0.22	1.75	0.77 - 3.99
Missing	1.16	0.24 - 5.23
Daytime Average Magnetic Field Weighted by Time Positron Worn or Kept Close By		
< 0.05	1.00	-
0.05 -	1.32	0.63 - 2.77
0.12 -	1.22	0.56 - 2.69
≥ 0.22	1.79	0.82 - 3.89
Nighttime Average Magnetic Field While Positron Worn		
< 0.04	1.00	-
0.04 -	0.41	0.11 - 1.48
0.09 -	0.63	0.15 - 2.70
≥ 0.16	2.74	0.93 - 8.07
Missing	0.94	0.39 - 2.26
Nighttime Average Magnetic Field While Positron Kept Close By		
< 0.02	1.00	-
0.02 -	1.60	0.75 - 3.38
0.06 -	1.50	0.70 - 3.23
≥ 0.14	1.45	0.67 - 3.16
Nighttime Average Magnetic Field Weighted by Time Positron Worn or Kept Close By		
< 0.03	1.00	-
0.03 -	1.30	0.63 - 2.71
0.06 -	1.71	0.80 - 3.67
≥ 0.15	1.67	0.77 - 3.63

* Quartiles based on distribution of exposure in controls

** Matched analysis/conditional logistic regression

TABLE 25

Childhood Leukaemia Risk in Relation to Electric Field Strength (V/meter) in the Child's Residence as Measured by the Positron ™ Monitor

Quartiles* of Exposure	Odds Ratio**	95% Confidence Interval
Average Electric Field Strength While Positron Worn During Day at Home		
<5.4	1.00	-
5.4 -	0.57	0.26-1.27
7.4 -	0.41	0.18-0.91
≥11.4	0.44	0.20-0.98
Missing	0.44	0.10-1.97
Average Magnetic Field While Positron Worn During Day and Night at Home		
<5.5	1.00	-
5.5 -	0.47	0.21 - 1.05
7.5 -	0.53	0.25 - 1.16
≥11.4	0.41	0.19 - 0.92
Missing	0.45	0.10 - 2.04

- Quartiles based on distribution of exposure in controls
- Matched analysis/conditional logistic regression

TABLE 26

Childhood Leukaemia Risk in Relation to Electric Field Strength (V/meter) and Magnetic Flux Density (μT) at School as Measured by the Positron ™ Monitor

Quartiles* of Exposure	Odds Ratio**	95% Confidence Interval
Average Electric Field Strength While Positron Worn at School		
<1.6	1.00	-
1.6 -	0.43	0.14-1.39
2.9 -	0.62	0.20-1.92
≥5.8	0.83	0.27-2.56
Missing	1.57	0.66-3.70
Average Magnetic Field While Positron Worn or Kept Close By at School		
<0.03	1.00	-
0.03 -	0.97	0.32-2.97
0.07 -	1.39	0.42-4.62
≥0.14	1.85	0.56-6.11
Missing	2.85	1.06-7.68

* Quartiles based on distribution of exposure in controls
** Matched analysis/conditional logistic regression

cut-points defining the quartiles of magnetic flux density. Elevated risks in both the third and fourth quartiles of exposure approached, but did not attain, statistical significance at the 0.05 level.

Schools As with daytime home exposures, increasing odds ratios with increasing levels of magnetic fields were observed, none achieving statistical significance. The odds ratio denoting missing exposure information reflects the fact that more cases than controls did not wear the monitor to school. This was not related to the age when the monitor was worn nor the time of year. Exposure to electric fields in schools showed no relation with leukaemia risk.

Other Electric field exposures received outside home and school show odds ratios below unity with the highest exposure level being associated with a statistically significant reduced risk of leukaemia (OR=0.28, 95% CI 0.11-0.71). Magnetic field exposures weighted by the time the monitor was worn and kept close by were associated with significantly increased risks in the lower two quartiles (OR=3.45, 95% CI 1.39-8.57 and OR=2.80, 95% CI 1.15-6.85) with an elevated risk also observed in the upper quartile, but which was not statistically significant (Table 27).

Summary Indices of Personal Monitoring Exposure

For the primary study hypotheses, summary measures of exposure were defined. These time weighted indices represented the electric and magnetic field exposures for the total monitored time in all locations and in the child's residence exposures (Table 28).

The average magnetic field weighted by the total time the Positron monitor was worn and/or kept close by at home, at school and in other locations, was associated with significantly elevated odds ratios for leukaemia in the second (OR=2.58, 95% CI 1.13-5.85) and fourth quartiles (OR=2.50, 95% CI 1.10-5.71) of exposure, and with no evidence of dose-response relationship.

Total average electric field exposure for the time the monitor was worn at home, school and in other locations was associated with reduced leukaemia risks with increasing

TABLE 27

Childhood Leukaemia Risk in Relation to Electric Field Strength (V/meter) and Magnetic Flux Density (μT) in 'Other'* Locations as Measured by the Positron ™ Monitor

Quartiles** of Exposure	OR***	95% Confidence Interval
Average Electric Field Strength While Positron Worn In 'Other' Locations		
<3.5	1.00	-
3.5 -	0.84	0.39-1.78
6.5 -	0.52	0.23-1.17
≥10.8	0.28	0.11-0.71
Missing	0.65	0.24-1.78
Average Magnetic Flux Density While Positron Worn or Kept Close By In 'Other' Locations		
<0.08	1.00	-
0.08 -	3.45	1.39-8.57
0.14 -	2.80	1.15-6.85
≥0.23	1.99	0.83-4.75
Missing	0.45	0.66-5.97

* 'Other' defined as locations other than home and school
** Quartiles based on distribution of exposure in controls
*** Matched analysis/conditional logistic regression

TABLE 28

Childhood Leukaemia Risk in Relation to Summary Indices of Magnetic Field Flux Density (μT) and Electric Field Strength (v/m) as Measured by the Positron ™ Monitor

Quartiles[1] of Exposure	Odds Ratio[4]	95% Confidence Interval
Average Magnetic Flux Density (μT) [2]- Home, School, Other		
<0.05	1.00	-
0.05 -	2.58	1.13-5.85
0.10 -	1.43	0.69-3.32
≥0.17	2.50	1.10-5.71
Average Magnetic Density (μT) [2] - Home		
<0.04	1.00	-
0.04 -	2.13	0.95-4.76
0.08 -	1.51	0.69-3.32
≥0.18	2.08	0.92-4.69
Electric Field Strength (v/m)[3]- Home, School, Other		
<4.5	1.00	-
4.5 -	0.61	0.28-1.34
6.6 -	0.41	0.18-0.94
≥9.5	0.46	0.20 -1.04
Missing	0.26	0.05-1.52
Electric Field Strength (v/m) [3]- Home		
<5.5	1.00	-
5.5 -	0.47	0.21-1.05
7.5 -	0.53	0.25-1.16
≥11.4	0.41	0.19-0.92
Missing	0.45	0.10-2.04

[1]Quartiles based on distribution of exposure in controls
[2] Weighted by time Positron worn or kept close by
[3]Weighted by time Positron worn
[4]Matched analysis/conditional logistic regression

levels of exposure. The reduction in risk attained statistical significance for the third quartile of exposure (OR=0.41, 95% CI 0.18-0.94).

To facilitate comparisons of odds ratios, magnetic field exposures for home, school and "other" were re-calculated using the cut-points defining the quartiles of the monitored exposure at home (Table 29). Risk estimates changed little for total exposures as home exposures were the major contributors to this total exposure. The estimates of risk based on "other" exposures lost some significance at the level of second quartile as it was redefined to a lower level of exposure.

Leukaemia risk was examined according to age at diagnosis (Table 30). Children who were less than six years of age at the time of diagnosis were observed to have statistically significant elevations in leukaemia risk in relation to total monitored magnetic field exposure. For total magnetic field exposure, the risk of leukaemia was statistically elevated in the second (OR=4.58, 95% CI 1.39-15.09) and fourth quartiles (OR=4.42, 95% CI 1.24-15.75). Similar elevations in risk were evident for home exposures, however, the findings were not statistically significant. In contrast, the corresponding risk estimates for children diagnosed at age six years or older were substantially lower and none attained statistical significance.

For total exposure and residential exposure to all levels of electric fields, leukaemia risk estimates were below unity with the exception of two levels of exposure in the home which were greater than one (Table 31).

Stratified analyses were carried out to evaluate leukaemia risk in relation to calendar year of diagnosis (Table 32). Children diagnosed before 1990 had higher risks of leukaemia than those diagnosed in 1990 or later. The highest risks were observed with the highest levels of exposure, but very wide confidence intervals for magnetic fields OR=7.51, 95% CI 1.2-46.9 (total); OR=4.80, 95% CI 0.86-26.84 (home) underlined the instability of the estimates.

TABLE 29

Childhood Leukaemia Risk in Relation to Average Exposure at Home, in School and "Other" Locations Using Common Levels of Exposure

Level of Exposure (μT)*	Source of Exposure							
	Home		School		Other		Total	
	OR**	95% CI	OR**	95% CI	OR**	95% CI	OR**	95% CI
<0.04	1.00	-	1.00	-	1.00	-	1.00	-
0.04 - 0.08	2.13	(0.95-4.76)	0.94	(0.31-2.82)	1.07	(0.24-4.78)	2.15	(0.88-5.24)
0.08 - 0.18	1.51	(0.69-3.31)	2.14	(0.70-6.54)	4.27	(1.02-17.86)	1.63	(0.66-4.03)
≥0.18	2.08	(0.92-4.69)	1.81	(0.53-6.15)	2.70	(0.65-11.20)	2.19	(0.88-5.43)
Missing	-		3.19	(1.22-8.28)	2.39	(0.49-11.80)	-	

* Based on distribution of quartiles of exposures for home among controls

** Matched analysis/conditional logistic regression

TABLE 30

Childhood Leukaemia Risk and Exposure to Magnetic Flux Density (μT) by Age at Diagnosis

Quartiles of Exposure* (μT)	Age at Diagnosis			
	<6 Years		≥6 Years	
	Odds Ratio**	95% CI	Odds Ratio**	95% CI
Average Magnetic Flux Density - Home, School and 'Other'				
<.05	1.00	-	1.00	-
.05 -	4.58	1.39 - 15.09	1.30	0.39 - 4.34
.10 -	2.50	0.78 - 7.96	0.75	0.23 - 2.47
≥.17	4.42	1.24 - 15.75	1.50	0.49 - 4.56
Average Magnetic Flux Density - Home				
<.04	1.00	-	1.00	-
.04 -	2.10	0.72 - 6.12	2.07	0.60 - 7.19
.08 -	2.50	0.87 - 7.20	0.76	0.21 - 2.68
≥.18	2.58	0.82 - 8.11	1.69	0.52 - 5.52

* Quartiles based on distribution of exposure in controls
** Matched analysis/conditional logistic regression

TABLE 31

Childhood Leukaemia Risk and Exposure to Electric Field Strength (v/m) by Age at Diagnosis

Quartiles of Exposure* (v/m)	Age at Diagnosis			
	<6 Years		≥6 Years	
	Odds Ratio**	95% CI	Odds Ratio**	95% CI
Average Electric Field Strength - Home, School and 'Other'				
<4.5	1.00	-	1.00	-
4.5 -	0.66	0.22 - 2.01	0.54	0.16 - 1.79
6.5 -	0.25	0.07 - 0.86	0.72	0.22 - 2.28
≥9.5	0.60	0.19 - 1.85	0.27	0.07 - 1.02
Missing	0.14	0.01 - 1.86	0.35	0.03 - 3.95
Average Electric Field Strength - Home				
<5.5	1.00		1.00	
5.5 -	1.63	0.50 - 5.29	0.08	0.01 - 0.44
7.5 -	0.64	0.22 - 1.87	0.45	0.12 - 1.64
≥11.4	1.14	0.39 - 3.35	0.13	0.03 - 0.55
Missing	0.98	0.13 - 7.40	0.27	0.02 - 3.14

* Quartiles based on distribution of exposure in controls
** Matched analysis/conditional logistic regression

TABLE 32

Childhood Leukaemia Risk and Exposure to Magnetic Flux Density (μT) by Year of Diagnosis

Quartiles of Exposure* (μT)	Year of Diagnosis of Case or Reference Year for Controls			
	Before 1990		1990 or Later	
	Odds Ratio**	95% CI	Odds Ratio**	95% CI
Average Magnetic Flux Density - Home, School and 'Other'				
<.05	1.00	-	1.00	-
.05 -	3.60	0.61 - 21.19	2.14	0.81 - 5.65
.10 -	2.42	0.78 - 15.85	1.09	0.43 - 2.78
≥.17	7.51	1.20 - 46.91	1.45	0.55 - 3.84
Average Magnetic Flux Density - Home				
<.04	1.00	-	1.00	-
.04 -	1.38	0.26 - 7.37	2.28	0.86 - 6.01
.08 -	1.73	0.33 - 9.08	1.19	0.47 - 3.00
≥.18	4.80	0.86 - 26.84	1.19	0.44 - 3.21

* Quartiles based on distribution of exposure in controls
** Matched analysis/conditional logistic regression

Acute lymphoblastic leukaemia (ALL) is the major histologic subtype of childhood leukaemia and this is reflected in this study population. The relationship observed for electric field exposures and ALL was essentially unchanged from that for all leukaemias, with all risk estimates but one less than unity (Table 33). Risk estimates in relation to magnetic field exposures increased slightly for ALL from those evaluated for all childhood leukaemias (Table 34).

When ALL was examined according to age at diagnosis, children diagnosed at less than six years of age were at significantly increased risk at the highest quartile of magnetic field exposure for total and residential magnetic field exposure although the estimates were not statistically stable as suggested by the width of the confidence intervals (Table 34). For children who were less than six years of age at diagnosis, a pattern of increasing risk with increasing exposure was observed for magnetic fields in the home.

The recent report by Miller et al. (1996) of electric power utility workers and occupational exposures to EMF suggested that there might be some interdependence of electric and magnetic fields with respect to adult leukaemia. To test the possibility that electric and magnetic fields might interact in some etiologic manner for childhood leukaemia, odds ratios were calculated using a model with categorically defined exposures of electric and magnetic fields (Tables 35, 36). For residential exposures, notably the odds ratio for the fourth quartile of electric field exposure ($\geq$11.4 v/m) within the lowest quartile of magnetic flux density (<0.04 μT) was above unity which is a reverse in direction from that consistently observed with the univariate analyses of electric field strength. The odds ratio for the fourth quartile of magnetic flux density ($\geq$0.18 μT) with low electric field strength (<5.5 v/m) in the child's residence attained borderline statistical significance (OR=6.39, 95% CI 1.00-40.68). None of the interaction terms were statistically significant. Risk estimates which included the interaction between total exposure to electric and magnetic fields were also calculated and similarly showed no significant interaction terms nor was there evidence of any important shifts of

TABLE 33

Acute Lymphoblastic Leukaemia Risk and Exposure to Electric Field Strength (v/m) by Age at Diagnosis

Quartiles* of Exposure	All Ages		Age at Diagnosis < 6 Years		Age at Diagnosis ≥ 6 Years	
	Odds Ratio**	95% CI	Odds Ratio**	95% CI	Odds Ratio**	95% CI
Average Electric Field Strength - Home, School, 'Other'						
<4.5	1.00	-	1.00	-	1.00	-
4.5 -	0.60	0.26 - 1.43	0.51	0.16 - 1.66	0.75	0.20 - 2.78
6.5 -	0.40	0.16 - 1.01	0.23	0.07 - 0.83	0.90	0.22 - 3.66
≥9.5	0.50	0.20 - 1.22	0.59	0.18 - 1.90	0.32	0.07 - 1.46
Missing	#	#	#	#	#	#
Average Electric Field Strength - Home						
<5.5	1.00	-	1.00	-	1.00	-
5.5 -	0.52	0.22 - 1.20	1.48	0.45 - 4.84	0.10	0.02 - 0.59
7.5 -	0.56	0.25 - 1.27	0.66	0.23 - 1.94	0.43	0.10 - 1.87
≥11.4	0.54	0.23 - 1.26	1.19	0.41 - 3.49	0.14	0.02 - 0.81
Missing	0.26	0.03 - 2.58	0.51	0.04 - 6.02	#	#

* Quartiles based on distribution of exposure in controls
** Conditional logistic regression

TABLE 34

Acute Lymphoblastic Leukaemia Risk and Exposure to Magnetic Flux Density (μT) by Age at Diagnosis

Quartiles of Exposure* (μT)	All Ages		Age at Diagnosis < 6 Years		Age at Diagnosis ≥ 6 Years	
	Odds Ratio**	95% CI	Odds Ratio**	95% CI	Odds Ratio**	95% CI
Average Magnetic Field - Home, School, 'Other'						
<0.04	1.00	-	1.00	-	1.00	-
0.04 -	2.78	1.15 - 6.76	5.13	1.42 - 18.51	1.33	0.35 - 5.11
0.08 -	1.60	0.67 - 3.81	3.33	0.96 - 11.57	0.66	0.16 - 2.72
≥0.17	2.98	1.21 - 7.33	6.98	1.71 - 28.41	1.41	0.41 - 4.79
Average Magnetic Field - Home						
<0.04	1.00	-	1.00	-	1.00	-
0.04 -	2.12	0.88 - 5.09	2.01	0.64 - 6.32	2.48	0.58 - 10.53
0.08 -	1.68	0.73 - 3.88	2.77	0.92 - 8.33	0.70	0.16 - 3.10
≥0.18	2.35	0.97 - 5.67	3.52	1.01 - 12.28	1.74	0.46 - 6.54

* Quartiles based on distribution of exposure in controls
** Matched analysis/conditional logistic regression

TABLE 35

Childhood Leukaemia Risk (Odds Ratios* and 95% Confidence Intervals) in Relation to Exposure to the Interactive Effects of Electric and Magnetic Fields - Home, School and Other

Magnetic Flux Density (μT)**	Electric Field Strength (v/m)**			
	<4.5	4.5-	6.5-	≥9.5
<0.05	1.00	0.25 (0.04-1.72)	0.10 (0.01-1.11)	0.79 (0.16-3.91)
0.05-	1.01 (0.25-4.04)	1.85 (0.19-4.30)	1.21 (0.24-6.13)	0.69 (0.12-4.13)
0.10-	2.93 (0.57-15.08)	0.90 (0.19-4.30)	0.34 (0.06-1.97)	0.25 (0.04-1.46)
≥0.17	1.26 (0.28-5.78)	0.73 (0.11-4.93)	1.29 (0.20-8.43)	0.92 (0.16-5.28)

* Matched analysis/conditional logistic regression
** Quartiles based on distribution of exposure among controls

TABLE 36

Childhood Leukaemia Risk (Odds Ratios* and 95% Confidence Intervals) in Relation to Exposure to the Interactive Effects of Electric and Magnetic Fields in the Child's Residence

Magnetic Flux Density (μT)**	Electric Field Strength (v/m)**			
	<5.5	5.5-	7.5-	≥11.4
<0.04	1.00	0.27 (0.04-1.63)	0.40 (0.08-1.99)	1.36 (0.25-7.41)
0.04-	1.66 (0.34-8.12)	1.69 (0.34-8.28)	1.12 (0.23-5.46)	0.38 (0.05-2.63)
0.08-	1.21 (0.29-5.12)	0.97 (0.23-4.04)	1.02 (0.23-4.61)	0.93 (0.16-5.40)
≥0.18	6.39 (1.00-40.68)	1.03 (0.18-5.90)	0.36 (0.07-1.90)	1.00 (0.18-5.51)

* Conditional logistic regression
** Quartiles based on distribution of exposure among controls

the exposures of interest from the estimates derived from univariate analyses. As assessed by the likelihood ratio test, overall the models with interaction did not improve the fit compared to the models without interaction (electric and magnetic fields in the model without an interaction term).

Wiring Configuration

In testing the association between wire codes and leukaemia risk with respect to current residence, small numbers in the VHCC necessitated a regrouping and therefore VHCC and OHCC were combined (Table 37). Odds ratios were also calculated with apartments, for which a wire code was not assigned, treated as a separate category to maintain the full representation of residences (Table 38). There was no evidence of increased risk associated with wire code although living in an apartment did show an elevated, but non-significant, risk (OR=2.12, 95% CI 0.68-6.69). Indeed, the more common situation was that most wire codes showed a decreased risk.

Residential Characteristics

How characteristics of the residence might cause and/or influence exposures to electric and magnetic fields has not been well studied. Information about the type of residence (eg. single family, apartment), age of the home, type of heating and construction materials were gathered as part of the interview process. When visiting the home for the purpose of taking inside and/or outside measurements, the technician also characterized the residential type. Each characteristic of the current residence was subsequently examined in relation to electric and magnetic fields based on personal monitoring while the Positron was worn at home (Tables 39, 40). With the exception of residential type and the age of the home, there was little heterogeneity in housing characteristics by which to evaluate leukaemia risk. Because these are current residences, and by definition located in the catchment area, construction material was almost uniformly brick which is in conformity with the building code in effect in the catchment area at the time the majority of these residences were built. It is possible that there will

TABLE 37

Childhood Leukaemia Risk and Wire Code of Current Residence
Unadjusted Odds Ratios and 95% Confidence Intervals

Type of Wire Code	Odds Ratio*	95% Confidence Interval
Wertheimer and Leeper		
VLCC	1.00	-
OLCC	0.81	0.40 - 1.64
OHCC/VHCC**	0.68	0.32 - 1.44
Wertheimer and Leeper (modified)		
Underground	1.00	-
VLCC	0.29	0.06 - 1.37
OLCC	0.75	0.37 - 1.52
OHCC/VHCC**	0.62	0.29 - 1.34
Kaune Code		
Low	1.00	-
Medium	1.58	0.76 - 3.30
High	0.10	0.01 - 0.75

* Matched analysis/conditional logistic regression
** Combined because of small numbers

TABLE 38

Childhood Leukaemia Risk and Wiring Configuration Including Apartments for Current Residence - Unadjusted Odds Ratios and 95% Confidence Intervals

Wire Code	OR*	95% Confidence Interval
Wertheimer and Leeper		
VLCC	1.00	-
OLCC	0.90	0.45 - 1.77
OHCC/VHCC**	0.68	0.32 - 1.43
Apartments	2.12	0.68 - 6.69
Kaune Code		
Low	1.00	-
Medium	1.60	0.79 - 3.27
High	0.09	0.01- 0.72
Apartments	2.29	0.72 - 7.26

* Matched analysis/conditional logistic regression
** Combined due to small numbers

TABLE 39

Characteristics of Current Residence and Magnetic Flux Density

	Cases			Controls		
	n	%	Magnetic Field (μT) - mean*	*n*	%	Magnetic Field (μT) - mean*
Type of Residence						
House/Duplex	74	68.5	0.12	181	78.7	0.12
Semi-Detached	7	6.5	0.10	20	8.7	0.25
Townhouse	12	11.1	0.22	17	7.4	0.21
Multi-unit dwelling	5	4.6	0.26	1	0.4	0.29
Apartment	10	9.3	0.12	11	4.8	0.24
Year Built						
Before 1930	7	6.5	0.23	20	8.7	0.29
1930 - 1949	5	4.6	0.23	11	4.8	0.23
1950 - 1969	25	23.2	0.20	61	26.5	0.14
1970 or later	65	60.2	0.08	131	57.0	0.12
Unknown	6	5.6	0.20	7	3.0	0.19
Construction Material						
Brick	98	90.7	0.14	206	89.6	0.15
Aluminum siding	3	2.8	0.07	8	3.5	0.09
Woodsiding	1	0.9	0.02	6	2.6	0.10
Other	6	5.5	0.07	8	3.5	0.12
Unknown	-	-	-	2	0.9	0.03
Type of Heating						
Water	7	6.5	0.12	9	3.9	0.13
Electric	11	10.2	0.17	32	13.9	0.11
Gas	71	65.7	0.12	156	67.8	0.15
Oil	11	10.2	0.18	25	10.9	0.19
Other	6	5.6	0.17	6	2.6	0.05
Unknown	2	1.9	0.18	2	0.9	0.03

• based on personal monitoring with Positron worn and/or close by

TABLE 40

Characteristics of Current Residence and Electric Field Strength

	Cases			Controls		
	n	%	Electric Field V/m - mean*	*n*	%	Electric Field V/m - mean*
Type of Residence						
House/Duplex	73	69.5	9.1	173	80.1	9.6
Semi-Detached	7	6.7	7.7	19	8.8	9.3
Townhouse	11	10.5	6.6	15	6.9	8.3
Multi-unit dwelling	4	3.8	4.9	1	0.5	4.8
Apartment	10	9.5	5.6	8	3.7	6.2
Year Built						
Before 1930	7	6.7	8.6	18	8.3	11.6
1930 - 1949	4	3.8	9.7	10	4.6	8.0
1950 - 1969	25	23.8	8.5	59	27.3	10.9
1970 or later	63	60.0	8.4	122	56.5	8.2
Unknown	6	5.7	3.8	7	3.2	11.4
Construction Material						
Brick	95	90.5	8.1	193	89.4	8.8
Aluminum siding	3	2.9	12.4	8	3.7	15.8
Woodsiding	1	1.0	7.0	6	2.8	7.4
Other	6	5.7	8.5	7	3.2	15.8
Unknown	-	-	-	2	0.9	14.9
Type of Heating						
Water	7	6.7	7.7	7	3.2	7.6
Electric	11	10.5	10.2	32	14.8	9.9
Gas	69	65.7	7.9	145	67.1	9.3
Oil	10	9.5	9.2	25	11.6	9.1
Other	6	5.7	9.6	5	2.3	8.6
Unknown	2	1.9	2.8	2	0.9	14.9

* based on personal monitoring with Positron worn

be an opportunity to examine more diverse characteristics when all previously reported residences are taken into account.

Multi-unit dwellings, other than apartments, had the highest levels of magnetic fields for both cases and controls, whereas houses/duplexes had the highest levels of electric fields. For proportionately more cases than controls, the current residence was an apartment. This is suggestive of a rental arrangement and is consistent with the observation of higher residential mobility among cases than controls. Cases residing in apartments had on average, lower measured magnetic fields than did controls.

Older homes tended to be associated with higher magnetic fields but no pattern was observed for electric fields by age of the residence.

When the effect of magnetic field exposures was evaluated while adjusting for age or type of residence, it was found that each influenced the estimate of leukaemia risk. However, because these parameters are related to magnetic flux density, it is possible that controlling for such characteristics could be regarded as overadjustment and the decision was taken not to include them in the multivariate model.

External Environmental Factors

Temperature, by influencing power consumption, is known to affect the load on power lines and the magnetic field exposures within the home. Hence, both temperature and power consumption influence residential magnetic flux densities. Cases and controls were compared with respect to calendar month at the time the Positron was worn, albeit a crude approximation to the measurement of temperature, and were found not to differ. To account more specifically for environmental influences such as temperature, the average daily temperature for Toronto was obtained for the date when the monitor was first worn (Environment Canada). Mean magnetic flux density was observed to change with temperature changes from moderate to extreme. For example, very hot and very cold temperatures are associated with the highest magnetic fields (Table 41).

TABLE 41

Ambient Air Temperature* and Magnetic Flux Density (μT) as Measured by Personal Monitoring Within the Child's Residence

	Magnetic Flux Density (μT) Mean and Standard Deviation	
Temperature °C	Cases	Controls
≥ 10 or < 20	0.12 ± 0.13	0.12 ± 0.15
≥ 5 or < 10	0.13 ± 0.20	0.14 ± 0.20
≥ 25 or < 5	0.16 ± 0.13	0.17 ± 0.12

*At date Positron was worn

Average daily power consumption (megawatts) for the province of Ontario was obtained for each day over the duration of the study (Ontario Hydro). A linear relationship exists between power consumption and magnetic fields. As for residential characteristics, these parameters might contribute to the misclassification of the exposure. It may be debated whether adjustment for temperature or power consumption represents "overadjustment" in the modelling process and therefore, may be inappropriate.

Rather than use post-hoc adjustment, a correction factor for power consumption was applied to magnetic field exposures in the home. Evidence from a separate survey of 12 homes in the catchment area in which a Positron monitor was placed in a fixed location in each home for a period of one to two years showed that the variance of the daily mean magnetic field was reduced by approximately 50% with the application of a correction factor for the daily average power consumption. This correction factor served to remove those differences in magnetic field strength which might be due to differences in power consumption: in other words, magnetic fields were "standardized" for power consumption over the period when all measurements were taken. Odds ratios for all subjects by age at diagnosis were calculated for magnetic fields in the home corrected for power consumption (Table 42) and differed from those without correction in that a more monotonic increase in leukaemia risk with increasing exposure was observed for children of all ages and those less than six years at the time of diagnosis.

Point-in-Time Measurements of Magnetic Flux Density Inside the Child's Residence

Leukaemia risk estimates (univariate) for point-in-time inside measurements (Table 43) are presented to provide a reference with some of the previously published studies. Magnetic field exposures in the child's bedroom and for a weighted average of exposures in the bedroom and two other rooms most frequently occupied by the child showed no significant associations with leukaemia risk.

TABLE 42

Childhood Leukaemia Risk in Relation to Exposure to Magnetic Fields in the Child's Residence (Corrected for Power Consumption) - Univariate Analysis

Quartiles* of Exposure	All Ages		Age at Diagnosis < 6 Years		Age at Diagnosis ≥ 6 Years	
	Odds Ratio**	95% CI	Odds Ratio**	95% CI	Odds Ratio**	95% CI
<0.04	1.00	-	1.00	-	1.00	-
0.04 -	1.51	0.67 - 3.40	1.62	0.55 - 4.76	1.40	0.40 - 4.95
0.08 -	1.68	0.77 - 3.64	2.86	0.95 - 8.65	0.94	0.29 - 3.00
≥0.17	2.07	0.94 - 4.56	3.03	0.94 - 9.76	1.54	0.52 - 4.60

* Quartiles based on distribution of exposure in controls
** Conditional logistic regression

TABLE 43

Childhood Leukaemia Risk in Relation to Magnetic Flux Density (μT) for Point-in-Time Measurements Inside the Child's Residence Univariate Analyses

Quartiles[1] of Exposure	OR[2]	95% Confidence Interval
Child's Bedroom		
<0.03	1.00	-
0.03-	1.15	0.57 - 2.31
0.06-	1.13	0.50 - 2.57
≥0.13	1.46	0.70 - 3.04
Child's Bedroom - Corrected for Power Consumption		
<0.03	1.00	-
0.03-	1.27	0.63 - 2.56
0.06-	1.23	0.56 - 2.68
≥0.13	1.31	0.61 - 2.80
Average[3] of Child's Bedroom, "Room 1" and "Room 2"		
<0.04	1.00	-
0.04-	1.19	0.56 - 2.53
0.07-	1.23	0.55 - 2.74
≥0.15	1.11	0.50 - 2.50
Average[3] of Child's Bedroom, "Room 1" and "Room 2" - Corrected for Power Consumption		
<0.04	1.00	-
0.04-	1.36	0.65 - 2.83
0.07-	1.23	0.57 - 2.68
≥0.15	1.48	0.67 - 3.26

[1] Quartiles based on distribution of exposure in controls
[2] Conditional logistic regression; matched analysis
[3] Average weighted by coefficients derived from regression of point in time measurements and personal monitoring in the home

Multivariate Analyses of Electric and Magnetic Field Exposures

The multivariate models evaluating leukaemia risk in relation to exposure to electric and magnetic fields included those variables identified from the non-EMF univariate analyses with a p-value of <0.20. These variables were included in a backward stepwise conditional logistic regression and the results, representing a fully adjusted model, are reported in Tables 44 and 45. Total magnetic field exposure over the time the monitor was worn showed an elevation in risk for each exposure level with the second and fourth quartiles attaining statistical significance. For average residential magnetic field exposures, which were higher than the overall average exposure, odds ratios were similarly elevated and statistical significance attained in second and fourth quartiles (OR=4.43, 95% CI 1.50-13.11 and OR=4.79, 95% CI 1.66-13.88). Adjusted odds ratios for residential magnetic fields corrected for power consumption reflected increasing risk with increasing exposure although the trend was not statistically significant. All levels of magnetic field exposure above the referent corrected for power consumption were statistically significant (Table 44).

Models with adjustment for potential confounders resulting from the application of stepwise regression showed odds ratios for electric field exposures consistent in magnitude and direction with the univariate analyses. All odds ratios for leukaemia risk were below unity with the upper quartile for electric field strength (≥11.4 v/m) in the home showing a significantly reduced odds ratio (OR=0.31, 95% CI 0.11-0.90).

Details relating to the models and the explanatory variables for magnetic field exposures within the home as measured by personal monitoring are presented in Appendix B.

Multivariate analyses were also carried out for point-in-time measurements of magnetic fields inside the home (Table 46). For the child's bedroom, the effect of adjustment for potential confounders was to increase the odds ratios for magnetic field exposures which were uncorrected and corrected for power consumption. The adjusted

TABLE 44

Adjusted Odds Ratios for Childhood Leukaemia Risk According to Summary Indices of Magnetic Flux Density (μT) as Measured by the Positron ™ Monitor

Quartiles of Exposure[1]	Adjusted Odds Ratio	95% Confidence Interval
Average Magnetic Flux Density[2] - Home, School, Other		
<0.05	1.00	-
0.05-	3.75	1.23 -11.47
0.10-	2.43	0.78 - 7.57
≥0.17	8.58	2.30 - 31.90
Average Magnetic Flux Density[3] - Home		
<0.04	1.00	-
0.04-	4.43	1.50 -13.11
0.08-	2.37	0.85 - 6.62
≥0.18	4.79	1.66 -13.88
Average Magnetic Flux Density[4] Corrected for Power Consumption - Home		
<0.04	1.00	-
0.04-	3.48	1.05 - 11.56
0.08-	4.52	1.34 - 15.22
≥0.17	7.57	1.95 - 29.34

[1] Based on distribution of exposure in controls

[2] Adjusted for family income; residential mobility; mother's education; mother's use of hair colouring products during or just prior to pregnancy; child's exposure to agricultural sprays, insecticides; maternal smoking during pregnancy; caesarean delivery; number of siblings; history of common childhood diseases

[3] Adjusted for family income; residential mobility; child's exposure to agricultural sprays and insecticides; mother's use of hair colouring products during or just prior to pregnancy; number of siblings; history or common childhood diseases

[4] Adjusted for family income; residential mobility; mother's education; child's exposure to agricultural sprays, household bleach (protective), insecticides; cesarean delivery; number of siblings; maternal smoking during pregnancy

TABLE 45

Adjusted Odds Ratios for Childhood Leukaemia Risk According to Summary Indices of Electric Field Strength (V/m) as Measured by the Positron ™ Monitor

Quartiles of Exposure[1]	Adjusted Odds Ratio	95% Confidence Interval
Total Electric Field Strength[2] - Home, School, Other		
<4.5	1.00	-
4.5 -	0.81	0.30 - 2.18
6.5 -	0.47	0.17 - 1.27
≥9.5	0.59	0.21 - 1.64
Missing	0.58	0.07 - 4.67
Total Electric Field Strength[3] - Home		
<5.5	1.00	-
5.5 -	0.39	0.14 - 1.11
7.5 -	0.41	0.14 - 1.15
≥11.4	0.31	0.11 - 0.90
Missing	0.49	0.07 - 3.41

[1] Based on distribution of exposure in controls

[2] Adjusted for family income; residential mobility; child's exposure to agricultural sprays, household bleach (protective), insecticides; infant feeding practice

[3] Adjusted for family income; residential mobility; child's exposure to agricultural sprays, household bleach (protective), insecticides; infant feeding practice; number of siblings

TABLE 46

Adjusted Odds Ratios for Childhood Leukaemia Risk for Magnetic Flux Density (μT) for Point-in-Time Measurements Inside the Child's Residence

Quartiles[1] of Exposure	OR[2]	95% Confidence Interval
Child's Bedroom[3]		
<0.03	1.00	-
0.03-	1.39	0.55 - 3.50
0.06-	1.84	0.65 - 5.20
≥0.13	2.59	0.97 - 6.92
Child's Bedroom[4] - Corrected for Power Consumption		
<0.03	1.00	-
0.03-	1.33	0.51 - 3.44
0.06-	2.04	0.74 - 5.62
≥0.13	2.00	0.76 - 5.27
Average[5,6] of Child's Bedroom, "Room 1" and "Room 2"		
<0.04	1.00	-
0.04-	1.09	0.41 - 2.91
0.07-	1.94	0.72 - 5.21
≥0.15	1.10	0.39 - 3.11
Average[5,7] of Child's Bedroom, "Room 1" and "Room 2" - Corrected for Power Consumption		
<0.04	1.00	-
0.04-	1.77	0.67 - 4.63
0.07-	3.00	1.05 - 8.52
≥0.15	2.51	0.92 - 6.85

[1] Quartiles based on distribution of exposure in controls
[2] Conditional logistic regression; matched analysis
[3] Adjusted for family income; residential mobility; child's exposure to agricultural sprays, insecticides, household bleach; infant feeding practices; siblingship
[4] Adjusted for family income; residential mobility; child's exposure to agricultural sprays, insecticides, household bleach; diseases in the mother during or just prior to pregnancy
[5] Average weighted by coefficients derived from regression of point in time measurements and personal monitoring in the home
[6] Adjusted for family income; residential mobility; child's exposure to agricultural sprays, insecticides; diseases in the mother during or just prior to pregnancy
[7] Adjusted for family income; residential mobility; child's exposure to agricultural sprays, insecticides, household bleach; siblingship

odds ratios for the average magnetic field exposure measured in three rooms occupied by the child (bedroom and two other frequently used rooms) uncorrected for power consumption showed no evidence of increasing risk with increasing magnetic field exposure. Corresponding odds ratios for this average exposure with corrections for power consumption showed a significant elevation in risk at the third quartile of exposure (OR=3.00, 95% CI 1.05-8.52) and an elevated risk approaching statistical significance at the fourth quartile of exposure (OR=2.51, 95% CI 0.92-6.85).

Adjusted odds ratios were calculated for the Wertheimer and Leeper and Kaune wiring codes. There was no relationship between any level of the Wertheimer and Leeper wire code and the risk of leukaemia. The risk estimates were similar to those prior to adjustment. However, the Kaune wire code designating 'medium' current configuration was associated with a statistically significant increased risk of leukaemia (OR=3.10, 95% CI 1.04-9.21) after adjustment. The Kaune 'high' current configuration wire code was associated with a significant decreased risk (OR=0.04, 95% CI 0.0003-0.40) with no overlap of the confidence intervals between these two categories (Table 47). The univariate estimation of risk for apartments showed a non-significant twofold elevation in risk, which attenuated notably with adjustment for those covariates specified in Table 47.

TABLE 47

Adjusted Odds Ratios for Childhood Leukaemia and Wiring Configuration

Wiring Configuration	Odds Ratio	95% Confidence Interval
Wertheimer and Leeper[1]		
VLCC	1.00	-
OLCC	0.97	0.40-2.35
OHCC/VHCC	0.52	0.22-1.25
Apartments	0.59	0.13-2.71
Kaune Code[2]		
Low	1.00	-
Medium	3.10	1.04 - 9.21
High	0.04	0.003 - 0.40
Apartments	0.47	0.06 - 3.45

[1] Adjusted for family income; residential mobility; child's exposure to household bleach, agricultural sprays, insecticides; mother's exposure to pesticides during or just prior to pregnancy; diseases in the mother during or just prior to pregnancy

[2] Adjusted for family income; residential mobility; race; child's exposure to household bleach, agricultural sprays, insecticides; mother's exposure to pesticides during or just prior to pregnancy; diseases in the mother during or just prior to pregnancy; infant feeding practices

Chapter 5

DISCUSSION

This study reports associations between childhood leukaemia and exposures to electric and magnetic fields as recorded by personal monitors worn by children, both those who have had leukaemia and those who have not. Exposures relate to the child's activities in the home, at school and elsewhere. Residential exposures are of particular interest, but especially for older children, do not represent the total exposure opportunity.

It is possible that studying children whose exposure opportunities are more limited than adults, most definitely in duration, but also likely in diversity, might facilitate the identification of a causal metric of electric and magnetic field exposure should one exist. This study has also endeavoured to obtain comprehensive information on known and possible risk factors for childhood leukaemia as well as confounders to adequately control for characteristics or circumstances which might confuse an association with leukaemia risk and the exposure of interest.

In its entirety this investigation offers more complete exposure information than previous studies about electric and magnetic field exposures not only in terms of previous residential exposures but also exposures other than in the home such as in schools and in child care settings. Although the findings presented here represent only a part of the comprehensive investigation which will consider exposures in previous residences and elsewhere, these findings provide information about EMF exposures which is the most comparable with completed studies to date as most have considered only the childrens' current residences. Notwithstanding this aspect of comparability, this is the only study to report electric and magnetic field exposures in children as measured by personal monitoring. There is one other study evaluating childhood leukaemia risk in which personal monitoring has been used as part of the exposure assessment (McBride et al., 1997). This study is in the final stages of analysis and hence the findings are not available for comparison. Among the published studies which offer the most meaningful comparison are those in which magnetic field exposures were assessed by point-in-time measurements or 24-hour continuous monitoring in specific locations.

It is well known that there are substantial spatial and temporal variations of magnetic fields within residences (Donnelly and Agnew, 1991; Dovan et al., 1993; Friedman et al., 1996). Power consumption fluctuates during the day and is elevated around 7:00 to 9:00 am and again around 5:00 to 7:00 pm, times which coincide with activities to start the day and the dinner hour. This is why several previous studies have taken measurements under what has been labeled "high" and "low" power conditions. The personal monitoring data presented here confirmed the presence of higher magnetic fields during the day and lower magnetic fields at nighttime. There are considerable differences in magnetic fields between rooms and it is to be expected that children will move throughout the home during the day and spend varying amounts of time in different rooms. Experience in the pilot study (Donnelly and Agnew, 1991) for this investigation showed for example, that the child's bedroom was often associated with the lowest exposures. For these reasons it was thought that a child wearing a monitor would best estimate the magnetic fields in the home thus providing the justification for the primary study hypothesis exploring the relationship between leukaemia risk and electric and magnetic fields derived from personal monitoring.

In this study there was evidence of an association between exposure to magnetic fields measured by monitoring the child's usual activities over a 48-hour period and the risk of developing leukaemia. The relationship existed for total magnetic field exposure recorded while the monitor was with the child as well as for exposures specific to the child's residence which was the primary source of exposure for all children. The association persisted after adjustment for potential confounders with some odds ratios increasing in magnitude and attaining statistical significance.

Of the multivariate analyses of leukaemia risk and EMF, those relating to exposures in the child's current residence are thought to be the most informative. Experience from the pilot study for this investigation showed that adults and children living in the same residence have similar magnetic field exposures. Therefore, even though the child was older at the time of wearing the Positron monitor (an average of 2.8

years had lapsed since diagnosis), the magnetic field exposures in the home were unlikely to have changed substantially over time or with home activities related to the age of the child. Hence, the current measurements of magnetic fields in the child's residence are thought to be a close approximation of those several years before. Moreover, for children, the home appears to be the most important source of exposure.

Although the summary measure of 'total average' represents magnetic field exposures of the child in all locations where the monitor was worn or kept close by, this may not be the best index of exposure for several reasons. Although magnetic field exposures in schools are expected to show similar stability as homes over the time period of study, for very few children the school attended at the time the monitor was worn was the same as the school attended (if applicable) during the period of inquiry. Furthermore, the location or activities in which the exposures were measured 'other' than home or school were not recorded in detail on the log sheets and therefore, it is not possible to assess how these might be representative of exposures in the time period of interest.

The subjects who wore the Positron monitor represented a subset of the entire study population defined by the fact that the residence in which they were living was relevant to the period of inquiry. For more than half of the subjects, 65% of the period of inquiry was represented by the time lived in the current residence.

It is for the reasons described above that in this study home exposures adjusted for potential confounders are thought to best describe the relationship between magnetic fields and childhood leukaemia.

If personal monitoring has in fact provided a superior estimate of exposure because it is a more direct measurement, this would explain why the findings differed from those observed by Savitz et al. (1988) who used point-in-time measurements and from the study by London et al. (1991) which used 24-hour continuous measurements in specific rooms such as the child's bedroom. Linet et al. (1997) claimed no relationship

between summary residential field exposures derived from 24-hour measurements in the child's bedroom and 30-second measurements in several other rooms, and the risk of acute lymphoblastic leukaemia. The stationary positioning of a monitor in a few rooms does not capture the spatial variation of magnetic fields within the home and point-in-time measurements do not reflect changes in magnetic fields throughout the day. In this study, the associations between childhood leukaemia and point-in-time measurements of magnetic fields in the child's bedroom and two other rooms were non-significantly elevated and were compatible with the findings of the studies noted above.

The strength of association with magnetic fields was more pronounced for children who were less than six years of age at the time of diagnosis. This might be attributed to differential susceptibility of younger children but it is also possible that the measured exposure is a better representation of the relevant etiologic time period for younger children than it is for older children. The different effect by age might also be due to the fact that the younger children are at home more than school age children. In terms of the period of inquiry, which is by definition shorter for younger children, the proportion of the time residing in the current residence relative to the total period is substantially higher for younger children although this did not differ between cases and controls. Further, magnetic field levels were generally higher in homes than schools and if cumulative exposure is an appropriate metric, this might be one explanation for the enhanced effect in children diagnosed at a younger age. Related to this was the more pronounced risk for children with acute lymphoblastic leukaemia, the cell type which accounts for proportionately more leukaemias in younger than older children.

No effect was observed for electric field exposure and childhood leukaemia in this study which is consistent with previous research (Savitz et al., 1988; London et al., 1991), although these studies evaluated electric fields derived from point-in-time or 24-hour measurements, a less accurate method of measurement. Several factors might explain why associations with different cancers and electric field exposures as measured by personal monitoring recently reported in occupational studies were not observed here.

Electric field exposures in the occupational environment are orders of magnitude higher and show far greater variation than those observed in residential settings or settings typically inhabited by children. If the risk of adult leukaemia associated with electric fields which was recently reported (Miller et al., 1996) was related to the level of exposure and its duration, exposure levels equivalent to those in the occupational environment are not achievable through usual childhood activities. Further, the occupational studies showed increased risk for acute non-lymphocytic leukaemia, specifically acute myelogenous leukaemia, whereas most of the children in this study had acute lymphoblastic leukaemia.

There is also the question of how well electric field exposure was measured by the Positron monitor. Electric fields are easily perturbed and therefore stable and reliable measures of personal exposures to electric fields are difficult to obtain. The distortion of the electric fields by the human body is so pronounced that measurements of electric fields by the Positron™ are strongly influenced by the wearing position of the monitor on the body, the size of the child and also by the ambient field characteristics. Although wearing position is important for the accurate measurement of electric fields, to enhance compliance, children were not asked to wear the monitor on a particular part of their body. Unfortunately, where the monitor was actually worn on the body was not recorded. As a result substantial variability could have been introduced to the measurements of electric fields and it is therefore not possible to rule out the possibility of a relationship with electric fields.

Nor was there evidence of an interaction between electric and magnetic fields, but this might be related to the relatively low exposures for electric fields as the one study in which interaction was demonstrated suggested that the effect of magnetic fields was accentuated in the presence of high electric fields (Miller et al. 1996).

While personal monitoring is intended to provide a superior estimate of the child's actual exposures because there is reason to believe that it more accurately captures electric and magnetic field exposures under conditions where there is considerable spatial and temporal variation, the interpretation of a causal association with leukaemia risk is dependent upon the representativeness of the child's activities to the etiologically relevant period during the two days that the monitor was worn. Activity patterns of a child change with his or her age and with family circumstances. There is no means by which to confirm whether the child's activities and associated exposures while the monitor was worn are etiologically relevant. If an association had not been observed in this study, one explanation might be that the measurement of exposure did not represent the etiologic period. However, an association was observed here and given that the current residence represents a significant proportion of the total period of interest, there are few explanations for this association apart from a possible etiologic relationship and selection and measurement bias. In this study, it would have been difficult for subjects wearing the monitor to artificially alter the recorded exposures as this would have required knowledge of the sources of high fields within the home, at school and in other locations. Even if the monitor was left near a source where fields were high, the data quality checks which were carried out looked for these possibilities and the suspect time periods and measurements were eliminated. Further, the technical staff responsible for carrying out consistency checks with the daily log sheets and personal monitors were blind to the case/control status of the subject. Thus, there seems to be little opportunity whereby the measured values could be differentially biased.

Cases and controls differed significantly with respect to residential mobility, a factor which is potentially related to a host of socioeconomic variables. There was an inverse relationship between number of residences and family income with lower income families moving more often. Children who moved more frequently had higher risks of leukaemia. Residential mobility was an influential variable in all the multivariate models as well as being indirectly related to the allocation of subjects to the matched analysis.

Wire code was intended to be the 'metric' of comparison with previously published studies. Wire codes, both Wertheimer and Leeper and Kaune codes, showed the expected changes in levels of measured magnetic flux density, however, no relationship was found with the risk of leukaemia. Previous research using wire configuration has provided no precedent for 'integrating' information for several wire codes over different time periods. Detailed analyses of the full data set and the other measures of EMF exposure has proceeded in parallel to the analysis reported here with respect to wire code for both previous and current residences within the catchment area taking into account duration lived in each residence, and thus far confirm those observed for current residences, which is essentially no relationship with leukaemia (data not presented). There is no readily apparent explanation why this finding is in contrast to the studies in Denver (Wertheimer and Leeper, 1979; Savitz et al., 1988) and Los Angeles (London et al., 1991). Although the Denver and Los Angeles studies were consistent in their findings of a significant excess risk associated with VHCC, it is still not known what it is about wiring configuration that could have contributed to the excess. Wire code has not previously been applied to the Canadian situation. The electricity distribution system in Toronto is extremely complex, more so than in Denver (Kaune 1992). Although wire codes showed the predicted relationship with measured magnetic field exposures as did earlier studies, whatever the underlying association was in Denver and Los Angeles that was related to the elevated risks of childhood cancer, does not seem to be present in Toronto. Electrical code standards vary between localities. There may be widely varying requirements of grounding practices, building codes, network arrangements, types of plumbing, all of which can potentially influence magnetic fields within a home. However, the findings of this study are consistent in direction and magnitude with the most recently published study of acute lymphoblastic leukaemia in children and exposures to magnetic fields (Linet et al., 1997).

Sources of Bias

A potential weakness of the case control study design is its susceptibility to several different kinds of bias. Specifically applicable to case control studies are

selection bias, information bias and confounding bias. The presence of any of these biases may compromise the validity of the results. Consideration has been given to possible sources of bias which might influence the findings reported here.

Selection bias may be present in a case control study if participation in the study is related to the combination of disease or exposure status. If exposed cases are more likely than exposed controls to be included, the result is an overestimate of the odds ratio of the disease among exposed persons. If the refusal rates are high in the cases and/or the controls, non-response bias is a concern. The limited information which was available to compare respondents with non-respondents, both cases and controls, to check for evidence of differential non-participation, suggested that there were no differences with respect to wire code. However, participants and non-participants did differ with respect to the type of current residence with significantly more non-participants living in an apartment which was also associated with higher residential mobility and lower family income. Univariate and multivariate analyses of the magnetic field summary indices excluding those subjects whose current residence was an apartment did not importantly change the risk estimates for leukaemia and therefore it is unlikely that this aspect of differential participation has introduced a bias. To further evaluate the possibility of selection bias, it would be informative to have EMF measurements derived from personal monitoring of those residences belonging to the non-respondents, but this does not appear to be a feasible task.

The retrospective nature of a case control study makes it particularly vulnerable to information bias. Random (non-differential) misclassification of either the exposure or the disease is claimed to be a bias and if present will drive the estimate of risk toward one or the null hypothesis of no association (Rothman, 1986). The absence of a trend of increasing risk with increasing exposure suggests the possibility of some misclassification of EMF exposure. This possibility is reinforced by the change in odds ratios after adjustment for power usage within the home. However, it is unlikely that the

applied correction was entirely adequate and therefore some residual misclassification probably remains.

Recall bias refers to the systematic misclassification of exposure information because cases' recall is influenced by their disease status. Both the quality and amount of information gathered may be affected. A parent of a leukaemic child, in an effort to "explain" the outcome, might be more likely to recall certain events than a parent who does not have an affected child. In this study the length of interview was significantly longer for cases than for controls. This could be due to the fact that the cases had other medical problems and hence more details were required, but it is also likely that parents of a child with leukaemia made more of an effort to recall past events which they felt might be important to the study. It is also possible that recall bias might operate such that the parents with a healthy child may be less likely to recall a true exposure. The effect of recall bias is to exaggerate the magnitude of the difference between cases and controls with respect to exposure and hence to increase the odds ratio. Although approvals to contact other sources for verification of interview-derived information were sought and obtained for most subjects, limited resources precluded this verification process.

Many of the self-reported exposures to certain substances and circumstances which showed significant differences between cases and controls and hence were included in the multivariate model estimating leukaemia risk, were those observed in previous investigations. Examples were the reported exposures to insecticides and other pesticides for both the child (OR= 2.22, 95% 1.44-4.08) and mother (OR=1.53, 95% 1.08-2.18). While the increased leukaemia risks associated with these exposures might be due to differential recall of cases and controls, they are also consistent with previously reported research (Leiss et al. 1995; Buckley et al., 1989).

It is unlikely that there has been any bias introduced to the measurement of the exposures of interest for reasons previously mentioned and this constitutes a major

strength of this study. Positron™-derived measurements were checked for consistencies and suspicious values and the associated time intervals and measures removed before the calculation of the time weighted average. Point-in-time measurements and the assignment of wire code were carried out by technicians blind to the case control status of the child and his/her home.

Age is one of the most important predictors of childhood leukaemia and this was taken into account in the study design. Close matching by age in the selection of controls ensured that any observed differences were not due to this factor.

To control for potential bias due to other confounding, multivariate modelling of the risk of leukaemia including variables identified through stepwise regression was carried out. The findings related to magnetic field exposure from the univariate analyses for the total duration of monitoring (home, school and other locations) and in the child's residence, with and without corrections for power consumption, all persisted after adjustment for a wide range of potential confounders and showed some statistical significance.

Future Work

Further analyses are in progress which will examine the EMF exposures in previous residences, in schools and in daycares with the objective of developing a comprehensive integrated estimate of exposure over the total etiologic period for each child. The personal monitoring data presented here will be considered as a 'gold standard' and inside point-in-time measurements and outside measurements of homes and schools will be evaluated with respect to their predictive value of the Positron™ measure in the home. Appropriate refinements will be applied to point-in-time measurements to achieve a more accurate estimate of exposure.

Electric and magnetic fields are in a constant state of flux and this makes their measurement exceedingly complex. Furthermore, there are several aspects of the fields which may be measured and it is not clear which characterization should be investigated in terms of carcinogenic potential. This study has examined weighted arithmetic averages of exposure but will be extended to include weighted geometric means, cumulative exposures and the presence of grounding currents (Wertheimer and Savitz, 1995). However, in light of the current findings further work is justified in assessing other metrics of exposure such as thresholds and peak exposures. The assessment of exposure is critical to the resolution of the question whether EMF exposure causes cancer in children and the complexities of exposure assessment cannot be underestimated. There is still much to be learned by refining approaches to the measurement of electric and magnetic fields as evidenced by this study and that by Feychting and Ahlbom (1993).

The risk estimates using magnetic field exposure corrected for power consumption suggest that further work aimed at refining the correction factor would be justified. It is possible this would further reduce the misclassification of exposure. The correction factor which was applied was a crude adjustment but the results of its use showing a more monotonic relationship with exposure suggest that it did help to reduce misclassification that could have arisen because of different power loadings at the time cases and controls were interviewed. The correction used here applied information from provincial power consumption but it is unknown how this represents the actual residences of the cases and controls. It is possible that using power consumption at the neighbourhood level, specific to the residences, would further improve the correction. It is therefore recommended that further work be devoted to refining the correction factor and applying it to the point-in-time measurements.

Conclusion

This represents the first study to report electric and magnetic field exposures recorded by personal monitors actually worn by children during their daily activities and to apply wire codes to residences served by a Canadian power distribution system. By

using improved methods to estimate electric and magnetic field exposures, it was hoped that the relationship with childhood leukaemia might be clarified.

The results of this study indicate that as exposure assessment is refined, the association between childhood leukaemia risk and magnetic fields becomes more pronounced. This study differed from previous research in its lack of evidence supporting a relationship between increased risk and wiring configuration. While the explanation for this is not clear, wire code is assumed to be an inferior measure of exposure, because it is indirect and what it actually means in terms of exposure is not well understood. A weak but non-significant association between leukaemia and magnetic fields using still imprecise point-in-time measurements in three rooms used by the child, was observed and was consistent with research using similar approaches to measurement. The demonstration of a relationship with magnetic fields measured by personal monitoring of the child's activities suggests that magnetic fields might increase the risk of leukaemia in children. The findings relating to residential exposures are particularly informative in that they represent a substantial fraction of the period which might be etiologically relevant, particularly for children diagnosed at a young age and for those diagnosed with acute lymphoblastic leukaemia. Although there is a need to interpret these results with those from the more comprehensive investigation, of which these are only part, the findings are suggestive of an etiologic relationship.

Exposures to electric and magnetic fields are ubiquitous, and therefore a need remains to more fully understand their potential health effects. Further work directed at improved exposure assessment and the demonstration of a biologic mechanism, is key to resolving the current inconsistencies.

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Appendix A

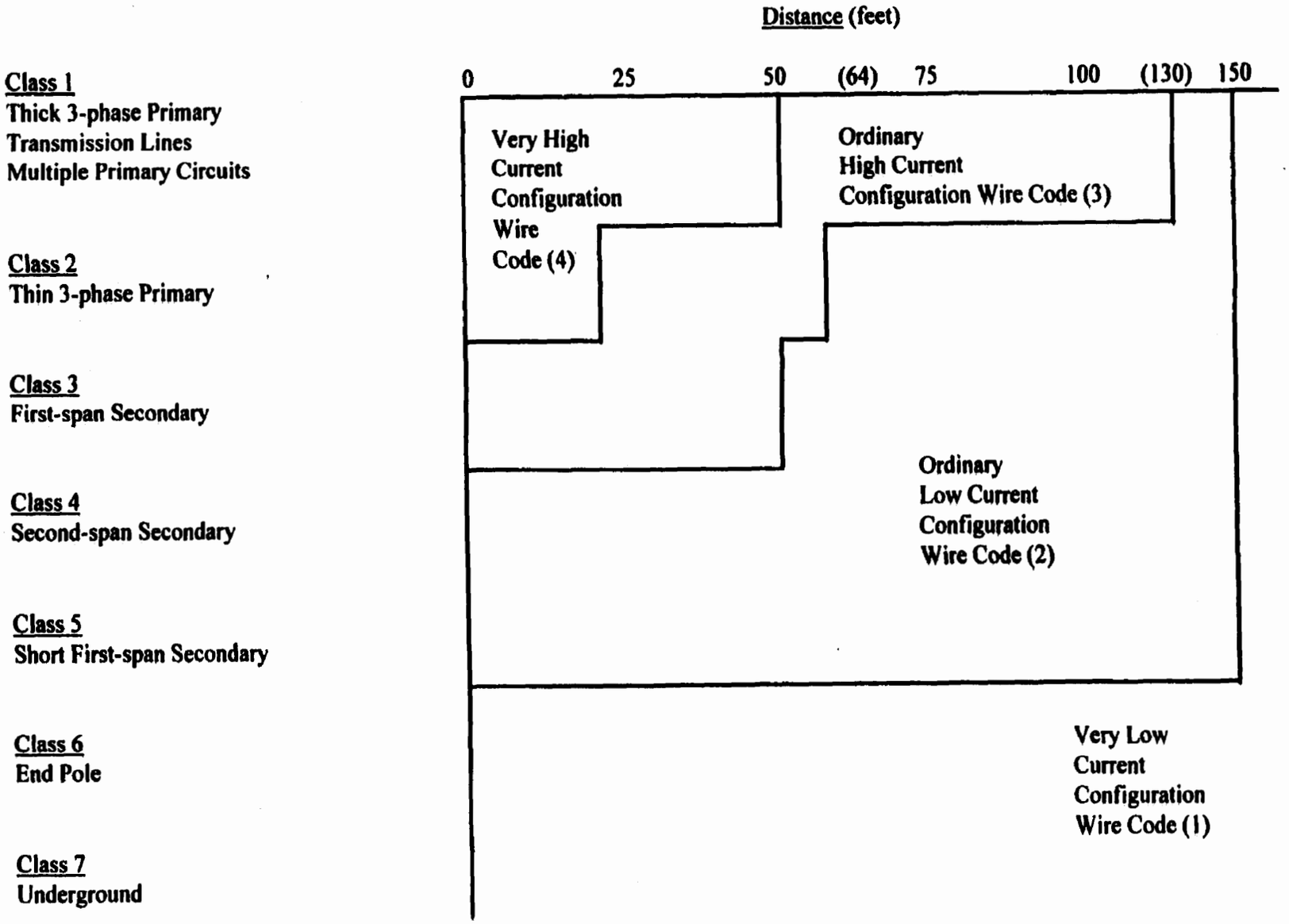
Criteria for Assigning Wiring Configurations

Wertheimer - Leeper Wire Code

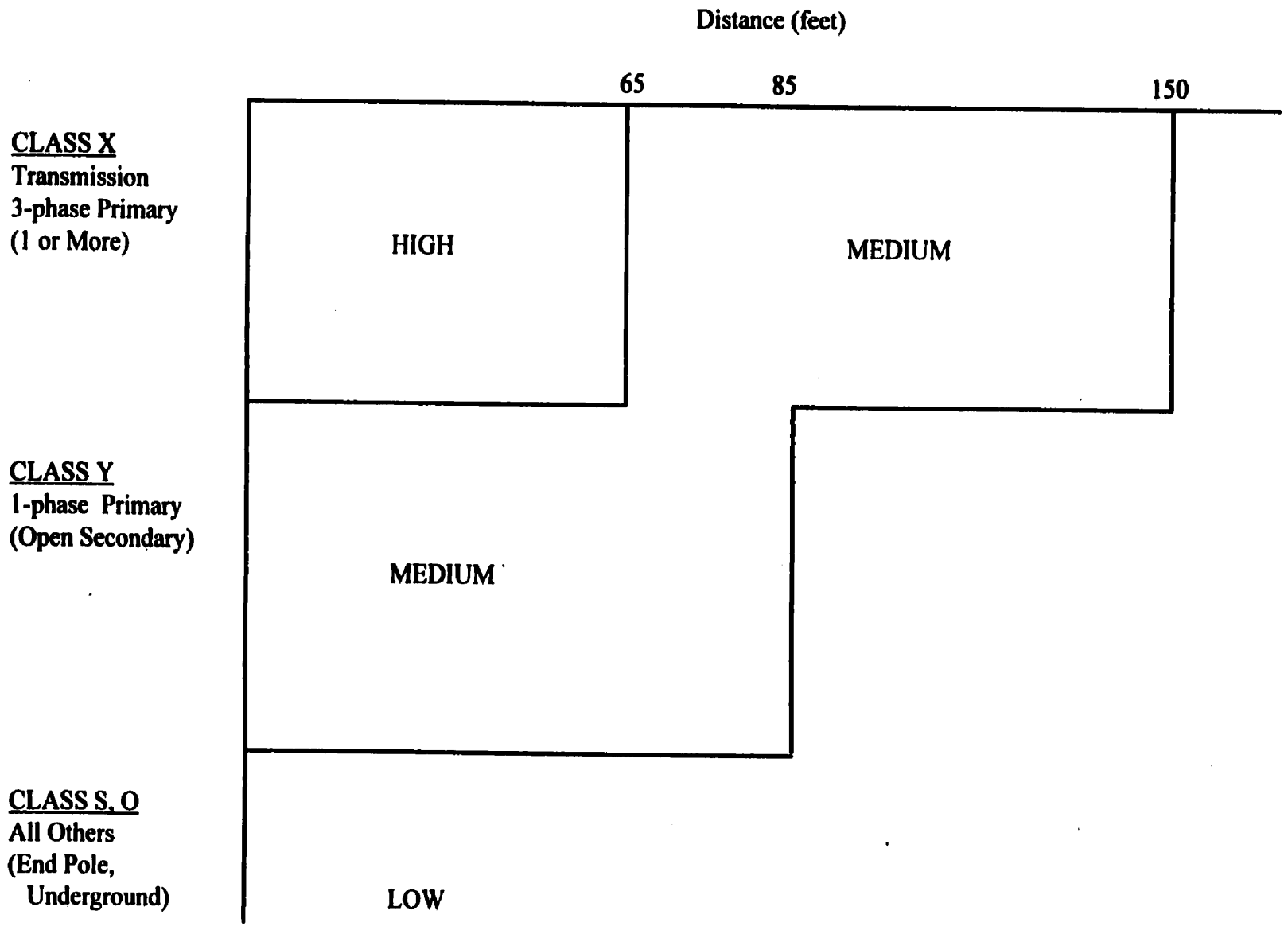
Kaune Wire Code ('92)

Wertheimer-Leeper Wiring Code

as a Function of Distribution Class and Distance to Residence



Kaune Wire Code ('92)



Appendix B

Details Relating to the Selection and Content of Multivariate Models for Selected Indices of EMF Exposure

B.1 Magnetic Flux Density (μT) - Home

(a) Comparison of Univariate and Multivariate Models for Selected Summary Indices of EMF Exposure
(b) Assessment of the Contribution of Factors to the Fully Adjusted Multivariate Model
(c) Beta Coefficients, Odds Ratios and 95% Confidence Intervals (CI) for Adjustment Factors Included in the Fully Adjusted Multivariate Models Assessing Childhood Leukaemia Risk

B.2 Magnetic Flux Density (μT) Corrected for Power Consumption - Home

(a) Comparison of Univariate and Multivariate Models for Selected Summary Indices of EMF Exposure
(b) Assessment of the Contribution of Factors to the Fully Adjusted Multivariate Model
(c) Beta Coefficients, Odds Ratios and 95% Confidence Intervals (CI) for Adjustment Factors Included in the Fully Adjusted Multivariate Models Assessing Childhood Leukaemia Risk

Appendix B.1 (a)

Comparison of Univariate and Multivariate Models for Selected Summary Indices of EMF Exposures

Magnetic Flux Density (μT) - Home

Model	Variable	Deviance[1]	df	Beta Coefficient ± Standard Error	OR
Null	0	158.01	0	-	-
Univariate	Magnetic field exposure - home	153.46	3		
	<0.04			0	1.00
	0.04 -			0.755 ± 0.411	2.12
	0.08 -			0.414 ± 0.401	1.51
	≥0.18			0.732 ± 0.416	2.08
Multivariate	Magnetic field exposure - home + confounders[2]	106.49	13		
	<0.04			0	1.00
	0.04 -			1.488 ± 0.554	4.43
	0.08 -			0.863 ± 0.524	2.37
	≥0.18			1.568 ± 0.542	4.80

[1] Deviance: -2(log likelihood)

[2] Fully adjusted model resulting from backward stepwise regression with the following :

Family income
History of common childhood diseases
Siblingship
Mother's use of hair colouring products during
Residential mobility
Child's exposure to agricultural sprays
Child's exposure to insecticides

Appendix B.1 (b)

Assessment of the Contribution of Factors to the Fully Adjusted* Multivariate Model

Model	Chi-square**	p-value***
Fully Adjusted Model - Main Effects of Magnetic Flux Density (Home) Plus all Confounders		
Adjusted model with family income removed	25.31	<0.0001
Adjusted model with residential mobility removed	6.17	0.0130
Adjusted model with siblingship removed	4.34	0.0372
Adjusted model with child's exposure to agricultural sprays removed	7.81	0.0052
Adjusted model with child's exposure to insecticides removed	1.10	0.2951
Adjusted model with history of common childhood diseases removed	5.28	0.0216
Adjusted model with mother's use of hair colouring products during or just prior to pregnancy removed	2.65	0.1033

* Fully adjusted model with confounders resulting from backward stepwise conditional logistic regression

** Chi-square derived from likelihood ratio test (fully adjusted model compared with model with specified term removed)

*** P-value associated with the likelihood ratio test

Appendix B.1 (c)

Beta Coefficients, Odds Ratios and 95% Confidence Intervals (CI) for Adjustment Factors Included in the Fully Adjusted Multivariate Models Assessing Childhood Leukaemia Risk

Risk Factors/Potential Confounders	Beta Coefficient	Odds Ratio	95% CI
Average Magnetic Flux Density (μT) - Home			
Magnetic field exposure - home			
<0.04	0	1.00	-
0.04 -	1.488	4.43	1.50 - 13.10
0.08 -	0.863	2.37	0.85 - 6.62
≥0.18	1.568	4.80	1.66 - 13.88
Family income			
$50,000-59,000	2.714	15.08	3.83 - 59.34
$30,000-49,000	0.771	2.16	0.87 - 5.38
<$30,000	2.452	11.61	2.51 - 53.82
Don't know/refused	1.603	4.97	0.50 - 49.55
Residential mobility			
≥ 4 moves	1.303	3.68	1.26 - 10.74

Appendix B.1(c) continued

Beta Coefficients, Odds Ratios and 95% Confidence Intervals (CI) for Adjustment Factors Included in the Fully Adjusted Multivariate Models Assessing Childhood Leukaemia Risk

Risk Factors/Potential Confounders	Beta Coefficient	Odds Ratio	95% CI
Child's exposure to agricultural sprays	1.389	4.01	1.46 - 11.03
Child's exposure to insecticides	0.513	1.67	0.64 - 4.38
Siblingship	-1.347	0.26	0.07- 0.97
History of common childhood diseases	-1.300	0.27	0.09 - 0.85
Mother's exposure to hair colouring products during or just prior to pregnancy	0.685	1.98	0.85- 4.62

Appendix B.2 (a)

Comparison of Univariate and Multivariate Models for Selected Summary Indices of EMF Exposures

Magnetic Flux Density (μT) Corrected for Power Consumption - Home

Model	Variable	Deviance[1]	df	Beta Coefficient ± Standard Error	OR
Null	0	158.01	0	-	-
Univariate	Magnetic field exposure - home	154.39	3		
	<0.04			0	1.00
	0.04 -			0.414 ± 0.413	1.51
	0.08 -			0.517 ± 0.395	1.68
	≥0.17			0.729 ± 0.403	2.07
Multivariate	Magnetic field exposure - home + confounders[2]	99.87	16		
	<0.04			0	1.00
	0.04 -			1.25 ± 0.612	3.48
	0.08 -			1.50 ± 0.619	4.52
	≥0.17			2.02 ± 0.691	7.57

[1] Deviance: -2(log likelihood)

[2] Fully adjusted model resulting from backward stepwise regression with the following:

Family income	Type of delivery	Child's exposure to household bleach
Mother's education	Residential mobility	Maternal smoking during pregnancy
Siblingship	Child's exposure to agricultural sprays	Child's exposure to insecticides

Appendix B.2 (b)

Assessment of the Contribution of Factors to the Fully Adjusted* Multivariate Model

Model	Chi-square**	p-value***
Fully Adjusted Model - Main Effects of Magnetic Flux Density Corrected for Power Consumption (Home) Plus all Confounders		
Adjusted model with family income removed	21.47	0.0003
Adjusted model with residential mobility removed	8.36	0.0038
Adjusted model with siblingship removed	3.92	0.0476
Adjusted model with child's exposure to agricultural sprays removed	8.29	0.0040
Adjusted model with child's exposure to insecticides removed	1.55	0.2125
Adjusted model with mother's education removed	6.39	0.0410
Adjusted model with maternal smoking during pregnancy removed	3.85	0.0498
Adjusted model with type of delivery removed	2.85	0.0914
Adjusted model with child's exposure to household bleach removed	1.79	0.1811

* Fully adjusted model with confounders resulting from backward stepwise conditional logistic regression

** Chi-square derived from likelihood ratio test (fully adjusted model compared with model with specified term removed)

*** P-value associated with the likelihood ratio test

Appendix B.2 (c)

Beta Coefficients, Odds Ratios and 95% Confidence Intervals (CI) for Adjustment Factors Included in the Fully Adjusted Multivariate Models Assessing Childhood Leukaemia Risk

Risk Factors/Potential Confounders	Beta Coefficient	Odds Ratio	95% CI
Average Magnetic Flux Density (μT) Corrected for Power Consumption - Home			
Magnetic field exposure - home			
<0.04	0	1.00	-
0.04 -	1.248	3.48	1.05 - 11.56
0.08 -	1.509	4.52	1.34 - 15.21
≥0.17	2.024	7.57	1.95 - 29.34
Family income			
$50,000-59,000	2.659	14.29	3.35 - 61.01
$30,000-49,000	0.897	2.45	0.90 - 6.71
<$30,000	2.204	9.05	1.74 - 47.23
Don't know/refused	1.006	2.74	0.15 - 48.83
Residential mobility			
≥ 4 moves	1.645	5.18	1.61 - 16.64

Appendix B.2 (c) continued

Beta Coefficients, Odds Ratios and 95% Confidence Intervals (CI) for Adjustment Factors Included in the Fully Adjusted Multivariate Models Assessing Childhood Leukaemia Risk

Risk Factors/Potential Confounders	Beta Coefficient	Odds Ratio	95% CI
Child's exposure to agricultural sprays	1.584	4.88	1.56 -15.25
Child's exposure to insecticides	0.626	1.87	0.70 - 5.03
Child's exposure to household bleach	-0.617	0.54	0.21 - 1.36
Mother's education			
Completed high school	0.821	2.27	0.75 - 6.90
High school incomplete	2.320	10.18	1.39 - 74.64
Type of delivery			
Caesarean	0.726	2.07	0.87 - 4.89
Maternal smoking during pregnancy	-1.131	0.32	0.10 - 1.05
Siblingship (none)	-1.307	0.27	0.07 - 1.04