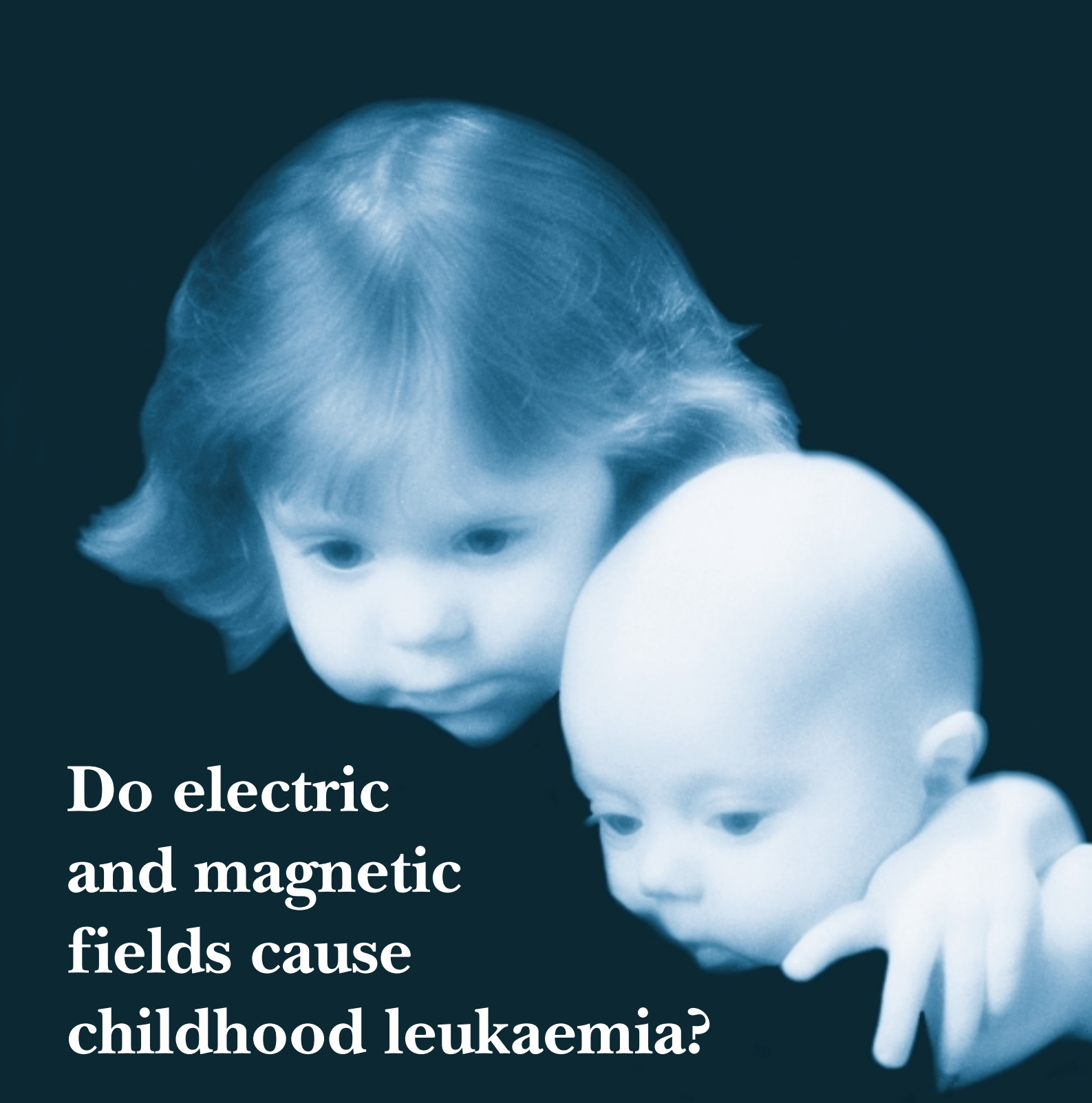

Do electric and magnetic fields cause childhood leukaemia?

A review of the scientific evidence

Prepared for CHILDREN with LEUKAEMIA
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Fighting Britain's biggest child killer disease

CHILDREN with LEUKAEMIA
Registered Charity No. 298405. Inaugurated in 1988 by Diana, Princess of Wales in memory of Jean and Paul O'Gorman

Contents

Tables and figures

Executive Summary

Electric and magnetic fields (EMF) are created by the presence of electricity. They surround us in modern life and are produced in varying degrees and strengths by all elements of the electricity supply system – from high voltage power lines to the electrical appliances in our homes. EMF have come under scrutiny as a possible source of harm and have been blamed for a wide range of adverse health effects. A great deal of research has been carried out investigating these possible effects, with mixed results. Perhaps the largest body of evidence relates to childhood leukaemia where there is now the strongest evidence of a link.

Epidemiology

The bulk of the evidence comes from epidemiological studies, looking at the pattern of childhood leukaemia in relation to levels of exposure to EMF. Since the first study was published in 1979, more than 25 epidemiological studies around the world have investigated the association between childhood leukaemia and exposure to EMF. These studies have varied in quality, size and in the way that they have assessed exposure, leading to conclusions that are sometimes inconsistent. Most of the individual studies have had very limited power to detect associations since they are constrained by the relative rarity of childhood leukaemia and further by the relatively low number of children exposed to high levels of EMF.

A number of researchers have pooled data from several individual studies to increase the ability to detect an association. The three most recent of these all report an increase in risk and these studies are discussed in detail in this report. The most recent study we include was published in 2005 in the British Medical Journal. It merits inclusion by virtue of being the largest single study of childhood cancer and power lines, with roughly twice the number of children living close to power lines than the next largest study. The authors reported an increased risk of leukaemia in children in England and Wales whose birth address fell within 600m of a high voltage power line.

No consensus

There remains a wide spectrum of opinion within the scientific community as to the meaning of the results of the epidemiological studies. Epidemiology has limitations but methods have become more sophisticated over time, and later studies address some of the shortcomings of earlier investigations. Interestingly, this hasn't significantly altered the relative risks reported and the consistency of findings in different populations strengthens the evidence of an association. However, there is still much debate as to whether the results are real or whether the observed relationships may reflect a coincidental association with some other factor. In any event, it is difficult to infer causal relationships based on epidemiological studies alone. The growing body of evidence relating to the biology and causal mechanisms should help to further our understanding of the relationship between EMF exposure and childhood leukaemia.

Biological effects

There are well-established mechanisms by which EMF *could* produce biological effects but results from many hundreds of experiments since 1979 are overall contradictory and inconclusive. Exposure to EMF has been shown to damage DNA, to alter cell function and accelerate tumour development. However, for each study which shows an effect, there are many good and reproducible studies which show no effect. This presents difficulties for the scientific community and there is still considerable controversy amongst the scientists working in this area.

Mechanistic theories

A number of theories have been advanced to explain both the scientific and the epidemiological evidence for a link between childhood leukaemia and EMF exposure. The three which have the most supporting evidence are that EMF could act: by directly increasing the level of free radicals within the body; by decreasing the level of the hormone melatonin; by affecting exposure to airborne pollutants. These theories aren't necessarily mutually exclusive.

Do electric and magnetic fields cause childhood leukaemia?

Following our review of the evidence, we have to say we don't know - yet. We believe that there is good epidemiological evidence for a doubling of risk of childhood leukaemia in children exposed to EMF above a certain level (0.4 μT). To progress from this to a proof that EMF are a cause of childhood leukaemia is a big jump and, at this stage, not clearly supported by the biological evidence although we have perhaps moved on from 'implausible' to 'plausible'. More research work needs to be done and this report ends with some recommendations for future studies.

1. Introduction

Leukaemia is the most common childhood cancer. Developments in treatment and care have led to a dramatic increase in survival rates in recent years but leukaemia still kills more children than any other disease in the UK.

The causes of leukaemia are uncertain. There are some factors which are known to cause the disease (such as exposure to high dose radiation) but these cannot account for all cases. Incidence of the disease increased throughout the 20th century, suggesting that aspects of our changing lifestyle may be partly to blame.

The first study linking electric and magnetic fields (EMF) and childhood leukaemia was published in the United States in 1979. Since then, more than 25 epidemiological studies investigating the association have been carried out around the world. There is also an accumulating body of scientific evidence relating to the possible biological mechanisms that might lie behind such an association. This report sets out to bring together the available evidence into one comprehensive document.

This report is not as daunting as it first appears. Primarily, we present the epidemiological (section 2.4) and biological (section 3) evidence for and against electric and magnetic fields increasing the risk of childhood leukaemia. But first we need to introduce a number of the concepts and ideas in those two sections: the nature of EMF (section 1.1); information about childhood leukaemia (section 1.2); and a number of issues related to the interpretation of the epidemiology (sections 2.2 and 2.3). After describing and discussing the epidemiology and biology we go on to discuss some of the theories proposed to explain the effects of EMF (section 4). Finally, we present our conclusions and some suggestions for further work.

1.1 Electric and Magnetic fields

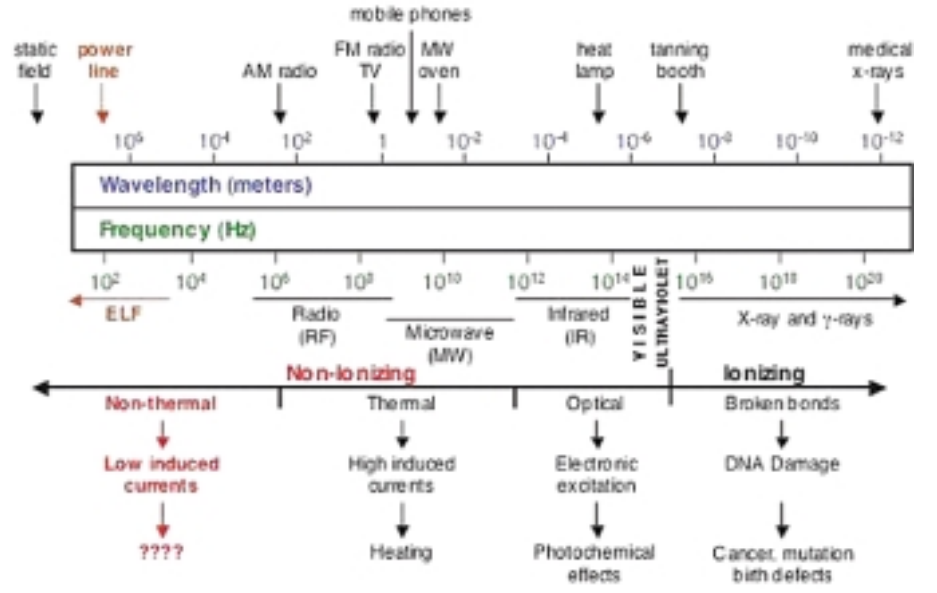
Electric and magnetic fields are created by the presence of electricity. The electric and magnetic fields created by the electricity supply system are part of the electromagnetic spectrum, which also includes X-rays, ultraviolet light, visible light, infrared light, microwaves and radio-frequency energy. The parts of the electromagnetic spectrum are characterized by their frequency or their wavelength which are inversely related - as the frequency rises the wavelength gets shorter. The frequency is the rate at which the electromagnetic field goes through one complete cycle and is measured in Hertz (Hz), where one Hz is one cycle per second.

See Figure 1. The Electromagnetic Spectrum.

The electricity supply system in the UK and most of the world has a frequency of 50 Hz and the USA 60 Hz. The electric and magnetic fields given out by the electricity supply system are therefore referred to as extremely low frequency (ELF) electromagnetic fields as they are at the lowest end of the electromagnetic spectrum. In this report we refer to these extremely low frequency electric and magnetic fields as EMF for the sake of simplicity.

Electricity is transmitted from power stations to the point of use (homes, offices, schools etc) via a network of power cables and substations (known as the national grid). The substations step down the voltage progressively as the electricity nears its point of use (voltage is the driving force behind the flow of electricity, somewhat like the pressure in a water pipe). The major power lines which are carried on the large pylons across much of the country operate at 400,000 volts (V), stepping down to 275,000 V and then 132,000 V as the supply nears the point of use. When the electricity supply enters the home it has been stepped down to 230 V.

Figure 1. The Electromagnetic Spectrum.



1.1.1 Magnetic fields

A magnetic field is a force field generated by moving electrical charges. An electric current running through a cable generates a magnetic field. The strength of the field depends on the current (the rate of flow of electricity). Magnetic fields are measured in tesla (T) usually microtesla (μT). The three most common sources of magnetic fields in the home are electric appliances, the earthing system of the home and nearby power lines. Ambient levels of magnetic fields in most homes are typically in the range of 0.01 - 0.3 μT. Close to high voltage power lines, magnetic fields are typically above 1 μT, although values can reach tens of μT. Some domestic appliances produce magnetic fields of 100 μT or more in their vicinity. The field drops off rapidly with increasing distance from the source.

1.1.2 Electric fields

An electric field surrounds any electrically charged object. If a power line is connected to the national grid or if an appliance is plugged in to the mains supply (regardless of whether the appliance is switched on), it is 'charged' and therefore will be surrounded by an electric field. This is in contrast to a magnetic field which will only be produced if the appliance is in use and there is actually electricity flowing through the appliance or cable. Electric fields are measured in volts/metre (V/m) and their strength depends upon the voltage on the wire and the distance from the line. The Electrical Power Research Institute found that the average personal exposure to electric fields in the home typically ranges from 5 to 10 V/m. Directly underneath a 400,000 V power line, the electric field might be as high as 10,000 V/m.

Figure 2. Electric and Magnetic Fields.

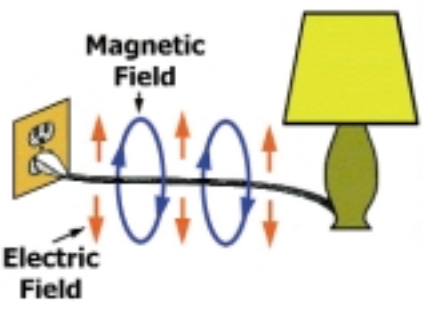
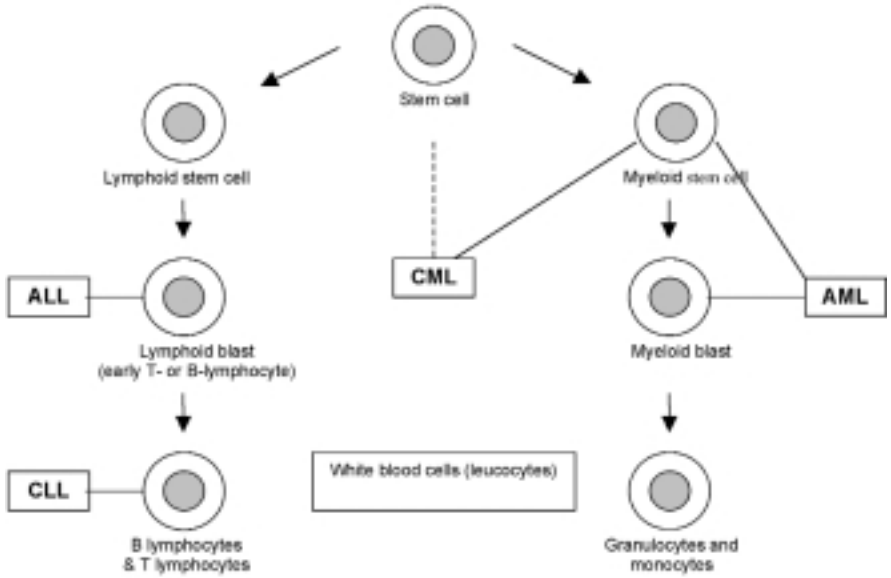


Figure 3. White blood cell lineages and the major leukaemias



1.2 Childhood leukaemia

The term 'leukaemia' describes a group of cancers involving an excess of white blood cells. Leukaemias are the most common childhood cancers, accounting for around one third of all cases – about 500 children per year in the UK (aged 0 to 14 years). Every year in the UK around 100 children are killed by leukaemia, more children than are killed by any other disease.

Leukaemic cells develop from cells in the bone marrow ("haemopoietic stem cells") that go on to become blood cells. Leukaemia arises from the abnormal transformation of a single cell. This single cell generates an expanding clone of abnormal cells via repeated cell divisions. The result is a proliferation of abnormal white blood cells and a disruption of the production of normal blood cells.

Haemopoietic cells divide frequently – undergoing some 100,000,000,000 divisions per day in the adult and even more *in utero* when the embryo is growing rapidly. The cells that go on to become white blood cells (lymphocytes) undergo DNA rearrangement to create the large number of different types of cells needed by the immune system. This process is intrinsically prone to DNA errors – which may occur either spontaneously or as a result of exposure to external carcinogens. This vulnerability to cancer development might be seen as an evolutionary trade-off for the otherwise highly advantageous properties of the immune system.

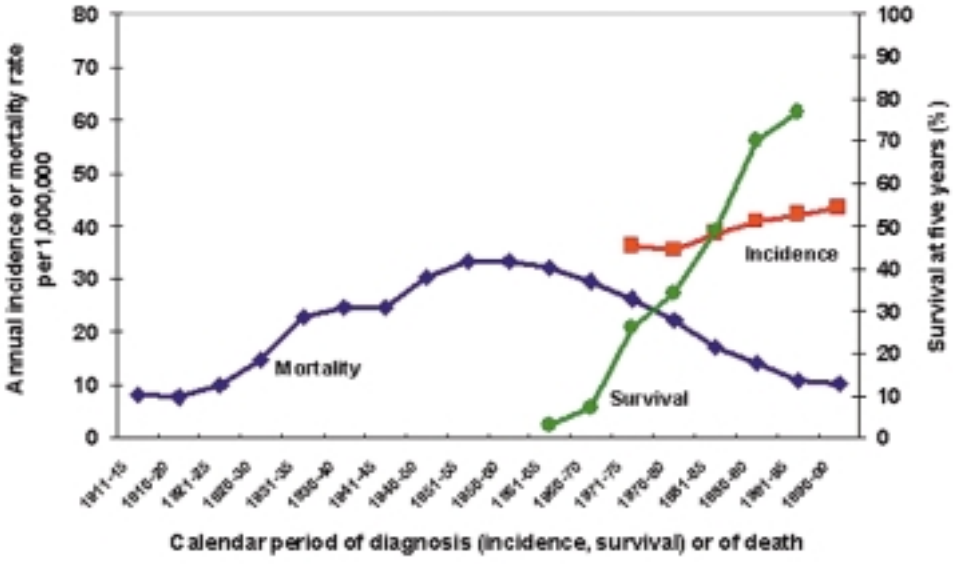
1.2.1 Types of childhood leukaemia

Leukaemia can be classified as either *lymphoid* or *myeloid*, denoting the type of white blood cell affected, and as either *acute* or *chronic*, reflecting the speed of progression.

Almost all childhood leukaemias are of the acute form. **Acute lymphoblastic (lymphoid) leukaemia (ALL)** accounts for more than 80 per cent of all cases of childhood leukaemia. It is the only form of leukaemia – and one of the few forms of cancer – that is more common in

Figure 4. Trends in childhood leukaemia incidence, survival and mortality, 0-14 years, England and Wales 1911-2000.

Incidence and mortality rates per million for England and Wales[4 5] five-year relative survival rates (%) for children diagnosed in South-East England 1960-88[6] and in Great Britain 1993-97 (Coleman, 2004[7]).



children than in adults. **Acute myeloid leukaemia (AML)** accounts for most of the remaining cases.

Chronic leukaemias are very rare in childhood. Chronic myeloid leukaemia (CML) accounts for less than 3 per cent of childhood leukaemias (less than 15 children per year in the UK) and chronic lymphocytic leukaemia (CLL) is unheard of in children.

1.2.2 The genetic basis of leukaemia

Leukaemic cells can carry a variety of abnormalities including chromosome gain or loss or structural changes like chromosome deletions, duplications, inversions and translocations.

In childhood leukaemia these chromosome rearrangements arise mainly before birth. However, they arise at a frequency far greater than the incidence rate of childhood leukaemia[1]. For example, the 'TEL-AML1' fusion is present in around one per cent of new born babies but less than one per cent of babies with the fusion will go on to develop leukaemia.

It therefore appears that, whilst the development of childhood leukaemia is frequently initiated in the womb, additional post-natal events are required for the child to develop full-blown leukaemia. This is known as the 'two hit hypothesis' and the very first evidence for this was derived from studies of identical twins. The rate of concordance between leukaemia in identical twins varies substantially according to subtype and age of onset of disease[2 3]. For infant ALL (ie. onset before one year of age), the concordance rate is greater than 50%. For typical childhood ALL, the concordance rate is much lower at around 10%. Adult leukaemia, by contrast, has a concordance rate of less than one per cent in identical twins, suggesting an increasing influence of environmental factors over genetic factors with increasing age.

1.2.3 Incidence of childhood leukaemia

Another observation which suggests the importance of environmental factors in the development of childhood leukaemia is that the incidence of the disease appears to have increased steadily throughout the 20th century, as shown in the chart above.

Incidence data were not collected prior to the 1970s but until the introduction of the first combination therapies in the 1960s childhood leukaemia was almost inevitably fatal and so the mortality figures provide a fairly accurate representation of incidence figures until the 1960s when the two curves dramatically diverge as survival rates begin to grow.

Since our genetic make-up does not change significantly over such a short time scale, the increasing incidence of childhood leukaemia must be a reflection of some aspect of our changing lifestyle or environment.

1.2.4 The causes of childhood leukaemia

As outlined in sections 1.2.1 and 1.2.2 above there are a variety of different types of leukaemia and a variety of different genetic mutations underlying these different types of the disease. Considerable advances have been made in understanding the biological mechanisms underpinning these different disease types and scientists have mapped out many of the chromosome translocations involved.

What this biological aetiology doesn't reveal, however, is the underlying causal factors. What factors (other than spontaneous error) cause the initial chromosome translocations to occur and what factors are the 'second hits' which predispose children with these translocations go on to actually develop leukaemia?

There is no single external factor which is either 'necessary' or 'sufficient' to cause leukaemia in children. That is, there is no single factor to which a child must be exposed if they are to develop leukaemia and there is no single factor, exposure to which is guaranteed to result in development of leukaemia.

Rather it is thought that leukaemia is multi-causal and multi-factorial, that is, there are many different factors which may cause leukaemia and exposure to more than one of these is probably necessary – probably at different stages of a child's life – perhaps, as already described, one 'hit' *in utero* and a second 'hit' in early childhood.

Most of the environmental and lifestyle factors which may be implicated in the causes of childhood leukaemia are extremely difficult to investigate in epidemiological studies. The difficulties which are explored in Section 2 in relation to EMF also apply to many of the other environmental and lifestyle factors which have been linked with childhood leukaemia.

The factors which have been linked to childhood leukaemia can be divided into three categories: exposure to *causative* factors increases the risk of a child developing the disease; exposure to *protective* factors reduces the risk of a child developing the disease; *linked* factors are correlated with the incidence of leukaemia but are not directly causative or protective, more likely they reflect the likelihood of exposure to another causative or protective factor.

Some of the main factors for which associations have been identified are set out in the three tables which follow. Space does not permit a detailed discussion of these factors, and we do not claim to have provided an exhaustive list of the evidence for and against each of the suggested factors, more we have aimed to sign-post the reader towards some of the relevant research.

Table 1. Possible causative factors in childhood leukaemia

Factor	Potential importance
1. Ionising radiation	It has been shown that exposure to ionising radiation (even at quite low doses) can cause leukaemia. Epidemiological evidence for this comes from studies of in utero irradiation of the foetus through obstetric xrays and studies of Japanese atomic bomb survivors. It is estimated that background ionising radiation is implicated in around 25% of cases of childhood leukaemia, with exposure both in utero and early in life being important. See Wakeford (2004)[8] for a review. There is some evidence that paternal pre-conceptual exposure (through irradiation in the work place) may be important (Gardner *et al*, 1990[9]).
2. Non-ionising radiation	
i) Light at night	There is a suggestion that our increasing exposure to light at night may be increasing the risk of childhood leukaemia through its disruption of our circadian rhythm and suppression of the hormone melatonin (Henshaw & Reiter, 2005[125]).
ii) ELF electric and magnetic fields	See section 2 onwards.
3. Chemical exposure	
i) Air pollution	The risk from air pollution is difficult to detect in epidemiological studies as a result of the ubiquitous exposure in developed countries. Knox (2005[10,11]) found an increased risk of childhood cancer for birth addresses within 1 km of hot spots for various air pollutants.
ii) Parental smoking	Epidemiological evidence to support a link with childhood leukaemia is inconsistent, however at least one study has found increased chromosomal abnormalities in amniocyte cells of foetuses of smoking mothers (De la Chica *et al*, 2005[12]).
iii) Pesticides	Associations have been reported between childhood leukaemia and either parental or child exposure to pesticides (e.g. Infante-Rivard, 1999[13]).
iv) Prescription drugs (pre-natal exposure)	One study has reported an association between childhood ALL and maternal use of antihistamines and allergy remedies (Wen *et al*, 2002[14]). Robison *et al* (1989)[15] reported a link between maternal use of antiemetic medication and AML.
v) Parental alcohol consumption	There is weak evidence for a possible link between maternal alcohol consumption during pregnancy and AML but no evidence for a link with ALL[16].
v) Recreational drugs and alcohol (pre-natal and pre-conceptual exposure)	Maternal use of marijuana has been reported to increase the risk of both childhood ALL (Wen *et al*, 2002[14]) and AML (Robison *et al*, 1989[15]). There is evidence that the risk may be higher when both parents use the drug.
vi) DNA topoisomerase inhibitors	This includes some drugs used in chemotherapy, benzene metabolites (from air pollution and cigarette smoke), certain fruits, tea, coffee, wine, soy and cocoa and many other substances[17,18] Topoisomerase inhibitors Inhibit DNA repair and are strongly associated with one of the chromosome rearrangements common in infant leukaemia[19].
vi) Diet	N-nitroso compounds (found in cured meats and hot dogs) have been linked with childhood leukaemia in at least one study (Peters, 1994[20]).
4. Infectious exposure	There is evidence of an excess of cases of childhood leukaemia in locations with an unusual type of population mixing. It has been proposed that this is due to an, as yet unidentified, infectious agent and that leukaemia is a rare consequence of exposure to this agent. In isolated communities a higher proportion of the population would have been previously unexposed to such an infection and a rapid influx of newcomers into such a community would lead to an increased level of contact between the infected newcomers and the susceptible original residents (Kinlen, 1995)[21].

Table 2. Possible protective factors in childhood leukaemia

Factor	Potential importance
1. Diet	Evidence from one study suggests that there is a strong protective effect of consumption of oranges and bananas in early life (Kwan *et al*, 2004[22]).
2. Folate and folate metabolism	Folate metabolism is thought to be important in the development of leukaemia. There is some evidence to suggest that maternal folate supplementation during pregnancy may protect against childhood leukaemia (Thompson *et al*, 2001[23]). There are also differences in the way that individuals metabolise folate and this may be important (Wiemels *et al*, 2001[24]).
3. Infectious exposure	Lack of exposure to infections in early life results in an immature immune system and this may increase risk of childhood leukaemia (Greaves, 1997)[25]. For example, a recent study found that children attending day care from young age are less likely to develop leukaemia. (Gilman *et al*, 2005[26]).
4. Breast feeding	There is a fairly substantial body of evidence pointing towards a protective effect of breast-feeding. A recent meta-analysis reported a relative risk of 0.76 (0.68 – 0.84) (Kwan *et al*, 2004[27]).

Table 3. Other factors associated with childhood leukaemia

Factor	Potential importance
Maternal age >35years	Most studies have observed an increased risk for childhood leukaemia with advanced maternal age (e.g. Reynolds, 2002[28]) although one study has reported a risk association in ALL with young maternal age (Shu, 2002[29]).
Miscarriage history	Maternal history of previous miscarriages is a frequently reported risk factor for development of ALL – and in some cases AML - in a subsequent child (e.g. Perrillat, 2002[30]).
Birth order	Being the first born child has been associated with increased risk in some studies (e.g. Dockerty, 2001[31]) although the opposite has also been reported (e.g. Shu, 2002[29]). One study identified being the only child as a risk factor (van Steensel-Moll, 1986[32]).
Socioeconomic status	Incidence of ALL is higher in areas of high social class (e.g. Alexander 1991[33], Stiller & Parkin, 1996[34]). Evidence from developing countries suggests that incidence of ALL in children aged 1-4 years is rising with improved socio-economic conditions (Hrusak, 2002[35]).
Birth weight	Higher birth weight is associated with increased risk of childhood leukaemia (Hjalgrim, 2003[36]).
Congenital disorders	Children with Down's Syndrome and certain other genetic syndromes are much more susceptible to leukaemia (Reynolds, 2002[28]).
Gender	The gender effect in incidence of ALL is well-established, with boys being approximately 20% more likely to develop ALL than girls (e.g. Pearce & Parker, 2001[37]. Males also have a worse prognosis (Eden, 2000[38]).
Ethnicity	Incidence of ALL is significantly lower among black children in the US (Reynolds, 2002[28]). This may be a social class effect.

Many of these factors may well be correlated with each other.

2. Epidemiology

Epidemiology is the study of the distribution of disease in populations and of the factors that influence this distribution. It is concerned with the *patterns* of disease among *groups* rather than with treating the disease at the individual level. Epidemiology is very valuable in assessing risks to human health from certain factors but it does have limitations and these are discussed under 2.1 below.

To investigate an association in a rare disease such as childhood leukaemia and EMF, epidemiologists generally use a *case-control study*. This is a way of comparing people who already have a particular disease (cases) with people who do not (controls). In the case of EMF, epidemiologists will recruit a group of people who have leukaemia and a group of people who do not and compare the exposure of the two groups to EMF to see if there are any differences. The controls are chosen to be as similar to the cases as possible in all characteristics except their exposure.

Since publication of the first study by Wertheimer and Leeper in 1979[39], more than 25 epidemiological studies have investigated the association between childhood leukaemia and exposure to magnetic fields. There have also been a number of published reviews and pooled analyses of these individual studies and we focus on these overviews because they provide stronger evidence than individual studies. Overall, a significant statistical association is found with the incidence of childhood leukaemia and exposure to power frequency magnetic fields of 0.3 - 0.4 μT, levels commonly found under or close to high voltage overhead power lines. More recently, associations have been found at greater distances from power lines suggesting a possible effect of electric as well as magnetic fields.

There remain deep divisions of opinion as to the meaning of the epidemiological evidence. In any event it is difficult to infer causal relationships based on epidemiological studies alone and the growing body of evidence relating to the biology and causal mechanisms (see sections 3 and 4) should help to further our understanding of the relationship between EMF exposure and childhood leukaemia.

Key considerations

2.1 Limitations of the epidemiological approach

Epidemiology is observational rather than experimental, meaning that the epidemiologist does not control who receives exposure. This may introduce bias (a systematic tendency to error as a consequence of design or conduct of the study) or confounding (spurious findings due to the effect of a variable that is correlated with both the exposure and the disease under study). These problems can be overcome by appropriate study design, including careful selection of controls, and analysis. But, it is not always possible to eliminate them completely.

Control selection bias

In a case-control study, cases are selected on the basis that they have leukaemia. Investigators then set out to recruit controls that 'match' the cases on key characteristics (such as age, gender, ethnic background). If the controls are not properly representative of the population as a whole, any association found in the study might not be real. As an example, in much American epidemiology the control group is recruited by telephone. This could result in socio-economic differences between the case and control groups as poorer families are less likely to have telephones and are therefore likely to be under-represented in the controls. This would introduce a bias. This problem of potential bias has to be considered in all case-control studies and it is not possible to know how much it affects the results.

Non-response bias

Not all controls will agree to take part in the study (nor all cases, although the response rate is higher amongst cases). Differential participation of controls as a function of their socio-economic status has been proposed as a possible explanation of the association between EMF and childhood cancer i.e. those with lower socio-economic status are less likely to take part and this may bias the results. This does not apply in studies where contact is not necessary – for example, the Nordic studies which are based on national population registries.

Confounding

A confounding factor is a factor that may also affect the relative risk but its effect cannot be separated out from the factor under investigation. For example, an association has been found between magnetic fields and cancer. On the face of it this may suggest that the fields increase the risk of cancer. But it could be that the risk of cancer is increased by something else that is also associated both with the fields and with the cancer.

For example, homes with high magnetic fields tend to be older, smaller properties, in areas of higher housing density, on busier roads, occupied by families with lower education, lower socio-economic status and younger children. If any of these factors – such as socio-economic status - are also associated with the development of cancer then they will confound the results of the study.

An association exists between the divorce rate in Britain and the level of sales of Golden Delicious apples. This association is due to the correlation of both factors with levels of prosperity. If we don't take prosperity into account as a confounding factor then we would end up with the conclusion that eating Golden Delicious apples increases the likelihood of your marriage ending in divorce!

Well designed studies attempt to adjust for the effects of possible confounding factors.

Statistical power

An important aspect of an epidemiological study is its statistical power – that is, the probability that if there really is an increase in risk of a

certain size the study is large enough to detect this. Small studies only have the power to detect large risks. This can be a major problem in epidemiological studies looking at the association between childhood leukaemia and EMF since both the disease and the exposure are relatively rare so the number of both cases and controls are limited.

This means that many studies have low statistical power and therefore a limited ability to detect small increases in risk. One way to overcome this is to pool results of individual, comparable studies into a *meta-analysis*. This increases the statistical power of the combined data to detect a smaller risk through increasing the number of subjects.

2.2 Exposure assessment
There are many difficulties inherent in trying to estimate the exposure of the child to EMF, including that i) exposure has multiple sources and can vary greatly over time and short distances; ii) the exposure period of relevance is before the date at which measurements can realistically be obtained and of unknown duration and induction period; and iii) the appropriate exposure metric is not known and there are no biological data from which to impute it (ICNIRP, 2001)[40].

Period of inquiry
There is little consensus as to which time period may be the most crucial in terms of the damaging effects of exposure to EMF and the 'period of inquiry' varies across the different studies. Some focus on the birth address, others look at the period leading up to diagnosis and some focus on the address at diagnosis. Only around 50 per cent of addresses are the same at diagnosis as at birth and this may dilute any observed effect. There is evidence that the mother's exposure during pregnancy may be important but this has so far received little attention in epidemiological studies. In whatever period is considered, it is difficult to reconstruct historical exposure accurately.

Exposure metrics
There has been a wide range of exposure metrics used in the studies carried out to date. The first study by Wertheimer and Leeper in 1979[39] (and many of the subsequent studies) used wire codes – an indirect measure of EMF exposure based upon proximity to particular types of transmission lines and distribution equipment. Studies in the Nordic countries especially have used available data to calculate historical fields. And more recent studies in other countries have utilised advances in methods for measuring exposure. The different approaches all have their strengths and weaknesses.

Wire codes. This indirect measure was used in the first epidemiologic study of exposure to magnetic fields and cancer risk (Wertheimer and Leeper, 1979[39]) and in many of the early residential studies of EMF in the US. Wire code calculations are based on the proximity to power lines and the voltage of the lines. Wire coding has become more sophisticated over time and it remains the most commonly used approach. Wire codes are not strong predictors of magnetic field strengths in homes but they do tend to distinguish relatively well between the very high and very low field homes.

Distance. Some of the initial European investigations examined risk of cancer in relation to distance of subjects' residences from electricity generating or transmission equipment. Because the magnetic field decreases with distance from such equipment, distance can be used as a crude predictor of the field. The electricity company will usually have records showing whether a particular line was operating during a particular period. Although this method is fairly crude, it may be the most appropriate predictor when investigating the effects of power lines on human health since there is still so much uncertainty about which aspect of fields may be damaging and should therefore be measured.

Calculated historical fields. Magnetic fields from power lines can be calculated accurately if the relevant variables are known. The most important variables for calculations are wire spacing and height, the current in each wire and distance from the home. Electricity companies rarely have records of the current in each wire for past years but they often have a record of power line load from which the current can be calculated – more reliably for high-voltage than low-voltage lines. This has been a popular approach in the Nordic studies where the relevant data is available.

Measured fields. As researchers in most countries do not have access to the information necessary to calculate historical fields, the most common approach is to estimate historical field levels based on measurements taken from the residence during the study. Two types of measurements are used most often: *spot measurements* (the average magnetic field over a period of seconds or minutes) and *time-weighted averages* or TWA (a long term measurement extending 24-48 hours). These two different types of measurement do not appear to correlate well.

In some studies children are given personal EMF meters to wear in order to ascertain their EMF exposure from all sources, including residential, school and other exposures. Although such measurements are the only practical way to determine the field from multiple sources, their major weakness is that they might not accurately reflect the conditions which prevailed years before – during the period in which the disease developed - since a child's lifestyle may change dramatically pre- and post-leukaemia.

2.3 Statistical methodology
Epidemiological studies always involve taking a **sample** of people with disease to obtain an estimate of risk associated with a particular exposure. This **observed** risk is an estimate of the true risk that we would see if we could measure the whole population,

everybody who has the disease. Because we have taken a sample there is uncertainty associated with our estimate and statistical techniques involve trying to quantify this uncertainty.

Relative risk
Risk itself is the probability that an event will happen. The risk of a child developing leukaemia (before the age of 16 years) is approximately 1 in 1,500. If a study investigating an association between magnetic fields and childhood leukaemia reported a relative risk (RR) of 2, this means that an exposed child is twice as likely as an unexposed child to develop leukaemia. The risk of an exposed child developing leukaemia would therefore be approximately 1 in 750. Relative Risks similar to an Odds Ratio (OR) in case control studies.

Confidence intervals
Most studies looking at the relationship between childhood leukaemia and magnetic fields have been based on relatively small samples (due to the limited availability of cases and controls) and are thus statistically imprecise. Statisticians can calculate a range (interval) in which we can be fairly confident that the "true value" lies. The true value is the value that we would get if we had data for the whole population. The observed relative risk is calculated from the particular sample of children taking part in the study and is an estimate of the true risk.

The precision of the study can be gauged by the width of the confidence interval (CI). Larger studies usually have a narrower CI because the larger numbers give a greater degree of certainty. The CI is usually shown in brackets after the relative risk e.g. 2.0 (1.65 - 2.7). Unless otherwise stated, the CIs shown in this paper are the 95% CIs, i.e. there is a 95% chance that the true value lies within the range shown.

Statistical significance
Statistical significance is a measure of how likely it is that the effect is real and not just a chance occurrence in this particular sample. If there were no effect (of exposure) the p-value tells us how likely we would be to see an effect as large as the one we have found purely by chance. A p-value of 0.05 means that the probability of an effect this large having happened by chance is 1 in 20. This is frequently the figure quoted as being statistically significant i.e. unlikely to have happened by chance. The lower the p-value, the less likely it is that the effect happened by chance and so the higher the significance of the finding.

2.4 Epidemiological evidence
Since the first study by Wertheimer and Leeper in 1979 which reported evidence of an association between childhood cancer and electrical wiring, more than 25 further studies have been published.

A number of pooled (meta) analyses have been carried out using data from various of these studies, the most recent of which are Greenland *et al* 2000[41], which included 15 studies, Ahlbom *et al* 2000[42] which included nine of the individual studies and Wartenberg 2001[43], which reviewed seven previous meta-analyses and extended them by adding data from four further, more recent studies.

We include details of just one individual study – by Draper *et al* 2005[44]. This recent study, conducted in England and Wales, is the largest ever study of childhood cancer and power lines. Details of most of the earlier individual studies can be found in the Appendix.

2.4.1 Greenland *et al* 2000.
Greenland *et al*[41] carried out a meta-analysis designed to answer the question: Are magnetic fields or wire codes consistently associated with childhood leukaemia?

The authors identified 24 relevant studies. To be eligible for inclusion, each study had to have obtained quantitative magnetic field measures for individual subjects or enough information to approximate Wertheimer-Leeper wire codes. Nineteen of the studies met these criteria. One study group refused to participate, two were unable to supply data in time and two from the same country were combined into one study for the purposes of the analysis. The investigators therefore had data from 15 studies.

Table 4 shows the numbers of cases and controls in the high exposure category (defined as ≤ 0.3 μT) and the relative risk (reference group <0.1 μT) of leukaemia from each of 12 studies supplying magnetic field exposure estimates for some or all individuals and Figure 5 illustrates these results.

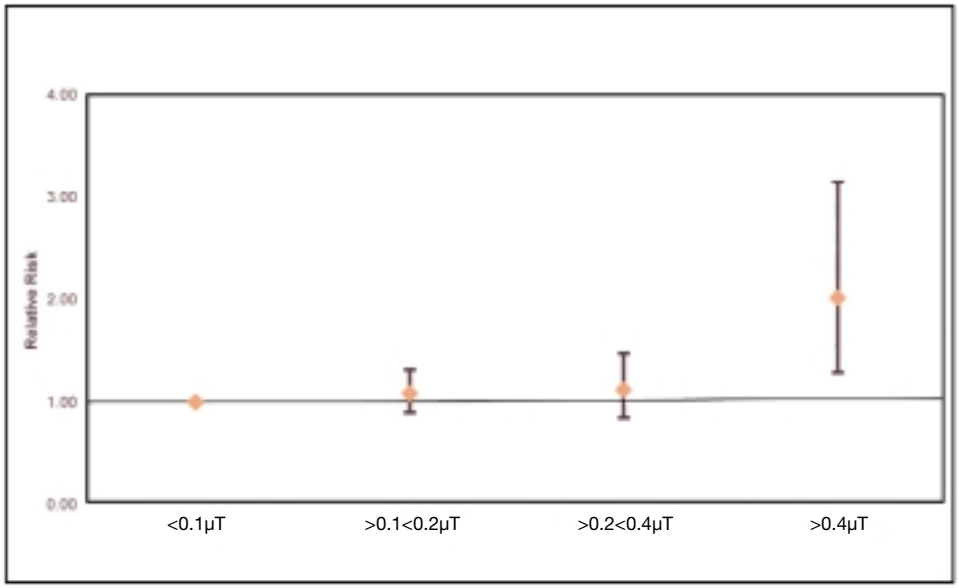
Table 4. From Greenland *et al*, 2000. Numbers of cases and controls in high exposure category (≤0.3 μT) and relative risk for each study.

Study	High exposure cases (≤ 0.3 μT)	High exposure controls (≤ 0.3 μT)	RR (95% CI) Ref group <0.1 μT
Coghill	1	0	-
Dockerty	3	0	-
Feychting	6	22	4.44 (1.67-11.7)
Linet	42	28	1.51 (0.92-2.49)
London	17	10	1.53 (0.67-3.50)
McBride	14	11	1.42 (0.63-3.21)
Michaelis	6	6	2.48 (0.79-7.81)
Olsen	3	3	2.00 (0.40-9.93)
Savitz	3	5	3.87 (0.87-17.3)
Tomenius	3	9	1.41 (0.38-5.29)
Tynes	0	31	-
Verkasalo	1	5	2.00 (0.23-17.7)
Total	**82**	**120**	**1.7 (1.2-2.3)**

Pooling these studies of power line fields and childhood leukaemia the authors reported a summary odds ratio of 1.7 (1.2 – 2.3) for children in the highest magnetic field exposure group of 0.3 μT or more compared with those in the lowest exposure category (0.1 μT or less).

The authors also found a suggestion of a dose response to increasing levels of magnetic field i.e. an increase in the relative risk of childhood leukaemia with increasing exposure level, as illustrated in figure 5 below.

Figure 5. Relative risks at 0.3 μT and their 95% confidence intervals reported in studies with children in the high magnetic field exposure group (from Greenland *et al*, 2000).



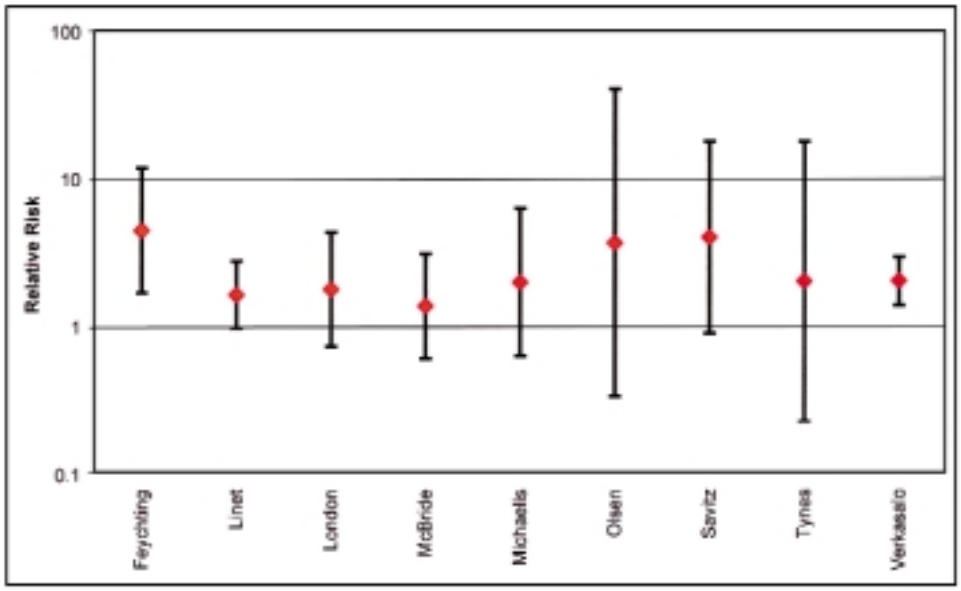


Figure 6. Relative risk against exposure level - results from individual studies which contributed to the pooled analysis (Greenland *et al*, 2000).

In their discussion, Greenland *et al* recognised a number of problems with their study:

• **Confounding factors.** Although the authors raise the possibility that confounders may partly account for the observed effect, they point out that a confounding explanation requires the confounder to have an effect considerably larger than the observed association, as well as a strong association with exposure. These attributes have not been demonstrated for the hypothesised confounders that display positive associations. They recommended that future studies attempt to collect more complete data on possible confounders – especially on traffic density and ambient pollution levels – since their data was incomplete.

• **Bias.** They acknowledge that biases are present in all studies and point out that one of the major problems in assessing bias is that there is no agreed-upon definition of target exposure. They suggest that all of the measures used are likely to suffer considerable error since they are all proxies for the yet-to-be-identified biologically relevant exposure measure.

They were unable to assess the impact of selection bias.

They concluded that it was likely that measurement and validity differences were responsible for some of the variation in study-specific results and acknowledge that this is a flaw in their study – in that they pooled different magnetic field measures without demonstrating that all of the measures were comparable or combinable. Although they observed that the degree of variation in the study-specific results was limited, they point out that other choices could lead to very different degrees of variation. This adds uncertainty to their results.

They conclude that "In light of the above problems, the inconclusiveness of our results seems inescapable; resolution will have to await considerably more data on high electric and magnetic-field exposures, childhood leukaemia and possible bias sources. It also appears to us that, if an effect exists below 0.2 μT, it is probably too small to reach consensus about it via epidemiologic investigation alone. In contrast, both our categorical and trend analyses indicate that there is some association comparing fields above 0.3 μT to lower exposures, although there are as yet insufficient data to provide more than a vague sense of its form and possible sources. We believe that individual-level studies that focus on highly exposed populations would be needed to clarify this association."

2.4.2 Ahlbom *et al* 2000

Ahlbom *et al* 2000[42] conducted a pooled analysis based on individual records from nine studies. Their analysis was designed to answer two main questions:

1. Do the combined results of these studies indicate that there is an association between EMF exposure and childhood leukaemia risk, which is larger than one would expect from random variability?

2. Does adjustment for confounding from socioeconomic class, mobility, level of urbanization, detached/not detached dwelling and level of traffic exhaust change the results?

The nine studies, which included a total of 3,247 children with leukaemia and 10,400 controls, were chosen because they met specified quality criteria as opposed to the Greenland study which included any study whose authors would provide data. Studies with 24/48-hour magnetic field measurements or calculated magnetic fields were included. These studies are described in the following table:

Table 5. From Ahlbom *et al*, 2000. Number of cases and controls in high exposure category from each study and relative risks. Reference level: <0.1 μT.

	Location	High exposure cases (≤ 0.4 μT)	High exposure controls (≤ 0.4 μT)	RR (95% CI)
Measurement studies:				
McBride *et al*, 1999.	Canada	13	10	1.55 (0.65-3.68)
Michaelis *et al*, 1998	Germany	2	2	2.00 (0.26-15.17)
Dockerty *et al*, 1998	New Zealand	0	0	-
UKCCS, 1999	UK	4	8	1.00 (0.30-3.37)
Linet *et al*, 1997	USA	17	5	3.44 (1.24-9.54)
Total		36	25	1.87 (1.10-3.18)
Calculated fields studies:				
Olsen *et al*, 1993	Denmark	2	0	-
Verkasalo *et al*, 1993	Finland	1	7	6.21 (0.68-56.9)
Tynes & Haldorsen, 1997	Norway	0	10	-
Feychting & Ahlbom, 1993	Sweden	5	20	3.74 (1.23-11.37)
Total		8	37	2.13 (0.93-4.88)
All studies:		**44**	**62**	**2.00 (1.27-3.13)**

The authors reported no statistically significant increase in risk of leukaemia for children with exposure levels below 0.4 μT. For children in the ≤ 0.4 μT exposure level, the estimated summary relative risk was 2.0 (1.27-3.13). This was highly statistically significant (p-value = 0.002). Adjustment for potential confounders (including age, gender, socioeconomic status, type of dwelling, mobility and exposure to car exhaust fumes) did not significantly affect the results.

The authors conclude "In summary, the 99.2% of children residing in homes with exposure levels < 0.4 μT had estimates compatible with no increased risk, while the 0.8% of children with exposures ≤ 0.4 μT had a relative risk estimate of approximately 2, which is unlikely to be due to random variability. The explanation for the elevated risk is unknown, but selection bias may have accounted for some of the increase."

The results from the individual studies across the three different exposure levels are shown in figure 7, below:

Figure 7. Relative risk by exposure levels – all studies. From Ahlbom *et al*, 2000.

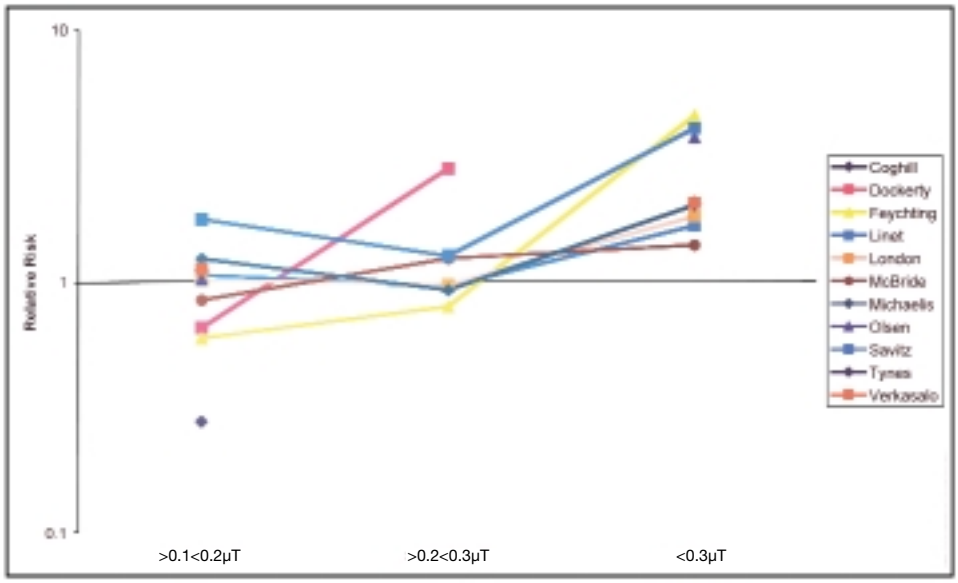


Table 6. From Wartenberg (2001). Meta-analysis and individual study results for studies of calculated and measured magnetic fields and childhood leukaemia.

Study	Exposed cases	Exposed controls	Unexp cases	Unexp controls	Individual OR (95% CI)
Tomenius, 1986	4	10	239	202	0.34 (0.10-1.09)
Myers *et al*, 1990	6	6	174	271	1.56 (0.49-4.91)
Savitz *et al*, 1988	5	16	31	191	1.93 (0.66-5.63)
London *et al*, 1991	20	11	144	133	1.68 (0.78-3.64)
Feychting & Ahlbom, 1993	7	46	31	508	2.49 (1.04-5.98)
Olsen *et al*, 1993	3	4	830	1662	1.50 (0.34-6.73)
Verkasalo *et al*, 1993	3	1.93	-	-	1.55 (0.29-3.81)
Linet *et al*, 1997	83	70	541	545	1.19 (0.85-1.68)
Tynes & Haldorsen, 1997	1	14	147	565	0.27 (0.04-2.10)
Michaelis *et al*, 1997a	9	8	167	406	2.74 (1.04-7.21)
McBride *et al*, 1999	49	42	248	287	1.35 (0.86-2.11)
Dockerty *et al*, 1998	5	2	35	38	2.71 (0.49-14.9)
Green *et al*, 1999	25	44	58	142	1.30 (0.78-2.48)
UKCCS, 1999	21	23	1052	1050	0.96 (0.50-1.66)
Combined	**241**	**298**	**3697**	**6000**	**1.31 (1.09-1.59)**

Table 7. From Wartenberg (2001). Meta-analysis and individual study results for studies of proximity to electrical facilities and childhood leukaemia.

Study	Exposed cases	Exposed controls	Unexp cases	Unexp controls	Individual OR (95% CI)
Wertheimer & Leeper, 1979	52	29	84	107	2.28 (1.34-3.91)
Savitz *et al*, 1988	27	52	70	207	1.54 (0.90-2.63)
London *et al*, 1991	122	92	89	113	1.68 (1.14-2.48)
Linet *et al*, 1997	111	113	291	289	0.98 (0.72-1.33)
McBride *et al*, 1999	122	128	229	234	0.97 (0.72-1.32)
Green *et al*, 1999	12	25	67	100	0.72 (0.34-1.52)
Fulton *et al*, 1980	42	56	131	169	0.95 (0.60-1.50)
Feychting & Ahlbom, 1993	6	34	32	520	2.87 (1.12-7.33)
Tynes & Haldorsen, 1997	9	55	139	524	0.62 (0.30-1.28)
Fajardo-Gutierrez *et al*, 1993	3	2	43	47	1.64 (0.26-10.29)
Coleman *et al*, 1989	3	3	81	138	1.70 (0.34-8.64)
Petridou *et al*, 1993	11	14	106	188	1.39 (0.61-3.18)
Myers *et al*, 1990	7	7	173	270	1.56 (0.54-4.53)
Combined	**527**	**610**	**1535**	**2906**	**1.18 (1.02-1.37)**

2.4.3 Wartenberg 2001

Wartenberg 2001[43] carried out a thorough review of seven previous meta-analyses, including his own 1998 paper, before going on to extend this 1998 paper with the inclusion of four subsequently published studies. His criteria for inclusion were that each study reported an exposure measure for the possible association of childhood leukaemia with residential exposure to magnetic fields and provided data on the exposure measure used. This resulted in the inclusion of 19 studies. These are set out in tables 6 and 7. Table 6 includes those studies which presented data on calculated and measured magnetic fields (14 studies) and table 7 includes those which presented data on proximity to electrical facilities (12 studies).

For the dichotomous exposure classifications (i.e. exposed vs unexposed), the combined relative risk for the calculated and measured magnetic field data was 1.3 (1.1 – 1.6) which is statistically significant. The combined risk for the proximity to electrical facilities data (table 7) was found to be elevated but not statistically significant at 1.2 (1.0 - 1.6). However Wartenberg reported that the difference in design between these proximity studies was such that the combined risk was not likely to be an adequate representation of the studies.

Wartenberg found that in most cases none of the individual studies were disproportionately influential. He says "This is important because many people believe there are no data to support an association between residential magnetic field exposure and childhood leukaemia. To the contrary, the data strongly and relatively consistently support such an association, although the estimated magnitude of the risk is moderate. Limitations due to design, confounding, or other biases may suggest alternative interpretations."

In conclusion he comments "Overall, I see largely positive results with small to moderate effect sizes…. These summaries are unlikely to be changed by additional studies unless those studies are extremely large and produce markedly different results. If one chooses to use these summary estimates for interpretation, given the widespread exposure to magnetic fields they suggest perhaps as much as a 15-25 % increase in the childhood leukaemia rate, which is a large and important public health impact."

2.4.4 Draper *et al* 2005

This study merits inclusion since it is the largest single study of childhood cancer and power lines, with roughly twice the number of children living close to power lines than the next largest study (Feychting and Ahlbom 1993[42]). Draper *et al* 2005[44] set out to determine whether an association exists between distance of home address at birth from high voltage power lines and incidence of leukaemia and other cancers in children in England and Wales. They used the UK Cancer Registry records of 29,081 children with cancer, including 9,700 with leukaemia, and National Grid records to determine the distance from birth address to the nearest high voltage overhead power line. For each case a healthy control was selected from birth registers matching sex, date of birth (to within 6 months) and birth registration district.

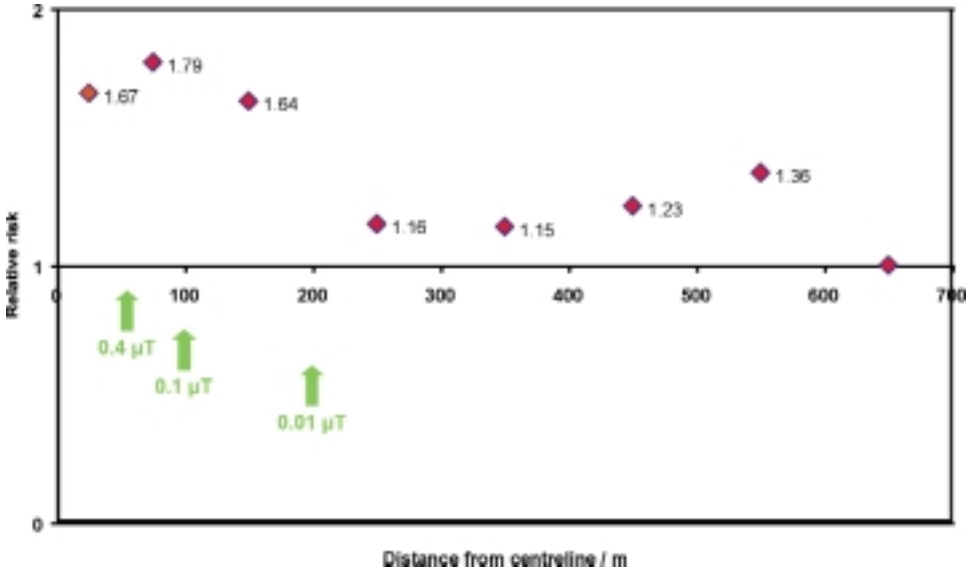
Table 8. From Draper *et al*, 2005. Distance of address at birth from nearest National Grid line for cases and controls and estimated relative risk

Distance to line (metres)	Leukaemia cases	Controls	Relative risk
0-49	5	3	1.67
50-99	19	11	1.79
100-199	40	25	1.64
200-299	44	39	1.16
300-399	61	54	1.15
400-499	78	65	1.23
500-599	75	56	1.36
=600 (ref. group)	9,378	9,447	1.0
Total	9,700	9,700	

Compared with those who lived more than 600 m from a line at birth, children who lived within 200 m had a relative risk of leukaemia of 1.7 (1.1-2.5); those living between 200 and 600 m had a relative risk of 1.2 (1.0-1.5). There was a significant ($P < 0.01$) trend in risk in relation to the reciprocal of distance from the line – i.e. the risk increased as the distance decreased.

Adjustment for socioeconomic status had no effect on the relative risks for distance.

Figure 8. Distance of address at birth from the nearest National Grid line and relative risk of childhood leukaemia. The approximate EMF exposure levels at distances up to 200m are shown.



The authors conclude: "There is an association between childhood leukaemia and proximity of home address at birth to high voltage power lines, and the apparent risk extends to a greater distance than would have been expected from previous studies…. There is no accepted biological mechanism to explain the epidemiological results; indeed, the relation may be due to chance or confounding."

2.5 Epidemiology: conclusions

As evident from the above, there has been a wealth of research in this area since Wertheimer and Leeper first reported a link between childhood cancer and electrical wiring. However the results of individual studies are variable and there remains a lack of consensus as to whether a link actually exists.

The limiting factor in most of the individual studies is the number of cases available for inclusion. Childhood leukaemia is a relatively rare disease (affecting some 500 children per year in the UK) and it is also relatively rare for children to be exposed to high levels of EMF (around 0.4% children in the UK according to the NRPB, 2004). This means that most studies have too few subjects in the highest exposure category to have enough statistical resolving power to detect even a doubling of risk, let alone a smaller effect.

A number of meta-analyses have pooled data from a number of individual studies to increase the statistical power. This paper outlines three of these meta-analyses (Greenland *et al,* 2000[41]; Ahlbom *et al,* 2000[42]; Wartenberg, 2001[43]). All of these studies report a small increase in risk.

Some of the methodological shortcomings of earlier investigations have been addressed and information has been collected on a broad range of possible confounding factors in an attempt to rule out any bias. Interestingly, this hasn't significantly altered the relative risks reported but there is still debate as to whether the results are real or whether the observed relationships may reflect confounding factors or other biases.

As far as exposure metrics are concerned, all studies have been criticised to some extent for using a less than perfect exposure measurement. However, the nature of these problems is such that they would not result in spurious associations between EMF and disease risk – if anything they would mask real associations or lead to underestimations of their magnitude. This also applies to discussions about the 'period of inquiry'. If an effect is still found, despite the fact that we may not be looking at the relevant window of exposure, then presumably the effect found is diluted compared to that which would be found if we knew what was the relevant window of exposure.

Hatch *et al* (2000)[45] published a paper in which they set out to identify the effects of any confounding factors and selection bias which may have been present in their earlier study (Linet *et al*, 1997[46]) into the association between childhood ALL and wire codes. They found that when they included rather than excluded partial participants (i.e. those who failed to complete all phases of the study) and controlled for all identified confounding variables the relative risk was reduced but still elevated (from 1.9 to 1.5).

In his 1965 paper "The Environment and Disease: Association or Causation?" Hill set out a systematic approach for using scientific judgment to infer causation from statistical associations, listing the criteria (set out below) to be considered when judging whether an observed association reflects a causal relationship. Hill's criteria are widely used in the evaluation of modern epidemiological research. It is important to note, however, that whilst each criterion that is met increases our confidence in claiming a causal relationship, failure to meet all criteria does not disprove such a relationship.

- **Temporal relationship** *ie. exposure always precedes the outcome.* This is clearly the case here, if exposure history precedes the disease.
- **Strength.** *The stronger the association, the more likely it is causal.* At higher exposures a doubling of risk has been demonstrated (Greenland reported a RR of 1.7, Ahlbom 2.0, Wartenberg 1.6 and Draper 1.7 in the highest versus lowest exposure categories).
- **Dose-response relationship.** *An increasing amount of exposure increases the risk.* It is important to note that not all causal relationships exhibit a dose-response. Some factors may have a 'switching' effect where exposure over a certain level switches on the damaging effect. Others may have damaging 'windows' of exposure. There is some evidence, however, of a dose response relationship between EMF and childhood leukaemia. Interestingly, the strongest evidence of a linear dose response relationship comes from Draper *et al* (2005) who reported a significant trend in risk in relation to the reciprocal of distance from the line (if this can be considered a 'dose'). Other individual studies and even the meta-analyses are limited by small numbers of cases in the high exposure groups although Greenland found a suggestion of a dose response in his analysis.
- **Consistency.** *The association is consistent when results are replicated in different studies using different methods.* The results of the individual studies vary widely but the lack of statistical power, combined with the use of different exposure metrics, in these studies is bound to lead to wide variance in the results. Combining the data in his 2001 meta-analysis however, Wartenberg concluded that 'the data strongly and relatively consistently support such an association'.
- **Plausibility.** *The association agrees with currently accepted understanding of pathological processes.* This is perhaps where the EMF/childhood leukaemia association has come in for the most criticism since the lack of any established biological mechanism by which EMF could cause childhood leukaemia has been cited by many as a reason for rejecting the association. However it is equally valid to suggest that a demonstrated epidemiological association should force a re-evaluation of accepted belief.
- **Consideration of alternate explanations.** *Have researchers ruled out other possible explanations for the results?* Every effort is made to control for confounding factors and studies have been carried out to assess their possible influence. When controlling for selection bias as well as confounders, Hatch *et al* (2000)[45] reported a decrease in observed risk from 1.9 to 1.5.
- **Experiment.** *The condition can be altered/prevented by an appropriate experimental regimen.* It is not possible to test this in relation to the childhood leukaemia/EMF association.
- **Specificity.** *This is established when a single putative cause produces a specific effect.* Like all environmental exposures thought to increase the risk of cancer, including smoking, EMF do not produce leukaemia in all those who are exposed. This is compatible with existing knowledge which suggests that some individuals are born with a predisposition to develop leukaemia, subject to exposure to 'triggering factors' later in life. EMF may be such a triggering factor.
- **Coherence.** *The association is compatible with existing theory and knowledge.* In this case, the epidemiological association is perhaps ahead of existing theory and knowledge when it comes to the mechanisms of the disease.

3. Biology - Experimental Evidence

How could electric and/or magnetic fields increase the risk of cancer? What could the mechanism be?

Prompted by Wertheimer and Leeper's original observation in 1979, of an increased incidence of leukaemia in children living near certain types of power lines, many hundreds of papers have been published on the biological effects of electric and magnetic fields (EMF). As reviewed earlier in this report, a number of epidemiological studies have indicated an association between exposure to EMF and an increased risk of childhood leukaemia. However, these observations have raised considerable scepticism in the scientific community due to the absence of reproducible and relevant laboratory experimental evidence that EMF exposure is carcinogenic, and the absence of any clear demonstrated biophysical mechanisms through which EMF could affect biological systems.

This part of this report concentrates on the experimental evidence of the effects of EMF in model systems: on cells grown in the laboratory *(in vitro)* and in animal models *(in vivo)*. We review the evidence relating to the three main areas of EMF research: the effects of EMF on the genetic material of the cell – the DNA (3.2); the effect of EMF on the functions of the cell, in particular intracellular calcium regulation and protein production (3.3); the effects of EMF on whole animals (3.4). Many different cell types, animal model systems and experimental methods have been used and the results are overall contradictory and inconclusive. Some laboratories have found clear evidence for EMF effects and other laboratories have failed to reproduce these results and their scientists are critical of techniques used. But, the fact that some effects have been observed is of concern and needs further investigation.

3.1 Effects of the electromagnetic spectrum on biological material

The effect of electromagnetic radiation on biological material depends on the frequency of the source. The electromagnetic spectrum produces waves of energy but can also behave like particles or photons - particularly at high frequencies. The particle nature of electromagnetic energy is important because it is the energy per photon that determines what biological effects electromagnetic energy will have.

At the very high frequencies, photons have sufficient energy to break chemical bonds and are therefore known as ionizing radiation. The well-known biological effects of X-rays and gamma radiation are associated with breaking chemical bonds in molecules. At lower frequencies the energy of a photon is below that needed to break chemical bonds. This part of the electromagnetic spectrum is termed non-ionizing. Because non-ionizing electromagnetic energy cannot break chemical bonds there is no analogy between the biological effects of ionizing and non-ionizing electromagnetic energy.

However non-ionizing electromagnetic fields can produce biological effects. The biological effects of high frequency electromagnetic radiation, including visible and infrared radiation, depend on the photon energy, and involve electronic excitation (adding energy to a molecule) rather than ionization. Radio- and microwave-frequency sources can cause effects by inducing electric currents in tissues, which cause heating. Continuing down the spectrum, EMF have frequencies that interact poorly with the bodies of humans and animals, and are inefficient at inducing electric currents and causing heating.

Electric fields associated with power sources have very little ability to penetrate buildings or even skin. In contrast, magnetic fields associated with power sources are difficult to shield, and easily penetrate buildings and people. Because electric fields do not penetrate the body, it is generally assumed that any direct biological effect from residential exposure to EMF must be due to the magnetic component of the field, or to the electric fields and currents that these magnetic fields induce in the body.

Although the EMF photon energy is too weak to break chemical bonds, there are well-established mechanisms by which EMF could produce biological effects without breaking chemical bonds[48 49 50 51]. EMF can exert forces on charged and uncharged molecules or cellular structures within a tissue. These forces can cause movement of charged particles, orient or deform cellular structures, orient dipolar molecules, or induce voltages across cell membranes. EMF can exert forces on cellular structures; but since biological materials are largely non-magnetic these forces are usually very weak.

3.2 Effect of EMF on DNA

Generally, agents that damage the genetic information within the cell – the DNA - can cause cancer. This section of the report reviews the effects of EMF on DNA. Does EMF cause DNA damage? Can this damage lead to cancer? This is the largest part of the experimental biology section as it is where most investigators have concentrated their efforts. In general, there are many good and reproducible studies that demonstrate no DNA damaging effects of EMF, but there are also those that do show effects.

3.2.1 Genetic and Promoter pathways
As discussed earlier in this report, the initiating event for childhood leukaemia appears to be particular DNA translocations (bits of one chromosome attached incorrectly to another) or hyperdiploidy (multiple copies of genes) in blood cell precursors (haematopoetic stem cells) in the foetus. These cells divide rapidly and frequently and are particularly susceptible to DNA damaging agents and to natural errors. One hundred times more infants are born with these DNA changes than go on to develop childhood leukaemia – so there must other additional biological events to cause clinical leukaemia – the "two hit hypothesis". It is possible that exposure to EMF may play a part in either or both of these events in some children.

There appear to be at least two pathways to the development of cancer and these are not mutually exclusive:

i) A **genetic** pathway where a single or a series of very specific damages to the DNA occurs in a cell. This could be caused by exposure to an environmental agent or as a result of natural error-prone processes. Gamma radiation is a known genotoxic agent. The huge variety and power of the immune system is generated by rearranging genes in immune cells in early infancy and is necessarily an error prone process which often goes wrong. The cells with damaged DNA either die or the DNA is repaired. If the DNA is repaired correctly there are no further problems but any unrepaired or misrepaired damage will lead to changes in chromosomes (deletions or hyperdiploidy), micronuclei (fragmentation of the nucleus), sister chromatid exchanges (translocations), and mutations, some of which may lead to the development of cancer.

ii) A **Promoter** pathway where environmental agents, which may not be genotoxic or carcinogenic by themselves, can contribute to cancer by increasing the genotoxic potential of other agents, interfering with the DNA repair processes, allowing a cell with DNA damage to survive and stimulating the cell division resulting in alteration of the normal functions of the cell[52]. The evidence for the promoting action of an agent, especially for its relevance to human carcinogenicity under real life exposure conditions, must be evaluated carefully since very few environmental agents are known to promote carcinogens[53].

There are more than 150 peer reviewed scientific publications on the effects of EMF on DNA in animal model systems and on cells grown in the laboratory. A detailed review of all of these papers is beyond the scope of this report, which will summarise five, representative, recently published reviews:

McCann *et al* 1993[54] reviewed 55 studies and concluded that "the preponderance of evidence suggests that neither EMF nor static electric or magnetic fields have a clearly demonstrated potential to cause genotoxic effects. However, there may be genotoxic activity from exposure under conditions where phenomena auxiliary to an electric field, such as spark discharges, electrical shocks, or corona can occur."

Murphy *et al* 1993[55] stated that "although most of the available evidence does not suggest that electric and/or magnetic fields cause DNA damage, the existence of some positive findings and limitations in the set of studies carried out suggest a need for additional work."

Moulder 1998[56] summarised that "there are approximately 100 published reports that have looked for evidence that power frequency fields have genotoxic or epigenetic activity. These studies have found no replicated evidence that power frequency fields have the potential to either cause or contribute to cancer."

McCann *et al* 1998[57] added a further 23 studies to their original 55 and concluded that "…the preponderance of evidence suggests that EMF do not have genotoxic potential. Nevertheless, a pool of positive results remains, which have not yet been tested by independent replication."

Vijayalaxmi & Obe 2005[58] say "Among the total of 63 reports published during 1990–2003, the conclusions from 29 investigations (46%) did not identify increased cytogenetic (chromosomal)

Figure 9. Mechanisms of Carcinogenesis.

Carcinogenesis

Genetic or Initiators	Promoters
Agents that cause direct genetic damage usually to DNA that may predispose cells to becoming cancerous	Agents that cause cancer by some other mechanism other than direct DNA damage and by promoting the effects of carcinogens

EMF could act as a Genetic carcinogen or be a Promoter.

damage following EMF exposure per se while those from 14 studies (22%) indicated a genotoxic potential of EMF exposure. The observations in 20 other reports (32%) were inconclusive. Among the 23 combination exposure investigations (i.e. where cells have been exposed to EMF in combination with a known carcinogen), the data from 10 studies did not identify epigenetic effects of EMF, while the data from one study indicated such an effect. The results from 12 other reports were inconclusive." This data is reproduced in table form in this report (tables 9, 10 and 11 overleaf)

Table 9. Effects of EMF on DNA single and double strand breaks and their repair in mammalian cells (from Vijayalaxmi & Obe, 2005).

Study	Cells used	Damage
Whole body exposure: animals		
Lai *et al* 1997a	Rat, whole brain	Increased
Lai *et al* 1997b	Rat, whole brain	Increased
Singh *et al* 1998	Rat, whole brain	Increased
Svedenstal *et al* 1999a	Mice (outdoor) brain cortex	Increased
Svedenstal *et al* 1999b	Mice (laboratory) brain cortex	Increased
McNamee *et al* 2002	Mice, brain cerebellum	Not increased
In vitro: human cells		
Fiorani *et al* 1992	Human tumour cells	Not increased
Ahuja *et al* 1997	Human blood lymphocytes	Increased
Ahuja *et al* 1999	Human blood lymphocytes	Increased
Pacini *et al* 1999	Human neuronal cells	Not increased
Kindzelskii *et al* 2000	Human blood lymphocytes	Increased
Maes *et al* 2000	Human blood lymphocytes	Not increased
Ivancsits *et al* 2002	Human skin fibroblasts	Increased

Vijayalaxmi & Obe[58] continue "Considering the 'weight of scientific evidence' approach for genotoxicity investigations, as adopted by IARC (2002), the preponderance of data thus far available in the literature shows that EMF exposure *per se* is not genotoxic (and little evidence for epigenetic influences) in mammalian cells. However, research must continue to resolve the controversial data published in the literature."

All of these reviews pointed to unconfirmed and/or inconclusive positive reports and suggested additional research.

3.2.2 Vijayalaxmi and Obe, 2005

A detailed review of the literature on EMF and DNA damage is beyond the scope of this report which presents data taken from the 2005 review by Vijayalaxmi & Obe58 as an example or snapshot of the available data.

Vijayalaxmi & Obe present data from experiments in different laboratories in which mammalian cells were exposed *in vivo* and *in vitro* to EMF and the effects on DNA damage measured.

The three tables which follow summarise the evidence for different types of cell damage. The term "increased", "no increased" or "inconclusive (increase and decrease)" for each type of damage indicates a comparison of the data in samples exposed to EMF with those observed in sham exposed and/or unexposed controls. The full references for each study can be found in Vijayalaxmi & Obe[58].

Table 9, summarises the findings of studies looking at single and double strand breaks in the DNA of cells exposed to EMF. The level of DNA strand breaks is important as it can represent the level of damage done to the genetic material of the cell. (It can also represent the level of cell division). Any damage is usually repaired by the cell but mistakes can happen. Genes can be changed and very occasionally the change is sufficient to produce a cancer cell. Some laboratories find an effect of EMF on DNA strand breaks and others do not. Where increases have been found these results have not been repeated in other laboratories.

Table 10, summarises the findings of studies looking at chromosomal aberrations, micronuclei and sister chromatid exchanges (translocations) in cells exposed to EMF. Chromosomal aberrations, micronuclei and sister chromatid exchanges are all indications of serious damage to DNA – usually caused by the normal DNA repair process going wrong. This type of damage is very dangerous and very similar to many of the translocations seen in cells from children with leukaemia. In general, these aberrations are rarely seen after treatment with EMF. One group, Scarfi *et al*, sometimes find changes and at other times do not, indicating the difficulties inherent in replicating these experiments.

Table 10. Effects of EMF on chromosomal aberrations, micronuclei and sister chromatid exchanges in mammalian cells (from Vijayalaxmi & Obe, 2005).

Study	Cells examined	Damage
Whole body exposure: animals		
Zwingberg *et al* 1993	Rat, blood lymphocytes	Not increased
Singh *et al* 1997	Mice, blood erythrocytes	Not increased
Svedenstal *et al* 1998	Mice, blood erythrocytes	Not increased
Whole body exposure: humans		
Ciccone *et al* 1993	Human blood lymphocytes	Not increased
Skyberg *et al* 1993	Human blood lymphocytes	Not increased
Khalil *et al* 1993	Human blood lymphocytes	Inconclusive
Valjus *et al* 1993	Human blood lymphocytes	Inconclusive
Skyberg *et al* 2001	Human blood lymphocytes	Not increased
In vitro: animal and human cells		
Garcia-Sagredo *et al* 1990	Human blood lymphocytes	Not increased
Garcia-Sagredo *et al* 1991	Human blood lymphocytes	Inconclusive
Khalil *et al* 1991	Human blood lymphocytes	Inconclusive
Livingston *et al* 1991	Human blood lymphocytes	Not increased
Livingston *et al* 1991	Chinese hamster ovary cells	Not increased
Nordenson *et al* 1994	Human amniotic cells	Inconclusive
Scarfi *et al* 1994	Human blood lymphocytes	Not increased
Antonopoulos *et al* 1995	Human blood lymphocytes	Not increased
D'Ambrosio *et al* 1995	Human blood lymphocytes	Inconclusive
Galt *et al* 1995	Human amniotic cells	Not increased
Paile *et al* 1995	Human blood lymphocytes	Not increased
Jacobson-Kram *et al* 1997	Chinese hamster ovary cells	Not increased
Scarfi *et al* 1997a	Human blood lymphocytes	Increased
Scarfi *et al* 1997b	Human blood lymphocytes	Increased
Scarfi *et al* 1997c	Human blood lymphocytes	Not increased
Simko *et al* 1998a	Human tumour cells	Inconclusive
Simko *et al* 1998a	Human amniotic cells	Inconclusive
Scarfi *et al* 1999	Human blood lymphocytes	Not increased
Zeni *et al* 2002	Human blood lymphocytes	Increased

Table 11. Genotoxic potential of EMF on mammalian cells exposed in vitro to genotoxic mutations (from Vijayalaxmi & Obe, 2005).

Study	Cells used	Damage
DNA strand breaks and repair		
Animal and human cells		
Frazier *et al* 1990	Human blood lymphocytes	Not increased
Fairbairn *et al* 1994	Human tumour and blood cells	Not increased
Cantoni *et al* 1995	Chinese hamster cells	Not increased
Cantoni *et al* 1996	Chinese hamster cells	Not increased
Miyakoshi *et al* 2000	Human tumour cells	Inconclusive
Zmyslony *et al* 2000	Rat blood lymphocytes	Inconclusive
Chromosomal aberrations, micronuclei and sister chromatid exchanges		
Animal cells		
Okongi *et al* 1996	Chinese hamster lung cells	Not increased
Lagroye *et al* 1997	Rat tracheal epithelial cells	Increased
Yaguchi *et al* 1999	Mouse embryonic skin cells	Inconclusive
Yaguchi *et al* 2000	Mouse embryonic skin cells	Inconclusive
Simko *et al* 2001	Syrian hamster embryo cells	Inconclusive
Nakahara *et al* 2002	Chinese hamster cells	Inconclusive
Human cells		
Scarfi *et al* 1991	Human blood lymphocytes	Not increased
Scarfi *et al* 1993	Human blood lymphocytes	Not increased
Hintenlang *et al* 1993	Human blood lymphocytes	Inconclusive
Tofani *et al* 1995	Human blood lymphocytes	Inconclusive
Simko *et al* 1998b	Human amniotic cells	Inconclusive
Simko *et al* 1999	Human amniotic cells	Inconclusive
Maes *et al* 2000	Human blood lymphocytes	Not increased
Heredia-Rojas *et al* 2001	Human blood lymphocytes	Not increased
Hone *et al* 2003	Human blood lymphocytes	Not increased
Cho *et al* 2003	Human blood lymphocytes	Inconclusive
Verheyen *et al* 2003	Human blood lymphocytes	Inconclusive

Table 11, brings together all the studies on the effects of EMF on animals treated with a known cancer causing agent – looking for an epigenetic or cancer-promoting effect. Most of the studies were inconclusive and no clear effect of EMF could be demonstrated.

And finally, Table 12, overleaf, is a summary of the 63 studies reviewed by Vijayalaxmi & Obe showing that 29 of the studies reported no increased damage as an effect of exposure to EMF, 14 showed clear effects and in 20 studies the results were inconclusive. Out of the 14 studies showing clear effects, 11 reported evidence of increased DNA single and double strand breaks and repair.

3.2.3 The REFLEX project

The REFLEX project[59] ("Risk Evaluation of Potential Environmental Hazards From Low Energy Electromagnetic Field Exposure Using Sensitive *in vitro* Methods") was funded by the European Union under the programme Quality of Life and Management of Living Resources.

The main goal of this project, which ran from 2000 to 2004, was to investigate the effects of EMF on single cells *in vitro* at the molecular level below the present safety levels. The project was designed to assess whether or not any of the disease-causing critical events (gene mutations, deregulated cell division and suppressed or exaggerated programmed cell death [apoptosis]) could be induced in living cells by EMF exposure. The authors' introduction suggested that they set out to provide a definitive answer "Failure to observe the key critical events in living cells in vitro after EMF exposure would suggest that further research efforts in this

Table 12. Summary of studies looking at DNA damage in cells exposed to EMF (from Vijayalaxmi & Obe, 2005).

Test system employed	No increased damage	Increased damage	Inconclusive damage	Total no. of studies
DNA single and double strand breaks and repair				
Whole body: animals	1	5	0	6
In vitro: human cells	3	6	0	9
In vitro: EMF + genotoxic mutations	4	0	2	6
Chromosomal aberrations, micronuclei, and sister chromatid exchanges				
Whole body: animals and humans	6	0	2	8
In vitro: animal and human cells	9	2	6	17
In vitro: EMF + genotoxic mutations animal cells	1	1	4	6
In vitro: EMF + genotoxic mutations human cells	5	0	6	11
Total	**29**	**14**	**20**	**63**
Percentage, %	46	22	32	

field could be suspended and financial resources should be reallocated for the investigation of more important issues."

Twelve laboratories from seven European countries contributed to the study. In order to compare the results of investigations carried out in the different laboratories and to ensure the conclusiveness of the data obtained in the studies, they took steps to ensure that the conditions of exposure were strictly controlled across the participating laboratories.

The data obtained in the course of the REFLEX project showed that EMF had genotoxic effects on primary cell cultures of human skin cells (fibroblasts) and on other cell lines. These results were obtained in two laboratories and confirmed in two additional laboratories outside the REFLEX project, while no such effects could be observed in a further laboratory.

- Exposure to EMF down to 35 μT generated DNA strand breaks in fibroblasts at a significant level. There was a strong positive correlation between both the intensity and duration of exposure to EMF and the increase in single and double strand DNA breaks and micronuclei frequencies. Surprisingly this genotoxic effect was only observed when cells were exposed to intermittent EMF, but not to continuous exposure.
- Responsiveness of fibroblasts to EMF increased with the age of the cell donor and in the presence of specific genetic repair defects.
- The effect differed among the other types of cells examined. In particular, cells of the immune system (lymphocytes) from adult donors were unaffected by EMF.
- Chromosomal aberrations were also observed after EMF exposure of human fibroblasts.
- No clear effects of EMF were found on DNA synthesis, cell cycle, cell differentiation, cell proliferation and apoptosis (described later) but there was some suggestion that EMF may activate several groups of genes that play a role in cell division, cell proliferation and cell differentiation.

The authors reported that "Genotoxic effects and a modified expression of numerous genes and proteins after EMF exposure could be demonstrated with great certainty, while effects on cell proliferation, differentiation and apoptosis were much less conclusive. Since all these observations were made using *in vitro* studies, the results neither preclude nor confirm a health risk due to EMF exposure, but they support such a possibility."

The authors concluded "Taken together, the results of the REFLEX project were exclusively obtained in *in vitro* studies and are, therefore, not suitable for the conclusion that EMF exposure below the presently valid safety limits causes a risk to the health of people. They move, however, such an assumption nearer into the range of the possible. Furthermore, there exists no justification any more to claim that we are not aware of any pathophysiological mechanisms which could be the basis for the development of functional disturbances and any kind of chronic diseases in animal and man".

So far, the only data from the REFLEX project that has been published in peer reviewed journals is the work of one investigator Ivancsits *et al* (2002[60], 2003[61 62], 2005[63 64]) who exposed human cultured fibroblasts to EMF and observed DNA strand breaks with intermittent but not continuous exposure. Crumpton & Collins[65] are critical of the methods used to measure DNA strand breaks as they would also include cells undergoing cell division. From a cell biologist's viewpoint, cultured fibroblasts are unusual cells. No tumour has ever developed from a fibroblast and continuously cultured cells generally have little relevance to cells *in vivo*.

3.2.4 Effects of EMF on DNA: Conclusions

There are many good and reproducible studies that demonstrate no genotoxic effect of EMF, but there are also those that do show effects. This presents difficulties for the scientific community and there is still considerable controversy amongst the scientists working in this area. Discussions range across the relevance of the cells used for the experiments to the methods used to estimate DNA damage to the often very high levels of

magnetic fields used. Effects, quite reproducible in one laboratory, often can't be repeated elsewhere. However, it cannot be ignored that in some laboratories EMF do cause genotoxic damage. Clearly more work needs to be done but perhaps the questions need to be asked in a different way.

The finding reported in the REFLEX study that the genotoxic effect was only observed when cells were exposed to intermittent rather than continuous EMF highlights the importance of metrics, raised in Section 2. More research is needed to establish which are the most damaging aspects of EMF exposure. It does appear that it is not just intensity and duration of exposure which we should be considering.

3.3 Effect of EMF on cell function
This section of the report looks at the effects of EMF at the cellular level. Do EMF interfere with normal cellular functions? Do they change the levels of important cellular proteins or ions and consequently affect cell function and cause cancer cells to develop? As with the effects of EMF on DNA, the experimental data is contradictory and inconclusive. Effects are observed but often other laboratories are unable to reproduce these same effects.

Multi-cellular organisms (like humans) remove unnecessary and damaged cells by intentional or programmed cell death – a process known as **apoptosis.** If this normal biological cleaning-up process is impaired in some way then damaged cells can survive and go on to become cancer cells. Apoptosis, and most other cellular functions, are effected by molecular messages being passed through the cell (known as intracellular signalling pathways). These signalling pathways can be interfered with at numerous points. If the natural process of cell death is prevented then a damaged cell will survive and may go on to become a cancer. There is evidence that EMF exposure has an effect on signalling pathways although this evidence is controversial and the effects have been difficult to reproduce.

3.3.1 Intracellular calcium ion levels
Calcium ions (Ca^{2+}) within the cell play a key role in intracellular signalling and cell death (apoptosis). The calcium levels within a cell ultimately determine the rate of cell division. Any agent that affects the levels of calcium ions within a cell would have profound effects on that cell's function.

Work on the effects of EMF on calcium levels in cells of the immune system (lymphocytes) was reviewed by Walleczek *et al* in 1992[66]. They reviewed work from 9 laboratories on the effects of EMF on Ca^{2+} metabolism and concluded "it is proposed that membrane mediated Ca^{2+} signalling processes are involved in the mediation of field effects on the immune system".

Liburdy *et al* 1992[67] and 1993[68] found raised levels of intracellular calcium after 22mT (= 22,000 µT) magnetic field exposure using stimulated human lymphocytes. Lindstrom *et al* 1993[69] found intracellular calcium changes were induced in a T-cell line (human lymphocytes modified to grow continuously in culture) by a 100 µT magnetic field and later showed a dose response, with no effect below 40 µT and a plateau at 150 µT. But, these results could not be reproduced by Wey *et al* 2000[70]. Galvanovskis *et al* 1999[71] reported that Ca^{2+} changes in human leukaemia T-cells are reduced by 50 Hz magnetic fields.

Attempts to reproduce the effects of EMF on intracellular calcium levels have been unsuccessful by Prasad *et al* 1991[72], Coulton and Barker 1993[73] and Lyle *et al* 1997[74].

Interestingly, Tonini *et al* 2001[75] confirm the effects of 120 µT magnetic fields on calcium levels within cells but also demonstrate a related protective effect on potassium (K) levels. They conclude "The simultaneous onset of both mechanisms prevents alterations in cell differentiation. We propose that cells are normally protected against electromagnetic insult. Pathologies may arise, however, if intracellular Ca regulation or K channel activation malfunctions." These results are an example of the complexities of the systems we are looking at.

In a recent review Santini *et al* 2005[76] present convincing evidence for an effect of magnetic fields on apoptosis. They conclude "Despite some differences, as a whole, the literature seems to demonstrate that magnetic fields induce changes in apoptosis in cells exposed to different experimental protocols." They hypothesise that magnetic fields act directly on Ca^{2+} ions and induce apoptosis.

3.3.2 B cell signalling pathways
B lymphocytes are cells which produce antibodies in response to stimuli from the environment for example bacteria and viruses. The cells need to be stimulated or activated to produce antibodies. This occurs through antibody molecules on the surface of the B cell and works through intracellular signalling. The first part of this signalling pathway within the cell is the addition of a phosphate to some proteins. This is known as phosphorylation and is caused by enzymes called tyrosine kinases. In B cells two of the important tyrosine kinase enzymes are Lyn and Syk and levels of these kinases affect the division and survival of the cell.

Changes to the levels of these critical cellular enzymes can turn an ordinary cell into a cancer cell.

Uckun *et al* 1995[77] reported that exposure of B lymphocytes to 45 mT magnetic fields stimulate up to nine- and three-fold increases in Lyn and Syk kinases respectively, resulting in a marked increase in the phosphorylation of multiple proteins. This means that the cell is in an "active" state and is more likely to divide and more likely to become a cancer cell. The authors conclude that activation of Lyn kinase is sufficient and necessary for EMF-induced cell signalling events in B-lineage lymphoid cells. This study was followed in 1998 by two more publications by the same authors that give further evidence for the roles of EMF-induced effects in B cells[78 79].

These studies report that exposure of B cells to EMF results in a tyrosine kinase-dependent activation. Since kinases play a critical role in the control of cell function, the authors suggested that the evidence in these three papers supports a model by which EMF-induced activation of Lyn kinase could alter the balance of growth regulation in lymphoid cells and could cause cancer cells to develop.

This series of studies by Uckun and colleagues has provided a body of evidence that includes the most provocative effects of EMF on cell function reported to date. The effects are large and consistent between the studies, and the observations being made in B cells suggest a possible link between exposure to EMF and the development of B-lineage ALL. Since these findings may play a key role in contributing to the understanding of the mechanisms underlying biological EMF effects, rigorous replication of the original study on which the latter studies are based is of the utmost importance.

However, Miller and Furniss 1998[80] failed to replicate the EMF-induced activation of B cells reported by Uckun *et al*. Woods *et al* 2000[81] attempted to replicate the original findings of Uckun *et al* and failed. They investigated the effects of exposure to a 100 µT 60 Hz magnetic field on the induction of protein tyrosine phosphorylation and on the activities of Lyn and Syk tyrosine kinases. The details of the experimental protocols used in the study were established with the cooperation of the Uckun laboratory and were followed closely but Woods *et al* did not observe any significant effect of a 100 µT 60 Hz magnetic field on the induction of protein tyrosine phosphorylation or on the activities of Lyn and Syk protein tyrosine kinases in B-lineage lymphoid cells. They conclude "It remains possible that the stimulation of Lyn and Syk kinase activities and protein tyrosine phosphorylation may be induced by certain EMF exposure conditions not investigated in the current study or that any changes induced under the conditions used were too small to be detected by the analytical techniques used. However, this study highlights the necessity for establishing experimental models of biological EMF effects that can be readily reproduced in independent laboratories so that the mechanisms underlying such putative effects can be satisfactorily investigated."

3.3.3 Gross transcription

Many studies have investigated possible effects of EMF on both general and specific cellular protein production (gene expression). Over expression of genes could cause cells to become cancerous. Early studies reported short-term increases in gross protein production (transcription) and are reviewed in the 2001 AGNIR report[82]. More recent and well conducted research using 2 mT 60 Hz magnetic fields found no evidence of a change in the levels of production of a large number of genes[83].

3.3.4 Specific gene expression

A number of studies suggest that magnetic fields of 100 µT or more may affect the levels of specific regulatory genes - three publications from the same group in 1994[84],[85] and 1998[86], Phillips *et al* 1992[87] and Lagroye & Poncy 1998[88]. These studies are, however, difficult to interpret due to the wide range of exposure conditions and cell types used and they have been criticised for methodological flaws. Other studies have shown changes in the proteins cells produce when exposed to high magnetic field levels of: 1.5 mT (Goodman *et al* 1994[85]); 1 mT (Pipkin *et al* 1999[89]); 0.15 mT (Junkersdorf *et al* 2000[90]); and 50 mT (Miyakoshi *et al* 2000[91]).

In contrast many other studies have not reported any changes in specific regulatory gene expression: Parker & Winters 1992[92]; Greene *et al* 1993[93]; Reipert *et al* 1996[94]; Desjobert *et al* 1995[95]; Lacy-Hulbert *et al* 1995[96]; Saffer & Thurston 1995[97]; Miyakoshi *et al* 1996[98]; Dees *et al* 1996[99]; Jahreis *et al* 1998[100]; and Loberg *et al* 1999[101] and 2000[102]

3.3.5 Effects of EMF on Cell Function: Conclusions

As with the effects of EMF on DNA, the experimental data relating to the effects of EMF on cell function is contradictory and inconclusive. Although there are many good and reproducible studies that demonstrate an effect of EMF on intracellular signalling and gene expression, there are also those that show no effects. Once again, this presents difficulties for the scientific community and there is still considerable controversy amongst the scientists working in this area. Effects, quite reproducible in one laboratory, often can't be repeated elsewhere. However, it cannot be

ignored that in some laboratories EMF do have an effect on cell function. Clearly more work needs to be done but perhaps the questions need to be asked in different ways with the emphasis on coordinated efforts to reproduce some of the effects of EMF.

3.4 Effect of EMF on tumour development in animal models

Do EMF cause cancer in animal model systems? Do EMF cause cancer directly or do they make other cancer-causing agents more carcinogenic? Once again, the experimental evidence is contradictory and inconclusive. Some laboratories show quite consistent and reliable cancer-causing and promoting effects of EMF and other laboratories are unable to reproduce these effects.

In general there is a good correlation between agents known to cause cancer in humans and those causing cancer in rodents. For many agents the cancer affects the same organ in humans as it does in at least one of the species tested. 100% of the chemicals that are known to cause leukaemia in humans cause some sort of cancer when tested in rats and mice. In 73% the chemical exposure results in leukaemia or lymphoma in rodents[103]. Consequently, animal experiments are very useful to the understanding of the causes of childhood leukaemia.

3.4.1 Spontaneous tumours and progression

There have been many studies into the effect of EMF on the spontaneous development of cancer in animals and into the possible enhancing effect of EMF on known cancer causing agents. Boorman *et al* 2000[104] conducted a review of the published experimental data of the incidence of leukaemia and lymphoma in rodents exposed to EMF.

Table 13. Tests of magnetic fields in mouse leukaemia models (Boorman *et al*, 2000).

Initiator	Duration of EMF exposure	Number of animals	Author's conclusions	Strengths/ weaknesses
X irradiation	28 months	2660 total	Negative	Good study with very large groups; multiple lymphoma types evaluated.
DMBA	32 weeks	408 total	Negative	Good study, large groups; DMBA model; limited engineering information.
Leukaemic cells	16-31 days	198 total	Negative	Adequate study with small groups; short latency.
None (tumour prone)	3 generations	142 total	Positive 3 generations	Inadequate study with fundamental deficits in controls, pathology and engineering.
None (leukaemia prone)	6 generations	360 total	Negative	Inadequate study with fundamental deficiencies in controls, pathology and engineering.
None (transgenic)	78 weeks	600 total	Negative	Good study with large groups; no histopathology on 'healthy animals', controls different from companion RF study.
ENU (Pim1 transgenic)	23 weeks	420 total	Negative	Good study but groups are small; predictive value of transgenic models not well understood; short study.
None (transgenic)	18 weeks	100 control 101 exposed	Significant increase	Lack of examination of animals at 18 months limits the value for late-occurring lymphomas.
None (cancer prone)	106 weeks	1000 total	Significant decrease	Good study with large groups and multiple exposures.

Table 14. Tests of magnetic fields in rat F344 spontaneous leukaemia models (Boorman *et al*, 2000).

Initiator	Duration of EMF exposure	Number of animals	Author's conclusions
None	106 weeks	1000 total	Negative
None	2 years	250 total	Negative
None	2 years	288 total	Negative
Leukaemia cells	18 weeks	72 total	Negative
Leukaemia cells	28 weeks	144 total	Significant increase

All of these studies with the spontaneous rat F344 leukaemia model were good with adequate group sizes and controls.

Boorman *et al* conclude "The combined animal bioassay results are nearly uniformly negative for magnetic-field exposures enhancing leukaemia and weaken the possible epidemiological association between magnetic-field exposures and leukaemia in humans as suggested by epidemiological data."

The studies included standard long term animal experiments where rodent strains have either been selected because they spontaneously develop leukaemia or lymphoma or have been treated with a tumour initiator or promoter (such as X irradiation, N-ethyl-N-nitrosourea [ENU], 7,12-dimethylbenz[a]anthracene [DMBA] or leukaemic cells). The results of this review are presented in tables 13 and 14 taken from that review where the references to the original data can be found.

3.4.2 Rat mammary carcinomas

Rat mammary carcinomas are a standard laboratory animal model for human breast cancer. Whilst this is a diversion from the main leukaemia thrust of this report, a series of experiments by two groups are worthy of note as they illustrate some of the complexities of the scientific data in this area.

In an extensive series of studies, one group in Europe (Hanover), Löscher, Mevissen and colleagues, have reported that magnetic fields of 100 μT cause an increase in chemically (DMBA) induced rat mammary carcinomas. Also, a significant linear correlation was found between increase in tumour incidence and EMF levels[105 106 107].

These well-performed experiments prompted the United States National Toxicology Program to initiate studies in an attempt to replicate the results using the same model. The studies were conducted by Anderson *et al* 1999 at Battelle (Washington, USA). In contrast to the Hanover data, the Battelle studies found no evidence for a co-carcinogenic or tumour-promoting effect of magnetic field exposure[108 109 110].

The investigators from the two groups discussed differences between their studies that might explain the apparent discrepancies between the results of magnetic exposure[111]. Probably the most important difference was the use of different sub-strains of out-bred Sprague-Dawley (SD) rats; the United States rats were much more susceptible to the carcinogen DMBA but possibly less sensitive to magnetic fields than the European rats used in the Hanover studies. It has been demonstrated previously that there are inherent differences between sub-strains of SD rats obtained in the United States and Europe in their sensitivity to DMBA induced tumours, as well as in their response to radiation[112].

Löscher's group went on to directly compare different sub-strains of SD out-bred rats with respect to; magnetic field effects on cell division in the mammary gland, susceptibility to DMBA-induced mammary cancer, and magnetic field effects on mammary tumour development and growth in the DMBA model. The SD sub-strain (SD1) used in all of Löscher's previous studies and magnetic field sensitive was used for comparison with other sub-strains. They found a sub-strain of SD rats (SD2) insensitive to the effect of magnetic field exposure[113].

3.4.3 Effects of EMF in animal models: Conclusions

The example above from two well respected groups illustrates some of the problems with EMF research. Despite their best efforts the two groups were unable to reproduce each other's results – one showing a clear and reproducible effect of EMF and the other not. The group in Hanover investigated further the possible effect of using different strains of rats and found some sensitive to EMF and others not.

This differential EMF sensitivity of the experimental rats is only one of the many possible differences in experimental procedures between different laboratories which inevitably lead to contradictory results with EMF. But the fact that EMF do have an effect in some laboratories cannot be ignored despite the problems of reproducibility. It is vital that coordinated work is organised to repeat the experiments where an effect of EMF has been found.

4. Biology - Theories

In Section 3 we looked at the scientific evidence for the effects of EMF on biological tissue. In this section we look at some of the theories that have been advanced to explain both the scientific and the epidemiological evidence.

It is suggested that EMF could act:

- By directly increasing the level of free radicals within the body
- By decreasing the level of the hormone melatonin
- By affecting exposure to airborne pollutants

4.1 Free radicals

Of particular interest are the possible effects of EMF on free radicals. A free radical is an atom or group of atoms with at least one unpaired electron. In the body it is usually an oxygen molecule than has lost an electron and will stabilize itself by stealing an electron from a nearby molecule. In animal tissue free radicals are dangerous high-energy particles that ricochet wildly, damage cells and can both cause and accelerate the progression of cancer.

The chemistry group in Oxford lead by Dr Christiane Timmel[114] were the first to show that exposure to EMF can increase the yield of free radicals by more than 60%. Simko & Mattsson 2004[115] review the literature from the premise that EMF do not directly damage DNA, cells or tissues but cause a general increase the levels of free radicals. This is compatible with the diverse and often inconsistent nature of observed effects of EMF, free radicals being intermediates in many natural processes.

They hypothesise "We envisage that EMF exposure can cause both acute and chronic effects that are mediated by increased free radical levels:

i) Direct activation of, for example macrophages (or other cells) by short-term exposure to EMF leads to phagocytosis (or other cell specific responses) and consequently, free radical production. This pathway may be utilized to positively influence certain aspects of the immune response, and could be useful for specific therapeutic applications.
ii) EMF-induced macrophage (cell) activation includes direct stimulation of free radical production.
iii) An increase in the lifetime of free radicals by EMF leads to persistently elevated free radical concentrations. In general, reactions in which radicals are involved become more frequent, increasing the possibility of DNA damage.
iv) Long-term EMF exposure leads to a chronically increased level of free radicals, subsequently causing an inhibition of the effects of the pineal gland hormone melatonin. Taken together, these EMF induced reactions could lead to a higher incidence of DNA damage and therefore, to an increased risk of tumour development."

4.2 The melatonin hypothesis

Melatonin is a hormone produced in the body by the pineal gland. Its production is triggered by a signal from the eye indicating that light is falling below a certain threshold. This means that blood melatonin concentrations are usually low during the day and high during the night. Melatonin receptors in the brain react to the presence of this hormone and synchronise the body to the 24 hour day/night (circadian) rhythm.

The historical pattern of bright days and dark nights maintained this 24 hour pattern of melatonin release in humans. However the development of electric lighting in the built environment has changed this. Typically humans are now exposed to insufficient light during the day and too much light at night.

There has been much research looking at a link between melatonin levels and breast cancer. Cohen *et al* (1978)[116] first suggested that reduced pineal melatonin production, brought about by environmental lighting, might increase human breast cancer risk. This suggestion was followed by Stevens (1987)[117] who proposed that the use of electric power might increase the risk of breast cancer. Stevens proposed that the increased risk arose from reduced production of nocturnal melatonin brought about by exposure to two principal agents: light-at-night (LAN) from domestic as well as street lighting and magnetic fields associated with electricity supply. Strong support for LAN affecting breast cancer risk has come from experiments in animals exposed to constant light (Stephens and Davis, 1996[118]). Additional support for increased risk in humans comes from the observation of reduced hormone-related cancer rates in the blind and partially sighted and the observation of increased breast cancer rates in nightshift workers (Hahn, 1991[119]; Feychting *et al*, 1998[120]; Verkasalo *et al*, 1999[121]; Hansen, 2001a[122],b[123]; Swerdlow, 2003[124]).

In 2005 Henshaw and Reiter published a paper[125] applying the melatonin hypothesis to childhood leukaemia, proposing that exposure to EMF causes increased risk of childhood leukaemia via the disruption of nocturnal production of melatonin in the pineal gland.

Does melatonin protect us against cancer?

Melatonin is thought to act in a number of ways to protect the body from cancer:

- By neutralising damaging free radicals, and therefore protecting cells, tissues and organs against potentially cancer-causing oxidative damage.
- By inhibiting the uptake of growth

factors by cancer cells.
- By increasing the likelihood of cancer cells undergoing apoptosis.
- By inhibiting the growth of blood vessels in tumours.

In animals, manipulation of melatonin levels has been found to affect the development of several different cancer types, including breast cancer, prostate cancer and melanoma. In particular, melatonin injection has been shown to inhibit chemically-induced mammary tumour development in rats by reducing the level of oestrogen receptors (oestrogen is the growth factor for the tumour). Conversely, blocking melatonin production (by removal of the pineal gland) enhances tumour development (Tamarkin *et al,* 1981[126]; Blask *et al,* 1991[127]).

In humans, night-time melatonin levels have been reported to be lower in women with a certain form of breast cancer (ER positive) than in women with ER negative breast cancer or healthy controls[128] and lower in cases of primary breast cancer than in women with benign (non-cancerous) breast disease. However, one study has reported higher daytime melatonin in women with breast cancer.

Although there is, as yet, no firm evidence linking melatonin levels and leukaemia the potential importance of melatonin suppression to leukaemia risk arises from the observation that the hormone is highly protective of oxidative damage to the human haemopoietic system, the blood production system in whose cells leukaemia arises.

Vijayalaxmi *et al* (1996)[129] administered melatonin to four healthy volunteers. Immediately and one and two hours later, blood samples were taken from the volunteers and irradiated. Compared with the blood samples taken immediately, those taken at two hours had significantly decreased (by 50 to 70%) chromosome aberrations and micronuclei, suggesting the melatonin could play a role in the protection of human lymphocytes from genetic damage induced by free radical producing mutagens and carcinogens.

Of direct relevance, to the issue of leukaemia and melatonin suppression, a variety of bone marrow cells have been shown to produce melatonin (Tan *et al,*1999[130]; Conti *et al,* 2000[131]; Carrillo-Vico *et al,* 2004[132]). Whilst the specific function of melatonin in these cells remains unknown, its suppression could have clear implications for leukaemia initiation and/or progression. A reduction in melatonin in the leucocyte precursor cells would be expected to enhance free radical-mediated DNA damage, thereby increasing the likelihood of these cells developing tumours.

Do EMF suppress melatonin production?
The central question is whether exposure to typical neighbourhood power frequency magnetic fields disrupts the nocturnal production of melatonin in the human pineal gland. This has been addressed in both laboratory and observational (population) studies.

A number of studies have been carried out in which volunteers were exposed to laboratory-generated magnetic fields well above those usually encountered by the general population. Most of these failed to produce statistically significant evidence of melatonin suppression.

However there is now a body of studies involving longer term exposures (more relevant to everyday exposure) which show evidence of nocturnal melatonin disruption. In their 2005 paper Henshaw and Reiter reviewed the 12 studies carried out to date. 11 of these show evidence of melatonin disruption by power frequency magnetic fields. In some cases there is evidence of a dose response effect and disruption for exposures to fields below 0.3 - 0.4 μT.

The melatonin hypothesis: Conclusion
Applying the melatonin hypothesis to childhood leukaemia rests on two assertions: i) that melatonin does play a role in protecting against the development of leukaemia and ii) that exposure to EMF suppresses the production of melatonin. There is some good evidence pointing towards the *possibility* of the former and an accumulating body of evidence pointing towards the latter. At this stage, however, the hypothesis remains speculative. In order to clarify the roles of EMF and melatonin in leukaemia clear and reproducible effects must be demonstrated and the underlying cellular mechanisms must be understood. Further research is clearly needed.

4.3 Effect of EMF on airborne particles
It has been suggested that the strong electric fields associated with high voltage power lines may affect exposure to other agents, which may themselves have the potential to exert a biological effect – such as the chemicals found in traffic pollution.

Airborne pollutant particles are known to have a significant effect on health and a number of studies have reported an association between childhood leukaemia and exposure to traffic pollution.

If inhaled, some airborne particles become deposited in the airways of the respiratory system and it has been shown that electrically charged particles are more likely to be deposited in the airways of the lung compared to uncharged particles.

The electric component of the EMF emitted by power lines can cause an increase in the proportion of pollutant particles which are charged and it has been proposed that this could lead to an increase in adverse health effects.

The corona ion hypothesis
The intense electric field on the surface of power line cables can ionise the surrounding air, producing *corona*

ions. In the air, these ions attach themselves to tiny particles of air pollution, thereby increasing the electrical charge on these particles. These charged particles are then carried away from the power line by the wind.

i) Emission of corona ions and charging of particles
Fews and colleagues in Bristol have observed that most power lines emit corona ions at some level (unpublished); that corona ion emission from power lines is variable but significant effects can be observed on average up to 400m downwind from power lines – and on one occasion effects were observed 7 km downwind (Fews *et al*, 1999a[133]); that the effect is modified by characteristics of the line (with ageing of the cable and the build up of dirt on its surface related to elevated emission) and possibly by the local weather conditions – more corona is emitted in damp and wet conditions (Fews *et al*, 1999b[134]).

A further paper by Fews *et al* (2002)[135] reported that between 10% and 60% of outdoor airborne particles gain excess charge by the attachment of corona ions. Downwind of one power line which was particularly prone to excessive corona discharge, the density of corona ion emission was such that 100% of airborne particles might gain excess charge.

ii) Inhalation of charged particles
The charge on a particle causes it to be attracted to a conducting surface as if there were an equal and opposite charge at an equal distance below the surface (like an image of an object in a mirror). When inhaled, charged particles are more likely than uncharged particles to be trapped in the lung.

Airborne particles can vary in size from a few nano-metres (nm) to tens of thousands of nano-metres. Current research suggests that very small particles (in the size range from a few tens to a few hundred nano-metres) are particularly hazardous because of their ability to penetrate deeply into the lung and pass into the bloodstream (e.g. Seaton *et al*, 1995[136]). This is the size range associated with vehicle exhaust pollutants containing potentially carcinogenic compounds known as hydrocarbons.

It is also the size range where electrical charging can significantly increase lung deposition on inhalation. Using a model airway, Cohen *et al* (1998)[137] demonstrated that deposition of small particles (20 and 125 nm) carrying a single charge was two to three times greater than for similar particles in normal air which are mainly uncharged.

Experiments with human volunteers, carried out in the context of the use of inhalers for treating breathing difficulties, have demonstrated increased lung deposition of particles with excess charge. These experiments have tended to use relatively large particles, for example around 10,000 nm (e.g. Melandri *et al*, 1977[138]; Melandri *et al*, 1983[139]; Hashish & Bailey, 1987[140]; Hashish & Bailey, 1991[141]). Further research is desirable, in particular to extend these findings to the smaller size range used by Cohen *et al*.

Conclusions: corona ion hypothesis
The basic physics of the corona ion hypothesis are not disputed but there remains much dispute over the size and significance of suggested effects, specifically the levels of particle charge that result and the extent to which charged particles are more likely to deposit in the respiratory tract.

An *ad hoc* group of the National Radiological Protection Board (NRPB, now part of the Health Protection Agency, HPA) was set up 'to provide the Advisory Group on Non-ionising Radiation with advice on the possible effects of corona ions or electric fields on intakes of radioactive particles or other airborne pollutants and to advise on the need for further work'. Their report, published in 2004[142], concludes: "The information reviewed suggests that some increase in lung deposition of pollutant particles seems likely as a result of charging by corona ions. Even if the effect of the corona ions were to cause all the particles to be deposited, the increase in lung deposition cannot be more than a factor of ten. In practice, though, the increase seems likely to be appreciably less and it is noted that Henshaw and Fews (2001) estimated it to be 20%-60%. Such estimates are, however, inherently imprecise since they depend on the use of an approximate model and on assumptions about the experimental conditions (the distributions of particle size and charge) which are not well known and not readily obtainable."

On the other hand, Henshaw (2002)[143] carried out a specific risk assessment of the annual number of excess cases of childhood leukaemia expected near high voltage power lines in the UK as a result of corona ion effects. The estimate was that two to six cases annually could arise in this way.

The recent report by Draper *et al* (see section 2.4.4) found increased incidence of leukaemia in children born within 600 m of National Grid 400 and 275 kV power lines. This finding cannot be explained by the direct effect of electric or magnetic fields which extends to around 200 m only. However the observation is supportive of the corona ion hypothesis, although the study alone does not prove the hypothesis. One important test, included in the Draper study and some other epidemiological studies is to include upwind or downwind status as a variable in order to assess the possible effects of corona ions, but these studies have been fraught with difficulties and have not, to date, produced any conclusive results.

5. Main conclusions and recommendations for further research

5.1 Is the association real?
As outlined in section 2, there is now a large body of evidence indicating an association between exposure to EMF and up to a doubling of risk of childhood leukaemia. Three major pooled analyses have all found an association and the largest and most recent study has also found an association.

Whilst we cannot rule out the possibility that the association is due to bias or confounding, it seems unlikely. The more recent studies in particular have made great efforts to eliminate both. The more recent studies which have gone to great lengths to control for possible confounding factors haven't reported lower risks than the earlier studies. As demonstrated by Hatch (2000)[45], selection bias may partly but not entirely account for the observed effect.

Studies of the childhood leukaemia/EMF association have also come under fire for the types of measurements used to assess exposure. The authors of the IARC review in 2001[144] draw attention to the misclassification to which all studies are subject, despite the dramatic improvements in the exposure assessment over time. However they point out that non-differential misclassification of exposure (similar degrees of misclassification in cases and controls) is likely to result in bias towards the null, meaning that the actual association between childhood leukaemia and EMF may be higher than the studies suggest.

Association versus causation
Even if we accept that the association between exposure to EMF and increased risk of childhood leukaemia is real, the leap from association to causation is a very large one indeed.

The scepticism surrounding the EMF/childhood leukaemia association has been largely a result of the failure to demonstrate a biological mechanism for such an association. Despite a growing body of evidence for an effect of EMF in biological systems there remains a lack of consistency. But, this is a problematic area of research. To single out a few examples: The positive results from the REFLEX[59] project on the effects on EMF on fibroblasts *in vitro* need confirmation in other laboratories and more relevant cell types and perhaps using more modern techniques. Further attempts must be made to repeat Uckun's[77] robust demonstration of effects of EMF on B cell activation. The development of two strains of rat with different sensitivities to EMF from Löscher's[106] group offer interesting opportunities to investigate the mechanism by which EMF act.

The use of animal models in studying animal exposure is limited by two major problems: i) the extrapolation of experimental findings from the animals under study to humans; ii) the extrapolation of laboratory experimental patterns to environmental exposure patterns. Laboratory exposure is generally much higher and has much greater uniformity in frequency and intensity than environmental exposure. And the actual agents responsible for the EMF 'dose' are not clear.

EMF exposure is complex, composed of not only pure 50 Hz electric and magnetic fields but also possibly transients (intermittent spikes and changes in the frequency of the field) and harmonies (multiples of the pure 50 Hz exposure: 100, 150, 200 Hz etc). This means that careful control is required to ensure that the exposure being tested is known.

Some interesting and increasingly plausible theories were introduced in section 4 and more research is needed to test these theories further and determine whether these really could be the mechanisms through which the biological effects of EMF are mediated. It is reasonably well-established that EMF exposure causes an increase in the level of free radicals and more work is required to develop this further and establish whether this could lead to an increased risk of childhood leukaemia.

There is a growing body of evidence relating to the role of melatonin. The melatonin hypothesis certainly appears plausible and also ties in with the free radical theory as melatonin scavenges free radicals so the two theories lend support to each other. But in order to clarify the roles of EMF and melatonin in leukaemia, clear and reproducible effects must be demonstrated and the underlying cellular mechanisms must be understood. Further research is clearly needed.

The corona ion theory is one area where the mechanistic research is ahead of the epidemiology. The epidemiological studies which have specifically sought to put the corona ion theory to the test have been fraught with difficulties and have proved inconclusive. There is no question, however, that it is a plausible mechanism and it could explain the far-reaching effect (out to 600 m from power lines) found in the Draper study.

5.2 Recommendations for future work

5.2.1 Epidemiology

There is already a wealth of data supporting the EMF/childhood leukaemia association. To add value, future studies must be very carefully designed to test very specific hypotheses. The authors of the ICNIRP report suggest "Further studies need to be designed to test specific hypotheses such as aspects of selection bias or exposure. To be of value, however, future studies must be of high methodological quality, of sufficient size and with sufficient numbers of highly exposed subjects, and must include appropriate exposure groups and sophisticated exposure assessment. Especially for childhood leukaemia, little is to be gained from further repetition of investigation of risks at moderate and low exposure levels, unless such studies can be designed to test specific hypotheses, such as selection bias or aspects of exposure not previously captured."

The authors of the NRPB (2001) report suggest further work to investigate the extent to which the methods of control selection that have been used could have affected the frequency with which relatively high exposures were recorded. They consider that there is nothing further to gain from further study of more cases of childhood leukaemia in relation to exposure to EMF in UK as the numbers are too small to provide useful information but that there is potential for studies in other EU countries where high exposures more common eg. Denmark and Sweden. Other countries with high exposures should also be identified.

The NRPB authors also suggest that if EMF do not produce a risk directly it is possible that they might do so in association with some specific alteration in DNA and that it might be useful to compare characteristics of DNA in ALL that occurred after exposure to EMF with those in children not exposed to EMF. This would only be worthwhile with international collaboration due to the small number of cases.

We suggest the following areas of investigation as being important:

- Exposure metrics have been identified as being of crucial importance throughout this report. Investigators need to be very clear about the exposure that is being measured and must take into account all characteristics of the EMF. Such a detailed approach and the measurements which it would entail would be very time consuming and expensive.
- The 2005 Draper Report found an elevated risk for children living within 600 m of high voltage power lines (275,000 V and above). It would be interesting to extend the study to include lower voltage lines and also underground cables and substations.
- We need to know more about the critical period of exposure. We could learn something by considering residence at birth and residence at diagnosis to see if there is a differential effect.
- We need to know more about possible confounding factors. There could be much to be gained from a study looking at other population characteristics of those who live in proximity to power lines or other sources of high EMF to identify any potential confounding factors.
- Many of the individual studies – and indeed the pooled analyses - have been limited by the small numbers of cases (and controls) in the high exposure categories. As suggested by the NRPB report, populations with high exposures should be identified and studied to provide more robust data.
- There is evidence of a gene-environment interaction in childhood leukaemia. Sub-groups of the population may be more vulnerable to the effects of EMF – as also referenced by the NRPB above. It may be possible to design studies to explore this hypothesis.
- There are many different sub-types of childhood leukaemia, with different genetic characteristics. It is likely that the different sub-types may have different causes. An analysis of EMF epidemiology data with reference to the sub-types of cases may yield some interesting data, although such studies may well be limited by lack of statistical power.

5.2.2 Biology

For the sceptical scientists to be convinced that there is an effect of EMF on biological systems there needs to be some evidence for a mechanism of action. And, the experimental results must be reproducible both within and between laboratories. Very few of the published experiments have been repeated in other laboratories - and indeed when they have been the results have rarely been reproduced. Part of the reason for this is that different types of cells and different strains of animals have been used as well as different EMF exposures. There needs to be a co-ordinated

effort to perform and reproduce key experiments. More research needs to be done between different laboratories under strictly controlled conditions, for example with genetically identical (inbred) and genetically modified (transgenic) rodent models, to determine the effects of EMF.

Exposure metrics are of key importance in the experimental studies since – in contrast to epidemiological studies where the effect may simply be diluted - use of the wrong type of exposure will fail to produce an effect.

In the area of cell function, Uckun *et al* 1995[77],[78],[79] (described in 3.3.2) demonstrated that exposure of B cells to EMF results in a tyrosine kinase-dependent activation. The effects they found are large and consistent between the studies, and the observations made in B cells suggest a plausible link between exposure to EMF and the development of B-lineage ALL. Since these findings may play a key role in contributing to the understanding of the mechanisms underlying biological EMF effects, rigorous replication of the studies are of the utmost importance. So far, Miller and Furniss 1998[80] and Woods *et al* 2000[81] have failed to replicate the EMF-induced activation of B cells reported by Uckun *et al*. This highlights the necessity for establishing experimental models of biological EMF effects that can be readily reproduced in independent laboratories so that the mechanisms underlying such putative effects can be satisfactorily investigated.

In animal models of cancer induction, Löscher, Mevissen and colleagues (described in 3.4.2) found that EMF cause an increase in chemically induced rat mammary carcinomas. Also, a significant linear correlation was found between increase in tumour incidence and EMF levels[105],[106],[107]. Anderson *et al* 1999 failed to reproduce these results and found no evidence for a co-carcinogenic or tumour-promoting effect of EMF[108],[109],[110]. The most likely difference between the two groups was the use of different sub-strains of rats. Löscher's group went on to directly compare different sub-strains of rats with respect to the effects of EMF and they now have two sub-strains: the SD1 sub-strain which is sensitive to EMF; and the SD2 which is insensitive[113]. Not only are the two sub-strains excellent experimental controls for each other but they could form the basis of studies investigating a genetic susceptibility to EMF. Determining the difference between these two sub-strains could provide a link to a biological mechanism for EMF effects.

A new approach to investigating DNA-damaging effects of EMF, and directly relevant to childhood leukaemia, would be to use the cells from which the immune system develops (haematopoietic stem cells) – easily obtained from the umbilical cord at birth. An example for an experimental approach derives from another area of research. Some (1-15%) cancer patients treated with anti-cancer agents that inhibit one of the enzymes involved in DNA replication (topoisomerase inhibitors) go on to develop a fatal therapy-related leukaemia . This is almost always associated with a mutation of the *MLL* gene which is also found in the majority of cases of infant leukaemia (Greaves & Wiemels 2003[19]). It has been suggested that maternal exposure to bioflavonoids (contained in such things as tea, coffee, apples and soya beans) may be causative agents for infant leukaemia[17,18]. These dietary bioflavonoids are known to be topoisomerase inhibitors. In in vitro experiments, haematopoietic stem cells exposed to dietary bioflavonoids were found to have significantly increased levels of MLL rearrangements[146]. It would be interesting to use this model system to test the effects of EMF.

5.2.3 Theories

Many of the aspects of the melatonin hypothesis can be investigated either epidemiologically or in experimental laboratory studies. There is scope for further human studies of melatonin disruption in populations exposed to both electric and magnetic fields, particularly in children. It would also be useful to probe in more detail the role of melatonin in the foetus and neonate.

Following the work of Vijayalaxmi *et al* and Ishido *et al* previously reviewed[58], cells of the human haemopoietic system could be exposed to melatonin and magnetic fields to test directly the effect of magnetic fields on the protective effects of melatonin.

5.3 And Finally

On behalf of CHILDREN with LEUKAEMIA, thank you for reading this report. We hope you have found it interesting and informative.

Dr Adrienne Morgan and Katie Martin BSc. December 2005

6. Appendix

Results of the epidemiological studies into the association between childhood leukaemia and EMF.

Taken from California EMF Risk Evaluation, June 2002

Study	Exposure classification	Leukaemia cases	RR (95% CI)	Acute Lymphoblastic Leukaemia cases	RR (95% CI)
***WIRE CODES**					
Wertheimer & Leeper, 1979[39]	Birth address:				
	LCC	84	Reference		
	HCC	52	2.28 (1.34-3.91)		
	Death address:				
	LCC	92	Reference		
	HCC	63	2.98 (1.78-4.98)		
Savitz *et al*, 1988[147]	HCC/LCC	27/70	1.54 (0.90-2.63)	<19/59	1.28 (0.70-2.34)
	VHCC/Buried	7/28	2.75 (0.94-8.04)	6/24	2.75 (0.90-8.44)
London *et al*, 1991[148]	UG+VL	31	References		
	OLCC	58	0.95 (0.53-1.69)		
	OHCC	80	1.44 (0.81-2.56)		
	VHCC	42	2.15 (1.08-4.26)		
Linet *et al*, 1997[149]	UG+VLCC			175	References
	OLCC			116	1.07 (0.74-1.54)
	OHCC			87	0.99 (0.67-1.48)
	VHCC			24	0.88 (0.48-1.63)
McBride *et al*, 1999[150]	VHCC+OHCC	351	0.97 (0.72-1.32)		
*LCC = low current configuration; HCC = high current configuration; VHCC = very high current configuration; UG = under ground; VL = very low; OLCC = ordinary low current configuration; OHCC = ordinary high current configuration					
CALCULATED FIELDS (shown in µT)					
Feychting & Ahlbom, 1993[151]	Unmatched analyses				
	<0.1	27	References		
	0.1-0.19	4	2.1 (0.6-6.1)		
	≥ 0.2	7	2.7 (1.0-6.3)		
	0.1-0.29	4	1.5 (0.4-4.2)		
	≥ 0.3	7	3.8 (1.4-9.3)		
	Matched analyses	4 (33 controls)	4.3 (1.0-8.9)		
	0.1-0.19	7 (46 controls)	3.5 (0.9-13.6)		
	≥ 0.2				
Olsen *et al*, 1993[152]	<0.1	829	References		
	0.1-0.24	1	0.5 (0.1-4.3)		
	≥ 0.25	3	1.5 (0.3-6.7)		
	≥ 0.40	3	6.0 (0.8-44)		
Verkasalo *et al*, 1993[153]	Cumulative exposure (µT/years)				
	0.01-0.39	32	0.90 (0.62-1.3)		
	≥ 0.40	3	1.2 (0.26-3.6)		
	≥ 1.0	3	3.5 (0.7-10)		
Verkasalo *et al*, 1994[154]	Average exposure				
	0.01-0.19	32	0.89 (0.61-1.3)		
	≥ 0.2	3	1.6 (0.32-4.5)		
Tynes & Haldorsen, 1997[155]	Average exposure				
	<0.05	139	References		
	0.05-0.13	8	1.8 (0.7-4.2)		
	≥ 0.14	1	0.3 (0.0-2.1)		
	Closest to diagnosis				
	<0.05	134	References		
	0.05-0.13	10	1.5 (0.7-3.3)		
	≥ 0.14	4	0.8 (0.3-2.4)		
	≥ 0.2	2	0.5 (0.1-2.2)		
PROXIMITY TO SOURCES					
Coleman *et al*, 1989[156]	≥ 25m substation	81	Reference		
	<25m substation	3	1.7 (0.31-8.64)		
Myers *et al*, 1990[157]	≥ 25m	173	Reference		
	<25m	7	1.56 (0.54-4.53)		
Fajardo, 1993[158]	≥ 20m distribution	43	Reference		
	<20m distribution	3	1.64 (0.26-10.29)		
Petridou, 1997[159]	Categories 1-3	106	Reference		
	Categories 4&5	11	1.39 (0.61-3.18)		

Taken from California EMF Risk Evaluation, June 2002 Continued

Study	Exposure classification	Leukaemia cases	RR (95% CI)	Acute Lymphoblastic Leukaemia cases	RR (95% CI)
HOME OR PERSONAL MEASUREMENTS (μT)					
Tomenius, 1986[160]	<0.3	239	Reference		
	≥ 0.3	4	0.34 (0.10-1.09)		
Myers *et al*, 1990[157]	<0.03 peak	174	Reference		
	≥ 0.03 peak	6	1.56 (0.49-4.91)		
Savitz *et al*, 1988[147]	Low power conditions				
	<0.2	31	Reference	23	Reference
	≥ 0.2	5	1.93 (0.67-5.56)	3	1.56 (0.42-5.75)
	High power conditions				
	<0.2	30	Reference	23	Reference
	≥ 0.2	7	1.41 (0.57-3.50)	4	1.05 (0.34-3.26)
	Electric fields (V/m)				
	<12	31	Reference	23	Reference
	≥ 12	6	0.75 (0.29-1.91)	4	0.67 (0.22-2.04)
London, 1991[148]	Low power conditions				
	<0.032	67	Reference		
	0.032-0.067	34	1.01 (0.61-1.69)		
	0.068-0.124	23	1.37 ((0.65-2.91)		
	≥ 0.125	16	1.22 (0.52-2.82)		
Michaelis, 1997a[161]	Short-term measurement				
	<0.2	170	Reference		
	≥ 0.2	6	0.7 (0.3-1.8)		
London, 1991[148]	24-hour measurements				
	<0.067	85	Reference		
	0.068-0.118	35	0.68 (0.39-1.17)		
	0.119-0.267	24	0.89 (0.46-1.71)		
	≥ 0.268	20	1.48 (0.66-3.29)		
Michaelis *et al*, 1997a[161]	Median of measurements				
	<0.2	125	Reference		
	≥ 0.2	4	3.2 (0.7-14.9)		
	Mean of measurements				
	<0.2	125	Reference		
	≥ 0.2	4	1.5 (0.4-5.5)		
	Median during the night				
	<0.2	125	Reference		
	≥ 0.2	4	3.9 (0.9-16.9)		
Michaelis *et al*, 1997b[162]	Median of measurements				
	<0.2	167	Reference		
	≥ 0.2	9	2.3 (0.8-6.7)		
	Median during the night				
	<0.2	167	Reference		
	≥ 0.2	9	3.8 (1.2-11.9)		
Linet *et al*, 1997[149]	Unmatched analysis				
	<0.065			267	Reference
	0.065-0.099			123	1.1 (0.81-1.50)
	0.1-0.199			151	1.1 (0.83-1.48)
	0.2-0.299			38	0.92 (0.57-1.48)
	0.3-0.399			22	1.39 (0.72-2.72)
	0.4-0.499			14	3.28 (1.15-9.39)
	≥ 0.5			9	1.41 (0.49-4.09)
	≥ 0.2			83	1.24 (0.86-1.79)
	≥ 0.3			45	1.7 (1.0-2.9)
	Matched analysis				
	<0.065			206	Reference
	0.065-0.099			92	0.96 (0.65-1.40)
	0.1-0.199			107	1.15 (0.79-1.65)
	0.2-0.299			29	1.31 (0.68-2.51)
	0.3-0.399			14	1.46 (0.61-3.50)
	0.4-0.499			10	6.41 (1.30-31.73)
	≥ 0.5			5	1.01 (0.26-3.99)
	≥ 0.2			58	1.53 (0.91-2.56)
UKCCS, 1999[163]	>2 mG	1,073	0.9 (0.49-1.63)	906	0.92 (0.47-1.79)
Green *et al*, 1999a[164]	>1.5 mG (average indoor)	201	1.74 (0.63 -4.82)	75	2.86 (0.88-9.29)
Green *et al*, 1999b[165]	>1.4 mG (personal exposure)	88	4.5 (1.3-1.9)	76	3.5 (0.9-13.9)
McBride *et al*, 1999	>2 mG	297	1.35 (0.86-2.11)		

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Facilities and projects around the UK

1 Paul O'Gorman Leukaemia Research Centre, University of Glasgow (due to open in 2006).

2 Minimal residual disease study, Royal Hospital for Sick Children, Glasgow.

3 Young Oncology Unit, Christie Hospital, Manchester.

4 Paul O'Gorman Blood Laboratory, Wolfson Molecular Imaging Centre, University of Manchester.

5 Paul O'Gorman Molecular Diagnostic Laboratory, The Paterson Institute, Christie Hospital, Manchester (due to open in 2006).

6 DNA sequencer, Cancer Immunogenetics Laboratory, University of Manchester.

7 Dr Ketal Patel, MRC Laboratory of Molecular Biology. Identification and characterisation of novel genes that function in the Fanconi anaemia tumour suppressor pathway.

8 Alasdair Philips. An exploration of the possible causes of childhood leukaemia and other cancers.

9 Paul O'Gorman Laboratory, Coghill Research Laboratories.

10 Professor Nick Priest, University of Middlesex. Environmental radioactivity as a cause of leukaemia in a high radiation area within central Asia: feasibility study.

11 Paul O'Gorman Building, Bristol Royal Hospital for Children.

12 Professor Denis Henshaw, Human Radiation Effects Group, University of Bristol. Programme funding – studies into environmental risk factors for childhood leukaemia.

13 Minimal residual disease study, University of Bristol/ Bristol Royal Hospital for Children.

14 Dr Craig Donaldson, University of the West of England. A study of human NKT cells in stem cell transplant recipients.

15 Professor Alan Preece, Bristol Haematology and Oncology Centre. Programme funding – studies of the association between childhood leukaemia and proximity to power lines.

16 CHASE Hospice. To support the provision of services for children with leukaemia.

17 Sussex Snowdrop Trust. To support the provision of services for children with leukaemia.

18 Paul O'Gorman Respite Centre, Angmering on Sea.

19 Professor Eric Wright, University of Dundee Medical School. Investigations of microenvironmentally-mediated damage as a promotional factor in childhood leukaemia.

20 Northern Institute of Cancer Research, Paul O'Gorman Building, University of Newcastle.

21 Dr Tevfik Dorak, University of Newcastle. Genes influencing body iron content and childhood leukaemia risk.

22 Dr Richard Feltbower, University of Leeds. Does population mixing measure infectious exposure at the community level?

23 Minimal residual disease study, Sheffield Children's Hospital.

24 Paul O'Gorman Patient Hotel, Great Ormond Street Hospital for Children.

25 Paul O'Gorman Leukaemia Research Centre, Institute of Child Health.

26 Institute of Cancer Sciences, Paul O'Gorman Building, University College London (due to open in 2006).

27 Expansion of Haematology and Oncology Services, Great Ormond Street Hospital.

28 Paul O'Gorman House. Parental accommodation facility at the Royal Free Hospital.

29 Laboratory of Cellular Therapeutics, Paul O'Gorman Childhood Leukaemia Centre, Royal Free Hospital.

30 Dr Hugh Brady. Paul O'Gorman Leukaemia Research Centre, Institute of Child Health. The role of MLL in the molecular pathogenesis of infant and childhood leukaemia.

31 Dr Paul Veys & Dr Persis Amrolia. Great Ormond Street Hospital. Anti CD34 immunotoxin study.

32 Minimal residual disease study, Hammersmith Hospital.

How we began

Paul's and Jean's first school photographs

In February 1987, leukaemia killed 14 year old Paul O'Gorman. Just nine months later, further tragedy struck the O'Gorman family when Paul's sister Jean was also killed by cancer.

Shortly before his death, Paul had made his parents promise to help other children with leukaemia. Within a few weeks the family was running a campaign to raise funds for research into the disease. In November 1987, just days after Jean's death, Paul's parents met the Princess of Wales. Deeply moved by their double tragedy she personally helped start this charity.

From its roots as a small memorial charity, CHILDREN with LEUKAEMIA has grown to become the UK's leading charity dedicated to the conquest of childhood leukaemia. Our first task as a new charity back in 1988 was to raise £2 million for a new leukaemia research centre at Great Ormond Street Hospital for Children. It took seven years before this target was reached but, such has been the growth in support for the life-saving work of the charity, we are now able to apply more than £8 million every year to the fight against childhood leukaemia.

The Paul O'Gorman Centre at Great Ormond Street, together with other Centres named after Paul in Bristol, London, Manchester and Newcastle, are all at the forefront of advances in research and treatment of childhood leukaemia. Three new Centres will soon be opening – at the Institute of Cancer Sciences in London, the University of Glasgow and the Paterson Institute in Manchester.

Teams of scientists funded by CHILDREN with LEUKAEMIA are working towards the development of more effective, less punishing treatments which will ultimately help more children to survive leukaemia. And in 2004 we launched a new grants round dedicated to research into the causes of this dreadful disease. From this we awarded 12 grants, totalling £1 million, to leading researchers around the world for projects which will help us to understand why children develop this devastating disease. A further round of grants for research into causes will be made in 2006.

We also fund a number of welfare initiatives designed to help ease the burden on families affected by leukaemia. Our newest welfare project is in conjunction with our friends at Great Ormond Street Hospital where we have contributed to the development of the Paul O'Gorman Patient Hotel which opened its doors to parents and children in 2004, making those frequent outpatient visits a little easier to bear.

The promise that Paul sought from his parents nearly 20 years ago has proved an immense legacy. His family – and our legions of supporters - have honoured his memory and the name Paul O'Gorman is now synonymous with excellence, commitment and hope in the research and treatment of childhood leukaemia. We will not rest until childhood leukaemia becomes a thing of the past and no other family need suffer the agony of childhood leukaemia.

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Fighting Britain's biggest child killer disease

CHILDREN with LEUKAEMIA

Registered Charity No. 298405. Inaugurated in 1988 by Diana, Princess of Wales in memory of Jean and Paul O'Gorman