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EMF AND HEALTH

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■ **Abstract** Electric and magnetic fields are ubiquitous in the modern society, and concerns have been expressed regarding possible adverse effects of these exposures. This review covers epidemiologic research on health effects of exposures to static, extremely low-frequency (ELF), and radio frequency (RF) fields. Research on ELF fields has been performed for more than two decades, and the methodology and quality of studies have improved over time. Studies have consistently shown increased risk for childhood leukemia associated with ELF magnetic fields, whereas ELF fields most likely are not a risk factor for breast cancer and cardiovascular disease. There are still inadequate data for other outcomes. More recently, focus has shifted toward RF exposures from mobile telephony. There are no persuasive data suggesting a health risk, but this research field is still immature with regard to the quantity and quality of available data. This technology is constantly changing and there is a need for continued research on this issue. Almost no epidemiologic data are available for static fields.

INTRODUCTION

Electric and magnetic fields (EMF) are ubiquitous in the modern society. Earth is surrounded by a static magnetic field that varies between 25 μT and 65 μT. Superimposed on the earth's magnetic field there may be manmade static magnetic fields. Power-frequency 50- and 60-Hz fields occupy the extremely low-frequency (ELF) nonionizing range of the electromagnetic spectrum (Figure 1). The ELF range includes frequencies from 3 Hz to 3000 Hz. Above 3000 Hz are, in order of increasing frequency and decreasing wavelength, radio waves, microwaves, infrared radiation, visible light, UV radiation, x-rays, and gamma rays. Microwaves have enough photon energy to heat tissue; ionizing radiation like x-rays and gamma rays can break chemical bonds, forming ions that can damage biological systems. Static and ELF electric and magnetic fields induce weak electric currents in the

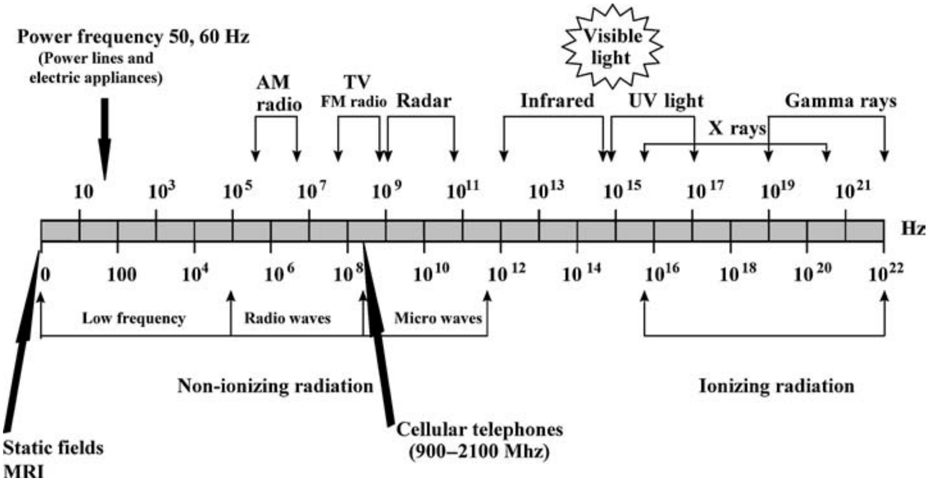

Figure 1 The electromagnetic spectrum.

body; however, they can neither break bonds nor heat tissue. Exposure guidelines for both ELF and RF fields are based on acute effects either from induced currents or from heating of tissue, respectively.

This review covers epidemiologic research on health effects of exposures to static magnetic fields, fields in the ELF range that are considerably lower than current exposure guidelines, and RF fields in the frequency ranges used for mobile telephony, which are close in magnitude to the existing guidelines but which cannot cause substantial heating of tissue (Table 1).

TABLE 1 International Commission on Non-Ionizing Radiation Protection (ICNIRP) exposure guidelines and some exposure sources

Exposure	ICNIRP's guidelines for the general population	Some exposure sources
Static fields	2 T	MRI: 1.5 or 3 T MAGLEV trains at floor level: 50 mT
50 Hz	100 μT	50 m from 400 kV power line: 0.4–1.5 μT
60 Hz	83 μT	In homes: usually <0.1 μT 0.5 m from TV: $\sim$ 0.2 μT 0.03 m from hair dryers: 6–2000 μT
900, 1800, 1900 MHz	SAR = 0.08 W/kg whole body exposure SAR = 2.0 W/kg localized exposure	Mobile phones, Specific Absorption Rate (SAR): <0.001–1.7 W/kg

STATIC FIELDS

Exposure Sources

Workers in industries such as aluminum production and chloralkali plants are exposed to static magnetic fields ranging from 4 mT to 50 mT (50), usually caused by strong rectified alternating current. Certain welding processes produce static fields, and railway workers on train systems operating from DC power supplies are exposed to static magnetic fields. Power systems for trains including magnetic levitation (MAGLEV trains) produce strong static magnetic fields, which will be an important exposure source when taken into operation in the future. Magnetic resonance imaging (MRI) systems used for medical diagnosis expose patients to flux densities as high as 2.5 T, and new machines are being developed in which exposure would be considerably higher. MRI operators are occupationally exposed to fields up to about 5 mT.

Summary of Data

Acute effects of static magnetic fields, e.g., nausea, vertigo, a metallic taste, and phosphenes, can be induced during movements in fields larger than $\sim$2 T. Adverse responses do not occur at field strengths below 2 T.

There is little information from animal studies regarding possible long-term effects of exposure to static magnetic fields, and there are only a few epidemiologic studies available. The majority of these have focused on cancer risks. There are also some reports on reproductive outcomes and sporadic studies of cardiovascular effects and immunological or musculoskeletal outcomes.

Cancer

A number of studies have investigated cancer risks in aluminum production workers or chloralkali workers. Most of these have focused on exposures other than static magnetic fields, e.g., polycyclic aromatic hydrocarbons, and consequently have poor or nonexistent assessment of exposure to static magnetic fields. The results from these studies are inconsistent; no patterns have emerged that can be clearly associated with effects of static magnetic field exposures. A few studies have attempted to estimate EMF exposures in broad categories (69–71, 81), but none of these found increased cancer risks related to EMF exposure.

There are a large number of studies on cancer risks among welders. However, none of these studies has estimated the exposure of welders to static magnetic fields, and it is impossible to distinguish between effects caused by welding fumes, static fields, ELF fields, or RF fields.

Other Outcomes

A few studies have reported results on reproductive outcomes among aluminum workers and MRI operators, but limitations in study designs prevent any conclusions from being drawn. Effects on immune function have been studied sporadically, producing inconsistent results, and single studies of cardiovascular or musculoskeletal outcomes have been reported.

Limitations

The available studies have several limitations apart from the crude exposure assessment. They generally compare the cancer incidence or mortality with that in the general population, which means that the "healthy worker effect" may have influenced the results. There are indeed several indications that this might be the case; many of the studies report decreased incidence or mortality rates overall. Most of the studies also have a very small number of exposed cases and do not have the power to detect modest risk increases. They also have little or no control of confounding.

A problem in occupational studies of possible health effects of static magnetic field exposure is that workers in exposed occupations are exposed also to a wide variety of other potentially harmful agents. Workers in aluminum production plants are exposed to petroleum coke and coal tar pitch volatiles, including, for example, polycyclic aromatic hydrocarbons, fluorides, sulfur dioxide, and heat (33, 34). Chloralkali workers are exposed to mercury, chlorine, and asbestos (6). Workers in both industries are exposed also to time-varying magnetic fields (mainly 50–300 Hz) ranging from 0.3 μT to 10 μT (87). Welders are exposed to welding fumes as well as high levels of ELF magnetic fields and also RF fields.

Summary of Major Reviews

Potential health effects from exposure to static fields have not received as much attention as have ELF or RF fields, and therefore few reviews have included this type of exposure in their assessments. The evaluation made by the International Agency for Research on Cancer (IARC) of static and ELF electric and magnetic fields (34) focused on ELF fields, although it reviewed epidemiologic studies of static fields also. IARC concluded that there is inadequate evidence in humans for determining the carcinogenicity of static electric or magnetic fields, and no relevant data from experimental animals is available; thus static fields were categorized as group 3, not classifiable as to their carcinogenicity to humans.

Overall Evaluation and Research Needs

The available evidence from epidemiologic studies is not sufficient to draw any conclusions about potential health effects of static magnetic field exposure at the levels encountered in the environment or the workplace. Increasing exposure to static magnetic fields in the general public is likely, e.g., with the development of new medical applications using very strong fields, and when magnetically levitated trains begin operation. Further research in this area is warranted, e.g., a cohort study of MRI workers or workers in industries where MRI systems are manufactured.

A cohort approach would allow studies with different types of outcomes. In new studies, improvement of the exposure assessment is crucial.

ELF FIELDS

Exposure Sources

Electric and magnetic fields are produced during electric power generation, transmission, and use. Electric field strength increases with increasing voltage or electric potential; magnetic field strength increases with increasing current. Both electric and magnetic fields decline rapidly with distance from their source, with a faster decline of fields from point sources such as equipment and a slower decline of fields from power lines. Electric fields are further reduced when shielded by conducting objects like buildings and have little penetrative ability; magnetic fields, in contrast, are capable of penetrating tissue and are not easily shielded.

Exposure Assessment

The early epidemiologic studies of residential magnetic fields estimated exposure through wire-codes, a categorization of homes based on distance to nearby electrical installations, e.g., power lines of different voltages (90). Subsequently, a more sophisticated method to assess magnetic field exposure from nearby power lines was developed, in which calculations were made of the fields generated by nearby power lines, on the basis of detailed information about the configuration of the lines and their historical loads (17). Also, new magnetic field meters were gradually developed, making it possible first to make spot measurements and later to assess personal or bedroom magnetic field exposure over periods of 24 or 48 h. Assessment of magnetic field exposure over a longer time period captures short-term temporal variations in the exposure levels.

A similar development of exposure assessment methods can be seen for occupational settings; early studies simply categorized certain occupational titles as "electrical occupations," whereas later studies have combined the use of systematic workplace measurements, individual job history descriptions, and the development of associated job-exposure matrices. Thus, exposure misclassification is likely to have decreased over time.

Summary of Data

Investigation of long-term ELF-EMF health effects has focused on cancer, reproductive disorders, as well as neurodegenerative and cardiovascular diseases.

In vitro studies on the possible carcinogenicity of electric and magnetic fields have investigated, under a wide range of exposure conditions, a variety of processes in a number of cell lines and tissue cultures. Because ELF EMF do not appear to initiate cancer, researchers have hypothesized that they may act as cancer promoters or progressors. In vitro research on the carcinogenicity of ELF EMF has been plagued by a lack of consistency and reproducibility. Recent reviews (34, 62, 63, 66) have concluded that cellular effects have been observed for exposures above 100 μT, although mechanisms for these effects are not known. Overall, a coherent picture is lacking. Although sporadic ELF-EMF effects have been reported in some animal studies, most results have been negative. Of the approaches to evaluating ELF EMF as a potential health hazard, toxicologic experiments provide the most consistently negative data (66). In particular, data on leukemia in experimental animals are negative (34). Epidemiologic evidence is summarized below.

Cancer

Generally studies have focused either on residential exposures or on occupational exposures; only a few studies have combined the different exposure sources (18, 20). Data on adult cancer and residential exposure to ELF EMF, including the use of appliances, are sparse and methodologically limited (56, 84). Because earlier evidence suggested that residential exposure is not a risk factor for adult cancers and because researchers expected that occupational studies would provide a more powerful test of adult cancer hypotheses than would residential ones, studies using the next generation of residential exposure assessment methods, such as long-term measurements and calculated fields, focused on children. One possible exception is breast cancer, for which several large studies with fairly sophisticated exposure assessment have been completed recently.

Effects in Children

Since the first report was published in 1979 (90), which suggested an association between residential ELF electric and magnetic fields and childhood leukemia, dozens of increasingly sophisticated studies have examined this association. In addition, there have been numerous comprehensive reviews, meta-analyses, and two recent pooled analyses. In one pooled analysis based on nine well-conducted studies, a twofold excess risk was seen for exposure above 0.4 μT (1). The other pooled analysis included 15 studies based on less-restrictive inclusion criteria and used 0.3 μT as the highest cutoff (25). A relative risk of 1.7 for exposure above 0.3 μT was reported. The two studies are closely consistent and represent the strongest association in ELF epidemiology.

No consistent relationship has been seen in studies of childhood brain tumors or other cancers and residential ELF electric and magnetic fields (44). However, these studies have generally been smaller and of lower quality, and a formal pooled analysis for brain cancer has not been done.

Several studies of the relationship between electrical appliance use and various childhood cancers have been published (56, 76). In general, these studies provide no discernable pattern of increased risk associated with increased duration and frequency of appliance use.

Effects in Adults

Data on adult cancer and residential exposure have been largely negative but fraught with limited exposure assessment and other methodological limitations. Three recently completed large breast cancer studies found no association with exposure to electric or magnetic fields (12, 53, 78).

Occupational studies conducted in the 1980s and early 1990s pointed to a possible increased risk of leukemia, brain tumors, and male breast cancer (14) in jobs with presumed exposure to ELF electric and magnetic fields above average levels. In light of a hypothesis that EMF can affect breast cancer through melatonin suppression (83), concern extended to female breast cancer and occupational exposures.

Several large studies, conducted in the 1990s, of both leukemia and brain cancer made use of improved methods for individual assessment of occupational exposure to magnetic fields and to potential occupational confounders. No consistent exposure-response relationship and no consistency in the association with specific subtypes of leukemia or brain tumors were found in either individual studies or in the meta- and pooled analyses (45–47).

Although some earlier registry-based studies provided some support for a possible association between EMF exposure and female breast cancer (48), the most recent very large study, which incorporated exposure measurements in female workers, did not find an association (20b).

Sporadic reports of elevated risk for other cancers have appeared in the literature, most notably for lung cancer (4), but none have been sufficiently suggestive to warrant presentation here.

Cardiovascular Disease

A hypothesis that EMF could affect heart rate variability (75), which in turn can influence acute cardiovascular events (13), gave Savitz et al. (77) the impetus to look at cardiovascular mortality. As postulated they observed an increased risk for acute myocardial infarction (AMI) and arrhythmia-related death but not from chronic cardiovascular disease. However, further studies specifically designed to test this hypothesis mostly failed to replicate this finding while approaching this hypothesis from different point of views: Two studies directly replicated the original study (73, 80); one study focused specifically on arrhythmia (40); and one study investigated cardiovascular morbidity and provided detailed confounding control (2).

The only support, very limited as it was, for the original observation comes from a study based on data from the Swedish twin registry (26), which observed a nonsignificantly increased risk for AMI. Thus only mortality studies of the association between occupational exposure to EMF and cardiovascular diseases have reported an association (26, 77). However, studies of cardiovascular diseases that rely on mortality records are questionable owing to inaccuracy of the diagnosis on the death certificates (J. Mant, S. Wilson, J. Parry, P. Bridge, R. Wilson, W. Murdoch, T. Quirke, M. Davies, M. Grammage, R. Harrison, A. Warfield, submitted manuscript). Thus, on balance, the evidence supporting an etiologic relation between occupational EMF exposures has been overturned by more focused and rigorous studies.

Neurodegenerative Diseases

Investigation of potential EMF effects on neurodegenerative diseases is still not well developed. Of the three neurodegenerative diseases that have been considered, Parkinson's disease has received the least attention. No study has provided clear evidence of an association between Parkinson's disease and above-average exposure to ELF EMF, and in the absence of laboratory evidence to the contrary, there is no good ground for believing that these fields are involved in the etiology of the disease.

The evidence relating to Alzheimer's disease is more difficult to assess. The initial reports that gave rise to the idea suggested that the increased risk could be substantial (79). Subsequent studies have been inconsistent, with no obvious pattern on the basis of study design, whether morbidity or mortality was examined, or the quality of exposure assessment. Thus the evidence that ELF EMF increases the risk of Alzheimer's disease is weak (3, 63).

More evidence is available for amyotrophic lateral sclerosis (ALS), where several studies suggested that employment in electrical occupations may increase the risk of ALS (11, 41). Currently, the most interesting suggestion is that electric shock, rather than increased exposure to EMF, may play a role in the development of ALS (63).

Reproduction

The association of electric and magnetic field exposure with human reproductive outcomes has been examined in a number of studies (32). Although several studies have reported adverse effects, more rigorous investigations have not corroborated these findings. Studies examining domestic exposures and use of electric blankets have found no increase in risk of pregnancy outcomes such as miscarriages or intrauterine growth retardation (7, 8). Two recent studies from California found an increased risk of miscarriages in women with exposures to relatively high (any exposure above 1.6 μT) intermittent fields (51, 52). In occupationally exposed groups, reported effects included congenital malformations, brain tumors, and spontaneous abortions among video display terminal operators (68). Methodological problems such as the difficulty of studying EMF exposure levels that are very close to background, possible omission of early miscarriages, and information and recall bias make firm conclusions difficult to obtain.

Limitations

Epidemiologic investigations of possible associations of EMF exposure with risk of chronic disease pose unique and substantial difficulties. Among them are difficulties specific to an outcome studied, assessment of exposure, and interpretation of findings.

Most of the chronic diseases considered are rare and have long latency periods for known risk factors. Thus a major challenge in EMF epidemiology is the small number of cases available in any given study and the necessity for retrospective study designs that make exposure assessment even more difficult. Small risks are notoriously difficult to evaluate, both because it is difficult to achieve enough precision to distinguish a small risk from no risk and because small risks are more vulnerable to subtle confounding and other biases that can go undetected. In particular, selection bias may account for part of the association. Case-control studies that relied on in-home measurements are especially vulnerable to this bias because of the low response rates in many studies. Studies conducted in the Nordic countries, which relied on historical calculated magnetic fields, are not subject to selection bias but suffer from very low numbers of exposed subjects.

Furthermore, the etiologies of many of the diseases studied are poorly understood, making difficult a search for confounding as an explanation for any observed association. For some of the more common diseases such as Alzheimer's and cardiovascular disease reliance on mortality records is particularly problematic.

EMF does not appear to be genotoxic, but biological evidence suggests that it could influence cellular function and proliferation. Therefore, it could act as a promoter or growth enhancer in carcinogenesis. The distinction between promotion and growth enhancement in cancer biology is primarily theoretical and is virtually impossible to discern in an epidemiologic study. However, the two processes can be considered as representing postinitiation events that enhance the development of cancer. As such, they can be studied by focusing on the populations that have been exposed previously to cancer initiators or who are at high cancer risk for genetic reasons. Epidemiologic studies that attempt to consider such secondary events are rare, and methodologic developments in this area are needed.

That assessment of exposure is a major weakness of epidemiologic EMF studies is not surprising because several factors make assessment of EMF exposure more difficult than assessment of many other environmental exposures. The exposure is imperceptible, ubiquitous, has multiple sources, and can vary greatly over time and short distances. Assessment of exposure to electric and magnetic fields over time has dramatically improved, yet our ability to predict exposure remains severely limited (43) and might be better for children than for adults (19).

In a 1000-person study, Zaffanella et al. (91) found that work exposures are often significantly higher and more variable than are other exposures; the highest mean and median exposures occur at work, followed by exposures at home and during travel. In contrast, in a small study of household appliance use, Mezei et al. (56) found that a large proportion of total exposure for most adults is accumulated at home. Given the large amount of time most people spend at home, ignoring either home or work exposure is likely to lead to a large misclassification.

The long latency of cancers necessitates estimation of exposure over long time periods, an exceptionally difficult task owing to the mobility and behavioral changes likely to occur over time. The situation is even worse for rapidly fatal or memory-debilitating diseases, such as brain cancer and Alzheimer's, when information is obtained from a large number of proxies.

The absence of a clearly elucidated, robust, and reproducible mechanism of interaction of EMF with biological systems deprives epidemiologic studies of focus in their measurement strategies. If some singular aspect of EMF plays a role in carcinogenesis, we have yet to identify and capture it. Given the plethora of field characteristics that could be measured, it would be difficult to undertake a truly comprehensive evaluation of exposures.

All these difficulties with EMF exposure assessment are likely to have led to substantial exposure misclassification, which is likely, in turn, to interfere with detection of an association between exposure and disease (if indeed such an association exists). If the true association is small or moderate, detecting associations with this amount of measurement error will be difficult.

Summary of Major Recent Reviews

Numerous national and international bodies have provided comprehensive reviews of this literature over the years. These reviews adhere to different philosophies: from strict focus on what is known (62), to narrative evaluation (63), to formal weight-of-evidence approach (34), to informal incorporation of prior beliefs (61). Conclusions varied somewhat with time and individuals involved; nevertheless, these reviews broadly agree that while the evidence is not conclusive, the possibility of the effect cannot be excluded and epidemiologic studies of childhood leukemia provide the strongest evidence of an association. The most formal of these, by IARC (34), concluded in 2002 that

> [t]here is limited evidence in humans for the carcinogenicity of extremely low-frequency magnetic fields in relation to childhood leukemia. There is inadequate evidence in humans for the carcinogenicity of extremely low-frequency magnetic fields in relation to all other cancers. There is inadequate evidence in experimental animals for the carcinogenicity of extremely low-frequency magnetic fields.

These evaluations have led to a classification of ELF magnetic fields as possibly carcinogenic to humans (Group 2B). The World Health Organization is developing a comprehensive risk assessment and policy recommendations with results expected in 2005.

Ongoing Work

There is little ongoing work in ELF epidemiology, and much of it relates to childhood leukemia. Of note is a cohort study in the United Kingdom, a case-control study in Italy, an evaluation of selection bias (24) (G. Mezei, L. Kheifets, manuscript in preparation), and an examination of a newly proposed contact current hypothesis (42).

Overall Evaluation and Future Research Needs

Among all the outcomes evaluated in epidemiologic studies of ELF EMF, there is most evidence of an association for childhood leukemia in relation to postnatal exposures above 0.3–0.4 μT. This association is unlikely to be caused by chance but may be partly due to bias, though it is difficult to interpret in the absence of a known mechanism or reproducible experimental support. The common chromosome translocations in childhood leukemia seem to initiate disease and often arise prenatally. However, it appears that the frequency of conversion of the preleukemic clone to overt disease is low. One or more additional postnatal event(s) is needed for leukemia development (23). Investigation of EMF as one of the postnatal exposures leading to an increased risk of childhood leukemia may prove informative.

Further studies designed to test specific hypotheses such as aspects of exposure or a possibility of selection bias are also needed. Past attempts to evaluate selection bias operating through socioeconomic status (SES) and low participation rates were largely ecological and/or focused on wire codes rather than measurements. New attempts need to focus on the interrelationship between SES and participation of cases and controls on one hand and measured fields on the other. Ultimately the question of selection bias can be resolved only in a large well-conducted cohort study or in a case-control study where exposure information can be collected independently of the included subjects. However, the rarity of both the outcome (childhood leukemia) and exposure (magnetic fields above 0.3–0.4 μT) will require either a prohibitively expensive study or an innovative study design.

Additionally, a pooled analysis of childhood brain tumors may prove informative in addressing either specificity of the association with ELF EMF or a possibility of selection bias.

Within the methodologic limitations described above, there is inadequate evidence that ELF EMF is carcinogenic to adults. Similarly, the evidence is inadequate for other diseases considered, including reproductive outcomes and cardiovascular and neurodegenerative diseases. Of all these diseases, we consider neurodegenerative disease, ALS in particular, to be the one in need of further investigation. Studies of ALS incorporating better exposure assessment methods, including assessment of contact currents, more accurate diagnosis of diseases, and adjustments for potential confounding from occupational exposures to substances such as solvents may clarify the issue.

RF FIELDS

Exposure Sources

There are different sources of RF exposure to which people may be exposed, but the most frequently discussed is exposures related to mobile telephony. This technology typically uses the frequencies from 450 to 2500 MHz, although new technology may extend this band. Other general population sources of exposure are radio and television transmitters operating at frequencies between 200 kHz and 900 MHz. Occupational exposures examples include RF PVC welding machines, plasma etchers, and military and civil radar systems, all operating at different frequencies. The main focus of this review is RF exposures related to mobile telephony. Exposure from the mobile phone is concentrated to the part of the head closest to the handset and the antenna. The exposure declines rapidly with distance to the antenna, and therefore, exposure from mobile phone base stations are several orders of magnitude lower than from the phones. Thus, most of the research has focused on mobile phone use. However, the exposure from base stations differs from that of mobile phones; base stations expose the whole body, and the exposure duration is considerably longer.

Summary of Data

There is no convincing evidence from cellular studies that RF fields are carcinogenic or promote carcinogenic agents. Isolated findings of DNA damage have not been replicated, results on micronuclei are contradictory, and the importance of the occurrence of micronuclei for human health is unclear. There is some evidence for an increase in expression of heat shock proteins after RF exposure; however, the few available studies are inconsistent. Different exposure conditions are needed to evoke the response, and the type of heat shock protein for which an increase was found has varied between models.

There have been sporadic reports of effects in animal models, but most studies have not reported dose-dependent responses in either gene expression or in increased permeability of the blood-brain barrier. Recent animal studies have not provided evidence that RF radiation below exposure guidelines could induce cancer or promote effects of known carcinogens. One earlier study reported a higher lymphoma incidence in transgenic mice (67) exposed to RF fields, but this finding was not confirmed in a recently published study (88). The comparability between these studies has been questioned (21, 22), and additional replication studies are ongoing.

Epidemiologic studies of health effects related to RF exposure from mobile telephony have primarily focused on cancer outcomes (mainly brain tumors), and a few studies focused on different types of symptoms. The mobile phone technology is relatively new, and therefore, the number of studies available is limited. Occupational studies have been performed over several decades, but the exposure frequencies may not always be relevant for an assessment of mobile telephony frequency effects. We are only beginning to measure and learn about RF exposures in various occupations.

Cancer

Handheld mobile phones have been available only since the later part of the 1980s and have become common in the general population only during recent years. In several countries, e.g., Finland and Sweden, more than 80% of the population are mobile phone users today, whereas the same statistic was less than 10% in the beginning of the 1990s. The first study of cancer in relation to mobile phone use was published in 1996 and had only a short period of follow-up (72). Subsequent studies have also been limited by short exposure durations and short latency, and no study to date has had the power to investigate potential long-term effects. Therefore, on the basis of the evidence at hand, it is possible only to evaluate short-term effects of mobile phone exposure.

Nine studies of mobile phone use and brain tumors have been published so far (5, 10, 27, 28, 37, 38, 59, 72, 89). The majority of these have found no effects on brain tumor risk. A Finnish register-based case-control study found an increased risk of glioma related to use of analog phones (5), with an increased risk found already after one to two years duration of subscription to an analog phone. This finding was not confirmed in a Danish cohort study with similar exposure assessment methods (38) or in other case-control studies. The glioma incidence in the Nordic countries, where mobile phone use in the general population started relatively early, has not increased since the introduction of handheld mobile phones (55). A Swedish case-control study reported a more-than-threefold risk increase of acoustic neuroma among users of analog mobile phones (27) but with no relation to induction period. Other studies have not provided evidence of an increased risk of acoustic neuroma (28, 37, 58) but have not had enough statistical power to adequately test the hypothesis. Two studies have investigated the risk of uveal melanoma but produced conflicting results (39, 82).

There are no studies of cancer risk related to mobile phone base stations, but a few studies have assessed cancer risk in relation to radio and TV transmitters (15, 16, 31, 57). Exposure assessment has simply been based on distance to the transmitter, and no account has been taken of the surrounding vegetation and buildings. The studies have been of an ecological design, with no data on individual exposures or confounders, and the number of observed cases has often been small. Several of the studies were conducted because of concerns for an apparent excess of cases in a certain area, and they have reported a higher incidence of leukemia close to the transmitters. However, other studies, conducted without a priori concern, have not confirmed these findings. Overall, the available data do not support the hypothesis that radiofrequency exposure from transmitters increases cancer risk; however, they do not provide strong evidence against the hypothesis either.

Occupational Studies

Occupational studies of RF exposure have been conducted for more than 20 years, and a variety of occupations have been investigated, e.g., radar technicians, radio and telegraph operators, or workers in dielectric heat sealing or in telecommunication manufacturing. The studies have several methodological weaknesses, especially regarding exposure assessment. None of the studies has made measurements of the RF exposure for the subjects included in the study, and exposure classification has often been based on the job title alone. No control or only limited control of confounding has been made. Although some increased risks have been found in certain studies, there is no consistent evidence of risk increases for any cancer sites. The exposure frequencies studied have generally been other than those used for mobile telephony.

Symptoms

All available epidemiologic studies of symptoms related either to mobile phone use (9, 65) or to exposures from mobile phone base stations (60, 74) are cross-sectional, which makes them of limited value in a health risk assessment. The subjects themselves have estimated their exposure, e.g., distance to nearest base station or amount of mobile phone use, as well as the health outcome, and no attempt has been made to verify the exposure or disease. The studies of base stations have not adequately described how subjects were selected, and there may be both selection and reporting bias. Therefore, the available epidemiologic studies on symptoms do not provide information that allows an evaluation of the effect of mobile phones or base stations on the occurrence of different types of symptoms.

Limitations

In all available mobile phone studies, exposure estimation has limitations. Exposure assessment has focused on amount of mobile phone use, with no attempt to incorporate other parameters that might influence the level of exposure while using a mobile phone, e.g., make and model of the phone or output power levels. Exposure information has been obtained either directly from the subjects included in the studies through questionnaires or interviews or from register-based information about mobile phone subscriptions. The former method may be subject to recall bias: Cases may be more prone to remember all occasions of exposure or even overestimate their exposure, whereas controls are not as motivated and may forget exposures. In contrast, a brain tumor may affect a person's memory, which could make it more difficult for cases to remember their mobile phone usage many years back in time. Thus, this type of bias can affect the risk estimates in both directions. The studies that have used register-based exposure information collected independently of case/control status do not have this potential for recall bias but have other limitations. They have not been able to identify corporate users and have no information about who is the actual user of the phone. This kind of exposure misclassification would tend to dilute risk estimates toward unity.

Some of the case-control studies used hospital controls selected among other patients at the hospitals where the brain tumor cases were treated (37, 59). It is difficult to know if these other patients are representative of the population from which the brain tumor cases come with regard to frequency of mobile phone use, and it is impossible to evaluate the potential for selection bias. Some of the case-control studies that have used population-based controls nevertheless have a large potential for selection bias because of the long time period between date of diagnosis and case recruitment, leading to a large proportion of cases having deceased before recruitment (27, 28). The remarkably high response rates (about 90% for the population-based controls) in these studies also limit the interpretability of these findings.

As described above, the occupational studies have severe limitations in the exposure assessment, and negative findings cannot be taken as evidence of a lack of an association. The limited confounding control makes positive findings hard to interpret; other exposures in the studied occupations may be responsible for increased risks observed.

Cross-sectional studies have only limited valuable information in the assessment of potential effects of RF exposure on different symptoms, and some of the available studies have severe problems with potential selection and reporting biases.

Summary of Major Reviews

During recent years the literature on potential health effects of RF exposure have been summarized and evaluated by a number of national bodies, e.g., the Royal Society of Canada (72a), the Stewart Commission in the United Kingdom (36, 64), the Health Council of the Netherlands (30), the Swedish Radiation Protection Agency (85), and the French Health General Directorate (92). These reviews come to more or less similar conclusions in their assessments of the science: The scientific evidence available does not give cause for concern, but the research has limitations and mobile telephones have been widespread only for a relatively short time. Therefore, the possibility that RF exposures from mobile telephony can have adverse health effects remains, and continued research is needed. In terms of public health recommendations, national bodies draw different conclusions; e.g., the Stewart commission in the United Kingdom recommends that children avoid unnecessary exposure, whereas the Health Council of the Netherlands finds no reason to recommend precaution.

Ongoing Work

Currently underway is a large international collaborative case-control study of brain tumors, acoustic neuroma, and parotid gland tumors in relation to mobile phone use. The study is being performed in 13 countries, and results from national analyses are expected in the near future—one has already been published (10). Results from the combined international analyses will be available in 2005 at the earliest.

Several countries have initiated research programs to clarify the question about possible health effects of mobile telecommunication. Thus, there are numerous studies ongoing, some of which are epidemiologic.

Feasibility studies have shown that establishment of a large cohort of mobile phone users is possible. Attempts are being made to establish such a cohort in several European countries. Exposure information will be based on records of incoming and outgoing calls from mobile phone operators, combined with questionnaire information. Outcomes will be determined through both questionnaires and linkage to different registries. It is urgent to begin a prospective cohort study capable of capturing rapidly changing exposures and addressing a broad range of health outcomes. Such a study, which has been identified as a high priority by WHO, will reduce scientific uncertainty and provide the most relevant data for future risk assessment.

Overall Evaluation and Future Research Needs

Although occasional significant associations between various brain tumors and mobile phone use have been found, no single association has been consistent. The few positive findings reported in two of the studies are difficult to interpret: They are either based on small numbers, have latency periods too short to be credible, or emerged only after a series of reanalyses that are reported in a way that is difficult to follow. Considering the short time period during which handheld mobile phones have been in use, and the limited use (both in terms of the number and duration of calls) among early users, it is not possible today to evaluate effects after a long induction period or for heavy use. Thus, the negative results of most of the studies cannot be taken as evidence against an effect either. The current evidence is inconclusive regarding cancer risk following RF exposure from mobile phones. The occupational studies available on cancer risks have such severe limitations that they provide little information about cancer risk related to RF exposures. Data regarding effects of RF exposure on symptoms are inadequate for an assessment.

Some investigators argue that children are more sensitive to RF exposure than are adults, and several countries (e.g., the United Kingdom) recommend special precautions for children. However, there are to date no available data on health effects in children. Mobile phone use is increasingly common among school children, and teenagers may be among the heaviest mobile phone users today. Therefore, studies assessing possible adverse health effects in children and teenagers are warranted.

Results from many ongoing case-control studies of head and neck tumors will be available in the near future, but these studies will also have limited ability to assess effects of long-term exposures. Analog mobile phones have been available for the longest time period, and some people have been users for more than 10 years. However, digital phones have been available for only $\sim$10 years.

A large cohort of mobile phone users capable of evaluating a number of different outcomes, e.g., brain tumors, neurodegenerative diseases, cognitive effects, symptoms, and other outcomes that may become of interest as a result of experimental research or public concern, is urgently needed. Additionally, the technology is constantly changing; the third generation of mobile phones is currently being introduced, and further changes in the future are likely. Therefore, there is a need for continued research on this issue.

Exposures from base stations are only an extremely small fraction of the exposure guidelines, but the possibility of health effects from continuous whole-body exposure is an area of major public concern. The feasibility of performing epidemiologic studies on base stations is being investigated currently.

Comparative Analysis of Scientific Developments

This section focuses on research on ELF and RF fields because there are only sporadic epidemiologic studies on health effects from static field exposure. Man-made exposure to static fields has been quite limited in the past, and therefore this exposure has not attracted public concern. This may change in the future with a more widespread use of MRI and the introduction of MAGLEV trains.

There has been a longstanding scientific interest in the possibility that prolonged exposure to weak EMF, at levels far below the current exposure standards, might assert health effects through mechanisms other than the established ones (49). A new phase in this research began after the publication of an epidemiologic study that implicated an association between ELF and childhood cancer mortality in 1979 (90).

This and later studies generated a considerable interest among the public, decision makers, and scientists. Scientists were intrigued by the original results, and studies were conducted to see whether the results could be replicated and to explore the associations from various perspectives. More than two decades later, this research avenue in a way seems to have been exhausted, at least temporarily. A considerable amount of knowledge has been accumulated, and broad consensus has been reached about a number of issues involved (3).

Now the focus has shifted from power frequency fields to RF fields. For RF fields, however, the research was not initiated by an epidemiologic finding or other scientific data on the possible existence of a health risk. Instead the driving force has been a concern over the fast dissemination and penetration of new communication techniques together with the notion that the biophysical interaction between RF fields and humans may not be fully known or understood. This argument was partially based on an analogy with the ELF results.

Thus, the starting points for the ELF and the RF EMF research are rather different. Despite this difference we propose that these two scientific areas are similar with respect to the methodological challenges and several other aspects, with the caveat that the ELF research is at least a decade ahead of the RF research. We also propose that the RF research can and does learn from the ELF studies. This section assesses this tenet by conducting a comparative analysis of scientific developments.

Exposures

Because there is no known mechanism by which ELF or RF fields might assert low-level biological effects, one does not know which aspect of the fields should be measured in a particular study. Studies are therefore measuring different aspects of the EMF but are influenced by the known mechanisms for acute effects. For ELF fields the only established effect is induced currents, and the corresponding environmental quantity is the magnetic flux density, measured in μT; for various reasons the magnetic component, rather than the electrical, has been implicated. For RF fields, the only established effect is heating, and the corresponding environmental quantity is power density, measured in W/m^2. Studies have also attempted to estimate the internal dose, however, measured in W/kg, rather than the environmental levels.

Because exposure to EMF is imperceptible it does not lend itself to self-reporting by subjects in epidemiologic studies, and therefore the epidemiologist is left with two options: to use direct measurements or to use proxies based on circumstances or conditions known or thought to entail exposure. When the attempts to replicate and explore the results of the seminal study on ELF and childhood cancer began, no magnetic field meters could measure such weak fields. The development of such instrumentation began shortly afterward, and the later generation of studies has used direct field measurements. For RF fields, a meter suitable for large-scale use in epidemiologic studies has just been developed; for obvious reasons the internal dose cannot be captured directly but must be assessed on the basis of a combination of measurements and modeling.

Sources of exposure to ELF and RF fields are different. Yet for both types of fields the sources can be divided into three main categories: occupational, environmental, and personal appliances. All of these have been used as markers of exposure both in ELF and RF research.

Occupational studies have played a considerable role both in ELF and RF research (3, 64). In the early ELF studies the major limitation of this line of research was the limited knowledge about actual exposure levels and distribution in the occupations that were studied. This limitation was later rectified through extensive measurement studies within occupational groups. In the RF studies the lack of details about exposure is still a major obstacle. Measurement studies have begun recently, but the results of these efforts are not yet available.

Some early ELF studies based their exposure assessment on the presence of power lines and assessed exposure from this source according to algorithms with a varying degree of sophistication. In retrospect this approach has proven to be rather successful, partly because power lines are an important source of ELF exposure. In contrast, this avenue has not yet been successful for RF and may not be in the future either because of the complex relation between the exposure at one geographic location and the output power from the source. Another factor, however, appears to be that the environmental levels of RF exposure are very low in relation to the exposure that a subject experiences from mobile phone use, for example. Indeed, the levels may differ by a factor of one thousand. Thus, one would expect biological effects, if they exist, to be easier to detect in studies based on phone use rather than in studies based on nearby antennas. In addition, mobile phone technology is rapidly changing, which further complicates exposure assessment.

Some attempts were made to include appliance use in ELF studies (29), but they have not been successful. There are too many different appliances to consider and the patterns of usage are quite diverse, which makes exposure from the different sources difficult to combine into one parameter, which would be desirable. Assessment of exposure from appliances is rather different for RF because the obvious appliance to consider here is the mobile phone. Studies so far have used rather crude characterizations of exposure from phones, such as years of use. However, considerable efforts are currently underway to determine the relative importance of various factors related to usage that can be incorporated in epidemiologic studies. One key consideration is to what extent the degree of down-regulation of the phone can be predicted on the basis of factors such as urban/rural use or indoor/outdoor use (54).

Biological Plausibility

The fields considered here both in the ELF and the RF research are too weak for any biological effects to be explained by the known mechanisms of interaction, induced currents, or heating, respectively. In neither case is there even a good candidate for a mechanism that might explain such effects. It may be worth noting, however, that the actual exposure levels considered in the ELF research are orders of magnitude below the exposure standards, whereas for RF, exposure from mobile phone use actually may be of the same order of magnitude as the exposure standards (35).

Yet, the epidemiologic studies of ELF have shown rather consistently effects for childhood leukemia that have been considered strong enough evidence for the IARC to classify ELF in category 2B, which is translated by IARC as a possible carcinogen (34). Other evaluators have reached similar conclusions. Thus, the lack of a known or even hypothetical mechanism has not prevented evaluators from concluding that weak ELF exposure possibly may cause cancer. However, with some hints as to the mechanism, or supportive toxicologic data, the IARC classification would have been higher. For RF, the epidemiology is still immature, and it is still too early for a corresponding discussion.

ELF research has also provided examples to the contrary. For both breast cancer and cardiovascular diseases, the research began with a biological hypothesis confirmed by some early studies. More rigorous epidemiologic studies that followed showed no effect, which has led to an overall conclusion that ELF fields are not involved in the development of these diseases.

The concept of biological plausibility is vague and rather ill defined and is therefore not particularly useful in this and similar contexts. Often our understanding of what is plausible changes over time, as science makes advances and paradigms shift. If an association appears to exist, one must test every candidate for explanation and eventually perform a risk evaluation.

Quality of Research

The quality of the ELF studies have improved over time, and new study protocols were designed on the basis of prior studies' experiences. This is particularly evident with respect to exposure assessment. The earliest studies used crude proxies for

ELF as markers for exposure, whereas later studies employed sophisticated meters and measurement schemes.

The current RF studies may be best compared to the early generation of ELF studies, with respect to exposure assessment. But as knowledge advances about exposure distribution and determinants, RF research will likely follow the same track as ELF research with improving quality over time.

ELF research also showed that accusations of epidemiology as a source of many false associations are not warranted when good studies are conducted. Furthermore, although in the strictest sense one cannot prove a negative association (or a positive one for that matter), in reality the weight-of-evidence approach can provide sufficient information to conclude a negative association, provided there is comprehensive and rigorous research.

Conclusions of Reviews and Historical Changes

For ELF there are indications that the childhood leukemia association is causal, but lack of a known mechanism at such low energy levels, negative animal data, and a possibility of selection bias require explanation. For some other endpoints, such as breast cancer and cardiovascular disease, enough data now exist to conclude that ELF is most likely not a risk factor. For several other endpoints the science is considerably weaker than for childhood leukemia, so it may be too early still to discount other possible associations with ELF. To further address the childhood leukemia issue, it is possible that one must await a better general understanding of the etiology. Thus, science has been quite successful during the two decades since this research was revitalized, in that it has brought several of the issues to reasonable conclusions.

The RF situation again is very different. First, no good data thus far suggest a health risk associated with RF. Second, this research is still immature, with regard to both the amount of available data and the quality of available studies. Thus, no conclusions can be drawn yet and we must await further results.

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