Update on Scientific Research Regarding Potential Health Effects of Power-Line Electric and Magnetic Fields (EMF)

September 12, 2006

Prepared for

Vermont Electric Power Company, Inc. (VELCO)
366 Pinnacle Ridge Road
Rutland, VT 05701

Prepared by:

Gradient Corporation
20 University Road
Cambridge, MA 02138
Introduction and Overview

This Gradient Corporation Report provides VELCO an update on published research literature regarding the science of potential health effects of electric-utility, power-line electric and magnetic fields (EMF). For the **2005 to Aug. 2006 time period**, this Report identifies and provides short summaries of key EMF research articles.

Potentially relevant, peer-reviewed EMF health-effect-research articles were identified through literature searches, and by examining EMF-specific databases. Search engines such as “PubMed” (National Library of Medicine) ([http://www.ncbi.nlm.nih.gov/Literature/](http://www.ncbi.nlm.nih.gov/Literature/)), Science Citation Index ([http://library.dialog.com/](http://library.dialog.com/)), and CSA Illumina ([http://ca2.csa.com/](http://ca2.csa.com/)) were used. In addition, a large EMF database, assembled by Information Ventures, Inc. was queried ([http://www.infoventures.com/emf.htm](http://www.infoventures.com/emf.htm)). Gradient also accessed reference lists available online from the World Health Organization (WHO) that are compiled as part of their International EMF Project ([http://www10.who.int/peh-emf/emfstudies/database.cfm](http://www10.who.int/peh-emf/emfstudies/database.cfm)) and from Dr. John Moulder’s (Medical College of Wisconsin) website on “Electromagnetic Fields and Human Health: Power Lines and Cancer Frequently Asked Questions (FAQs)” ([http://www.mcw.edu/gcrc/cop/powerlines-cancer-FAQ/toc.html#1](http://www.mcw.edu/gcrc/cop/powerlines-cancer-FAQ/toc.html#1)). Additional details on the article results and selection procedures are provided in the next section, “Methods.” A listing and Abstract Summaries of the identified articles make up the final section of this Report.

The selection of the articles identified in this Report placed emphasis on potential relevance to health effects of EMF from electric-utility power lines, and on integration of the three main lines of scientific evidence: (A) Epidemiology, (B) Animal Studies, and (C) Mechanisms of Action.

A central focus of our literature search was on power-line EMF and health endpoints related to cancer, specifically childhood leukemia. The following three general summaries of the main lines of scientific evidence, which were discussed at the Public Service Board’s hearings on VELCO’s NRP Project, remain overall valid, and in each case, a few recent key publications are listed (the full list of identified references is at the end of this Report). A more complete listing and summary of all recent publications, selected to be relevant to VELCO’s EMF concerns, makes up the remainder of Gradient’s Report.

(A) Over the past two and a half decades, some epidemiology studies have reported weak associations between surrogate markers of power-line magnetic field exposure and risk of childhood leukemia. Because of these studies, the International Agency for Research on Cancer (IARC) classified power-line EMF as a “possible” carcinogen in 2002. A recent study in Japan and a recent study in the UK reported associations of childhood leukemia with distance from power lines, the latter at surprisingly large distances, where EMF levels from the lines were essentially at background. Even though epidemiology continues to provide the strongest suggestions of health effects, the results among the studies remain weak and inconsistent, and poorly linked to actual EMF exposures. In addition, these statistical, correlative results are not able to establish causation. That is, while a laboratory scientist can precisely set exposure conditions, randomly allocate groups to be exposed or non-exposed, do careful pathology on the outcome, and can read the results blindly (*i.e.*, without knowing the exposure history), epidemiology is an observational science and cannot apply such rigorous scientific methods. Other problems cloud the interpretation of the epidemiology. None of the exposure assessments used in epidemiological studies are based on mechanisms of interaction, or on possible EMF regulatory policies. An epidemiologic study that reports “statistically significant” associations is only testing that significance against the role of random chance. If other sources of uncertainty in epidemiologic studies were to be quantitatively included in the confidence interval (*e.g.*, confounding factors, measurement error, selection bias, misclassification), the error bars would be much broader and would likely overlap a null outcome (*i.e.*, “no association”). Reviews of EMF epidemiology emphasize this point, namely, that the error bars in reported results reflect no other sources of uncertainty aside from random error (*i.e.*, population size),
and consequently the results are less indicative of an association than one might think. The error bars include only chance, and not the possible roles of confounding, selection bias, and misclassification bias.


(B) Not only is the interpretation of power-line EMF epidemiology clouded and uncertain, but also, other lines of scientific evidence weigh against assigning a causal basis to the associations. To date, there is no established laboratory bioassay or animal model by which power line EMF has been shown to initiate or accelerate biological changes related to cancer risk. Although lifetime exposure to high levels of 60-Hz magnetic fields has been tested in many animal studies, the results have failed to show that 60-Hz magnetic fields can initiate or exacerbate any disease or pre-disease condition, even in genetically modified and susceptible animals. Even though it is now a 7-year-old result, the National Toxicology Program (NTP) testing of 60-Hz EMF, listed below, remains the largest laboratory study, because its scope and number of animals tested is unlikely to ever be duplicated. The NTP study found no cancer risks at elevated EMF exposures (10,000 to 20,000 mG). Such animal testing is the foundation (or “gold standard”) for probing health effects, because it is through such exhaustive studies that regulators can determine what (if any) aspect of an exposure (e.g., chemicals or “EMF”) should potentially be regulated.

(1) National Toxicology Program (NTP), lifetime laboratory-animal tumorigenicity studies:


(C) Research to date, reporting extensive efforts by scientists worldwide, has not identified plausible mechanisms by which public exposure to power-line EMF can cause adverse health effects. EMF interactions with biological systems have been analyzed carefully in light of the biophysics of electromagnetic field interactions with matter. The applicability of fundamental physics to all systems, and to biology in particular, permits evaluation of the interaction of EMF with ions, molecules, cells, and
organisms. The conclusions are that the effects of typical power-line EMF are not detectable above the many sources of disturbance (electrical and other “noise”) in living systems. Examination of all possible aspects of EMF exposure have revealed no firm basis on which to attribute a potential for adverse effects specifically to, for example, electric fields or to magnetic fields, to the fundamental frequency or to harmonics, to continuous exposure or to intermittent exposure, to time-average fields or to peak fields, to constant amplitude EMF or to transients in EMF. A new mechanism being evaluated is “contact currents,” which, if true, would mean that the epidemiological associations arise through factors that are not EMF at all, but happen to vary with EMF. Over the years, many ideas have been proposed in this area, and many analyses have been performed, but diligent attention by scientists has not yielded identified aspects, levels, or durations of EMF exposure that lead to increased cancer risk. Without any understanding of mechanism, it remains unknown as to what, if any, aspect of EMF exposure should be controlled.


A variety of international scientific “blue-ribbon” panels have reviewed, and continue to review, EMF health effects research. Overall, the absence of robust findings from careful, replicated laboratory studies causes health agencies to be cautious about the reported epidemiological links. The statistical results are suspected to be due to such factors as selection bias and unmeasured or uncontrolled confounding. Scientific guideline-setting committees do not consider the epidemiologic evidence to be adequate for guideline development. No major public-health agency has set guidelines based on distance from power-line rights-of-way. Some agencies have provided guidelines for acceptable, continuous-exposure of the general public to power-line magnetic-field levels, and these values range from about 800 mG to 9,000 mG.


Gradient Corporation reviewed the most current literature on the biological effects of non-ionizing electromagnetic waves using several computerized comprehensive databases that covered international journals literature, books, reports, monographs, government publications and meeting abstracts. We searched the literature for the years 2005 and 2006 (Jan. – Aug.) and retrieved a total of 1,623 potentially relevant references. These references covered a wide range of sources (e.g. power lines, video display terminals, medical devices, cellular phones, etc.) and wide spectrum of frequencies, from static electric and magnetic fields to microwaves. We next limited our search to electric and magnetic fields exclusively from power-line (50 and 60 Hz) sources. This more limited search returned 663 references of which 99 had potential relevance to cancer or leukemia. Even this group had references that were related to use of cellular phones or exposures to industrial radiofrequency, as well as including conference or meeting abstracts, and these were removed. The remaining 62 article abstracts were evaluated for relevance. Additional citations were obtained by searching for authors names that publish in this area (e.g. Greenland, Kheifets, Ahlbom, Feychtig, etc.) and any relevant articles were added to the list. The following pages provide the list of references by topic area, author, year with full citation, and an abstract or detailed summary written by Information Ventures, Inc. (IVI summary), when available.

A total of 44 references were identified as relevant to the current state of knowledge of health effects associated with exposures to extremely low frequency electromagnetic fields (ELF-EMF), 28 from 2005 and 16 from 2006. Of these, 11 are epidemiological or human studies, 5 are animal studies, 16 are in vitro or mechanistic studies, and 12 are review articles.

Two new epidemiological studies have recently been published, a UK study (Draper et al. 2005) and a Japanese study (Kabuto et al. 2006). Using postcode for residence location at birth, Draper et al. found an increased relative risk of leukemia (RR=1.69; 95% CI: 1.13-2.53) for children who lived at birth within 200 meters of high-voltage power lines compared to those who were born >600 m. For those that lived at birth within 200 and 600 m the RR was 1.23 (1.02-1.49). There was a significant trend in risk in relation to the reciprocal of distance to the line (no EMF measurements were made). No excess risk for any other childhood cancer was found to be related to proximity to lines. The results are puzzling because Draper et al. found significant associations at much larger distances from the line than would be expected from any EMF impact. The authors acknowledge that at these distances the average magnetic field exposure would be much less that any residential exposure from other sources. The Kabuto et al. study used weekly mean MF levels determined in a child's bedroom. A total of 312 cases with acute lymphoblastic leukemia (ALL) or acute myelocytic leukemia (AML) and 603 controls matched for gender, age and residential area were analyzed. Results showed that children whose bedrooms had MF levels of 0.4 μT or higher had odds ratios of 2.6 (95% CI = 0.76-8.6) compared with the reference (MF<0.1 μT) for AML + ALL and 4.7 (1.15-19.0) for ALL only.

Both the animal studies and the in vitro/mechanistic studies yielded mixed results. In animals, no genotoxicity was observed in brain cells from exposed rats and mice (McNamee et al., 2005), whereas there was some evidence of DNA damage in rat leukocytes in another study (Yokus, et al., 2005). A large chronic study of high-level EMF exposures found no evidence to support the hypothesis that exposure to magnetic fields is a significant risk factor for hematopoietic diseases (Sommer et al. 2006). Of the in vitro/mechanistic studies, 4 found no effects from MF exposures. Interestingly, one study sought to replicate results from a previous study and was unsuccessful (Scarfi et al. 2005). Ivancsits et al. (2005) found that differential results from different cells exposed to intermittent 50-Hz MFs.

The meaning of the new epidemiological results will need to be evaluated, however, as several of the reviews point out, numerous limitations to epidemiological studies introduce substantial uncertainty. Thus, a spurious association cannot be ruled out. Also, a neither a reproducible animal bioassay system
nor a plausible biological mechanism of action has been found, and the epidemiological results are not supported by scientific evidence in these other areas of investigation.

The following pages list the articles identified for this update and provide summaries or abstracts for the individual articles. (More detailed summaries, designated “IVI” were provided by the Information Ventures, Inc. EMF database.) The 44 articles are identified as follows:

E1 – E11: 11 Epidemiology studies
ER1 – ER9 9 Reviews or analyses of epidemiology
A1 – A5 5 Laboratory animal studies
M1 – M16 16 Mechanistic or in vitro studies
MR1 – MR3 3 Reviews of mechanistic or in vitro studies
Epidemiological/Human Studies

E1: Residential Exposure to Overhead High-Voltage Lines and the Risk of Testicular Cancer: Results of a Population-Based Case-Control Study in Hamburg (Germany).

Baumgardt-Elms, C.; Schumann, M.; Ahrens, W.; Bromen, K.; Stang, A.; Jahn, I.; Stegmaier, C.; Jockel, K. H. Fachabteilung Patientenschutz und Sicherheit in der Medizin, Hamburg Cancer Registry, State Ministry of Sci. and Health, Adolph-Schonfelder-Strasse 5, 22083 Hamburg, Germany, e-mail: Cornelia.Baumgardt-Elms@bwg.hamburg.de (C.B.-E.); Working Group Epidemiology, State Ministry of Science and Health and Inst. for Mathematics and Computer Science in Medicine of Univ. Clinics of Hamburg, Hamburg, Germany (C.S.); Bremen Inst. for Prevention Res. and Social Medicine, Bremen, Germany (W.A., I.J.); Inst. for Medical Informatics, Biometry and Epidemiology, Univ. Clinics of Essen, Essen, Germany (W.E., K.B., A.S., K.H.J.); Saarland Cancer Registry, Saarbrucken, Germany (C.S.)

Int Arch Occup Environ Health 78(1):20-26
2005
Funding: Federal Ministry for Education and Research (BMBF No. 01HP 684/8).

ABSTRACT:
BACKGROUND: In a population-based case-control study we examined the association between residential exposure to overhead high-voltage lines and testicular cancer.

METHODS: We recorded the residential biography of cases with testicular cancer identified by the Hamburg Cancer Registry and of controls that were randomly selected from the mandatory registry of residents in Hamburg. The study included 145 incident cases between 15 and 69 yr of age, diagnosed between 1995 and 1997, and 313 controls, matched for age in 5-yr strata. In model A, exposure was defined by distance (ever vs never). Model B took into account residence time and the inverse distance from the nearest high-voltage line. It distinguished between low and high exposure, the never exposed persons serving as a reference group. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated by unconditional logistic regression. For men below the age of 40 yr and men aged 40 yr and over separate analyses were carried out.

RESULTS: Within a corridor of 100 m the prevalence of exposure to high-voltage lines in Hamburg was 6.9% in cases and 5.8% in controls (OR=1.3; 95% CI=0.56-2.80). In the more complex model B we found an OR of 1.2 (95% CI=0.60-2.47) for low exposure and 1.7 (95% CI=0.91-3.32) for high exposure. Younger men show slightly increased risks in both models.

CONCLUSIONS: In all, residential exposure to high-voltage lines did not seem to be a major risk factor for testicular cancer in our study. Yet, the fact that risks for men below the age of 40 yr were slightly increased in both exposure models deserves further attention.

(44 Refs).

AUTHOR KEY WORDS: Testicular cancer, Electromagnetic fields, EMF, Overhead high-voltage lines, Case-control study
ECG Changes in Humans Exposed to 50 Hz Magnetic Fields.

Borjanovic, S. S.; Jankovic, S. M.; Pejovic, Z.
Inst. of Occupational Health "Dr. Dragomir Karajovic," Deligradska 29, 11000 Belgrade, Serbia and Montenegro, e-mail: drsrle@sezampro.yu (S.S.B., S.M.J.); Occupational Safety and Environmental Protection Co. "Beograd," Serbia and Montenegro (Z.P.)
J Occup Health 47(5):391-396
2005

IVI SUMMARY: The authors examined electrocardiogram (ECG) changes in workers occupationally exposed to 50-Hz magnetic fields (MFs). Fifty-nine males, mean age 41.8 +/- 9.4 yr, who worked at transformer substations of the Municipal Light and Power Utility Company, Belgrade, Serbia and Montenegro were enrolled in the study. All had been exposed to 50-Hz MFs for a minimum of 5 yr as a result of their employment. The mean duration of occupational 50-Hz MF exposure of the group was 17.7 +/- 10.8 yr. Workers were selected from 3 sites based on their expected MF exposures: low, medium, and high. The low exposure group consisted of 20 workers who were primarily employed in constructing new substations and were therefore assumed to have MF exposures comparable to natural background levels. The medium exposure group consisted of 19 workers at a power transformer substation. The high exposure group consisted of 20 workers employed at a second high-voltage power transformer substation. Both substations included 2 sections that handled 35- and 10-kV voltages, stepping them down to 10 kV and 380 V, respectively. Most of the workers were employed on 12-hr shifts. The facilities included dormitory rooms where the workers typically spent an average of 7 hr per night sleeping. MFs at the work sites were monitored using a Wandel-Goltermann EFA-3 instrument with an isotropic probe. Measurements were made at a height of 1.5 m from floor level while the substations were operating at nominal loads. A 12-hr time-weighted average (TWA) exposure computed from the data was used as the exposure metric. ECGs were recorded with workers in resting position at the Occupational Health Center of the Utility Distribution Company, Belgrade during a periodic physical examination. Five parameters were extracted from the ECG data: (1) heart rate, (2) duration of P wave, (3) duration of QRS wave, (4) duration of the PR interval, and (5) duration of the QT interval. The QT intervals were corrected by the Bazett equation to give a corrected value (QTc), as described in Goldman (Definitions of electrocardiographic configurations. In: Principles of clinical electrocardiography. Los Altos: Lange Medical Publications, p. 25-30, 1970). The effect of occupational 50-Hz MF exposure on ECG function was tested statistically by analysis of covariance (ANCOVA) techniques. The estimated 12-hr TWA 50-Hz MF exposures of workers in the low, medium, and high exposure groups were 0.067, 1.18, and 5.2 µT, respectively. The only evidence of an effect of occupational 50-Hz MF exposure on ECG function was a significant smaller QTc interval value seen in workers in the medium exposure group (0.370 +/- 0.025 sec) compared to workers in the low and high exposure groups (0.391 +/- 0.027 and 0.396 +/- 0.022 sec, respectively). This effect was evident also after the QTc values were adjusted for years of MF exposure, the adjusted QTc in the medium exposure group being 0.368 sec vs. 0.388 and 0.392 sec for workers in the low and high exposure groups, respectively. The authors concluded that they have detected a nonlinear effect of occupational 50-Hz MF exposure on one ECG parameter, the adjusted QTc. The adjusted QTc values were similar in the low and medium exposure groups but significantly lower in the medium exposure group, a finding that is not consistent with an expected simple dose-response model in which adjusted QTc values would increase with increasing peak or TWA MF exposures. The authors postulated that the observed nonlinear effect on the adjusted QTc variable may reflect a specific MF exposure pattern that is not captured by using simple averaged metrics such as the TWA exposure.

(12 Refs).
AUTHOR KEY WORDS: ECG, ELF, Power frequency, Magnetic field exposure
E3: Childhood Cancer in Relation to Distance from High Voltage Power Lines in England And Wales: A Case-Control Study.

Draper, G. J.; Vincent, T.; Kroll, M. E.; Swanson, J. Childhood Cancer Res. Group, Univ. of Oxford, Oxford OX2 6HJ, e-mail: gerald.draper@ccrg.ox.ac.uk (G.D., T.V., M.E.K.); Natl. Grid Transco plc, London WC2N 5EH (J.S.)


2005

Funding: United Kingdom Dept. of Health Radiation Protection Programme; Dept. of Health and the Scottish Ministers

IVI SUMMARY: The authors conducted a case-control study to examine a possible association between distance of home address at birth from high-voltage power lines and incidence of leukemia and other cancers in children living in England and Wales. A similar, previously published power line study conducted as part of the UK Childhood Cancer Study (UKCCS) examined possible associations based on the address the child lived in for the longest period in the year prior to diagnosis (Skinner et al., Br J Cancer 83:1573-1580, 2000). Skinner et al. found no significantly increased risks of cancer in a group of 3,380 childhood cancer cases and 3,390 controls, but only 3.8% of the children were living in homes considered "exposed" (located at a distance of 100 m or less from 66- and 132-kV lines and 50 m or less from 11-, 20-, and 33-kV lines). For the present study, nearly 33,000 cases of childhood cancer in children (aged 0-14 yr) born in England and Wales from 1962 to 1995 and diagnosed in England, Wales, or Scotland over the same period were identified from the National Registry of Childhood Tumours at the Childhood Cancer Research Group. Birth information was available for just over 31,000 cases, and complete records, including the grid reference for the address at birth, were obtained for 29,081 children with cancer, including 9,700 with leukemia. Controls were individually matched for sex, approximate date of birth, and birth registration district [control selection method not specified]. No active participation by study subjects was required. Using data on overhead power lines from the National Grid Transco, the authors obtained grid references for 275 and 400 kV overhead lines and a fraction of 132 kV lines, plotting the grid references for 21,800 pylons and 7000 km of lines. Using the postcode for the residence at birth, the authors identified subjects living within 1 km of a transmission line. For most of these addresses (93%), the authors obtained a 0.1 m grid reference from the Ordnance Survey Product, providing precise locations of postal addresses that could be used to calculate the shortest distance to any transmission lines that had existed in the year of birth (recreating previous locations of lines when possible). For calculated distances of less than 50 m, the average of the nearest and furthest points of the building was determined on a large scale map. Children in residences over 600 m from the lines were used as the reference group. The authors were able to match 88% of eligible cases to controls, giving them a relatively high "participation rate" for the study. The authors used conditional logistic regression on the matched case-control pairs to calculate relative risks and chi square values. Relative risk (RR) estimates for leukemia, adjusted for socioeconomic status, were increased for children born in homes within 200 m of an overhead line, RR of 1.69 (95% confidence interval (CI) 1.13-2.53); those born in homes between 200 and 600 m had a relative risk of 1.23 (CI 1.02-1.49). There was a significant (p<0.01) trend in risk in relation to the reciprocal of distance from the line, although the distance trend was not smooth. For example, leukemia RRs in 7 "exposed" categories (relative to the 600 m or more reference group of 9,378 cases and 9,447 controls) was 1.67 for 0-49 m (5 cases, 3 controls), 1.79 for 50-99 m (19 cases, 11 controls), 1.64 for 100-199 m (40 cases, 25 controls), 1.16 for 200-299 m (44 cases, 39 controls), 1.15 for 300-399 m (61 cases, 54 controls), 1.23 for 400-499 m (78 cases, 65 controls), and 1.36 for 500-599 m (75 cases, 56 controls). Chi square values were 8.76 (p=0.003) for ranked distances, 6.72 (p=0.0095) for 1/distance, and 1.47 (p=0.225) for 1/distance squared. The risk of leukemia was also analyzed in bands of 0-199 m and 200-599 m (relative to 600 m or more), and this grouping did not change the pattern of relative risks (RR of 1.69 and 1.23) or the significance of the test for trend (p<0.01). Socioeconomic status, estimated by the Carstairs deprivation index applied to the census ward for each child, confirmed a previously established significant association between affluence and childhood leukemia risk, but adjusting for socioeconomic status had no effect on the relative risks for distance. RRs for CNS/brain tumors and other diagnoses were not significantly increased at any distance. As in the Skinner et al. study conducted in the UK, most residences (97%) were 600 m or more from power lines. The 1,582 cases of leukemia diagnosed from 1992-1996 analyzed for the Skinner et al. (2000) study were mostly included in the 9,700 leukemia cases of the present study, and the non-significant indication of increased risk of acute lymphocytic leukemia associated with living within 400 m of 275 and 400 kV lines (RR of 1.42, CI 0.85-2.37) reported by Skinner et al. is consistent with results of the present study. In general, the
magnitude of the increased risk of childhood leukemia found in a pooled analysis of 6 other major epidemiologic studies (Ahlbom et al., Br J Cancer 83:692-698, 2000), but none of the estimates relates to distances as large as those in the present study (some component studies used reference distances where the authors found an increased risk). The 4 mG average level associated with a significantly increased risk of childhood leukemia in the Ahlborn et al. pooled analysis would correspond to a distance of about 60 m from the lines evaluated in this study, based on calculations performed with a sample of 42 lines using average load characteristics. The authors estimated that average magnetic field levels at 200 m might be as low as 0.1 µT (and in some cases below 0.01 µT), less than the average magnetic fields in homes from other sources. Thus the apparent association between childhood leukemia risk and proximity of home address at birth to high-voltage power lines is consistent with previous studies, but the apparent risk extends to a greater distance than would have been expected based on previous studies. There also may be some effect of using birth address rather than the address at some other time. Approximately half the cases in the present study had the same address at diagnosis as at birth (corresponding information was not available for the control group). About 4% of children in England and Wales live within 600 m of high-voltage lines at birth. If the association is causal, about 1% of childhood leukemia cases occurring annually in England and Wales (about 5 of the 400-420 cases of childhood leukemia) would be attributable to this exposure, although this estimate has considerable statistical uncertainty. The authors note that there is no accepted biological mechanism to explain the epidemiologic results, and suggest that it is possible the relationship may be due to chance or confounding. (15 Refs).
ABSTRACT:
OBJECTIVE: To investigate cause-specific mortality in a population exposed to high levels of 50 Hz magnetic fields, in a district of Rome.

DESIGN: A cohort of 357 subjects that are resident in an area of about 100 meters on the two sides of a 60 kV power line was studied. Exposure to 50 Hz magnetic fields was evaluated by spot and long-term measurements and by adopting a model based on current load, characteristics of the line and distance of dwellings from conductors. The mortality experience of the cohort was observed from January 1st, 1980 through December 31st, 2003. Analysis took into account duration of residence and latency. Separate analyses were performed for three subcohorts characterized by different distances from the line and different estimated and measured field levels.

MAIN OUTCOMES: Cause-specific standardized mortality ratios (SMRs) were computed comparing the observed number of deaths with the corresponding expected figures derived from the Latium Region mortality rates. This was done both in the overall cohort and in the subcohorts.

RESULTS: All-causes mortality of the cohort did not differ from expected values (SMR 0.99; 95% CI 0.73-1.35; 40 observed). All cancers mortality showed a non-significant increase (SMR 1.34; 95% CI 0.82-2.18; 16 observed), that reached statistical significance in the analyses limited to subjects with more than 30 years of residence (SMR 2.09; 95% CI 1.05-4.19; 8 observed). Mortality from lymphohaematopoietic malignancies was increased, based on two cases of leukemia. All cancers mortality was highest in the subcohort closest to the power line and exposed to highest levels of magnetic fields. An increased risk for digestive tract neoplasms (SMR 3.57; 95% CI 1.49-8.58; 5 observed) was observed, which was mainly caused by pancreatic cancer.

DISCUSSION AND CONCLUSION: Some increase in mortality of the overall cohort and especially of the highly exposed sub cohort was detected, notwithstanding the low power of the study. Other studies are currently on-going in the same area: a cross-sectional investigation on health status, an analysis of hospital discharge cards, a project for estimating individual exposure levels and a research in veterinary epidemiology. It is recommended to replicate the present study in areas presenting similar exposure patterns, in order to be able to pool data with the aim of estimating risk associated with the exposure levels of interest.

Forssen, U. M.; Rutqvist, L. E.; Ahlbom, A.; Feychting, M.
Inst. of Environmental Medicine, Karolinska Institutet, P.O. Box 210, SE-171 77 Stockholm, Sweden, e-mail: ulla.forssen@imm.ki.se (U.M.F., A.A., M.F.); Dept. of Medicine, Huddinge Univ. Hosp., Karolinska Institutet, Stockholm, Sweden (L.E.R.); Div. of Epidemiology, Stockholm Center of Public Health, Stockholm, Sweden (A.A.)
Am J Epidemiol 161(3):250-259
2005
Funding: Swedish Council for Working Life and Social Res.

IVI SUMMARY: The authors conducted a register-based case-control study of occupational magnetic field (MF) exposure and female breast cancer risk using a job exposure matrix (JEM) for women. The study base consisted of a cohort of all women who were gainfully employed in Stockholm and Gotland county, Sweden, between 1976 and 1999, as identified from censuses performed from 1960 to 1990. The subjects entered the cohort either in 1976 or on their 15th birthday, which ever came first, and were followed through 1999 or to the time of breast cancer diagnosis, if that came before 1999. All cases of breast cancer in the cohort were identified through linkage to the Regional Cancer Registry in Stockholm. This process identified 20,400 cases of breast cancer, who were matched to 116,227 randomly selected controls from the cohort according to year of the cases’ diagnosis (referent year). MF exposures were assessed by linkage of the cases and controls to a newly developed JEM, described by Forssen et al. (Occup Environ Med 61:594-602, 2004). The JEM included 49 of the most common occupations held by women in Stockholm County and covered about 85% of all gainfully employed women according to the 1980 census. MF exposure estimates in the JEM were collected by volunteer women (5 to 24 subjects for each occupation) who wore EMDEX Lite meters (Enertech Consultants, Campbell, CA) on a belt by their hip for 24 hr. During the measurement periods, subjects kept a diary of their movements, from which data on time spent at work could be extracted. The EMDEX Lite meters recorded MF exposure data every 4th second. The time-weighted average MF, maximum MF (TWA max), a short-term rate-of-change (RC) metric (calculated from differences in successive MF measurements), and the proportion of a workday exposed to MFs exceeding 0.3 µT (3 mG) were computed from the EMDEX data. To reduce the influence of individual extreme values, the geometric mean (GM) and median were used when summing the TWA max, RC, and time spent above 0.30 µT over occupations. MF exposures described as the GM of the TWA max were divided into 4 categories: <0.10 µT, 0.10-0.19 µT, 0.20-0.29 µT, and 0.30 µT or greater. MF exposures at the last census that provided information on occupation were examined, based on the assumption that MFs act as a tumor promoter. Exposures occurring at least 10 yr before the referent yr and before the age of 35 yr were also investigated. The study period was also split into 2 parts to evaluate exposures before and after 1985. The year 1985 was chosen for this because this was the census year that most closely split the study period in half. Ever vs. never being exposed was defined as ever holding an occupation that had MF exposures of 0.30 µT or greater, compared with never being employed in an occupation having a MF exposure of more than 0.10 µT. Possible time window effects were also examined by evaluating the effect of being exposed to MFs of 0.30 µT or greater in at least 2, 3, or 4 consecutive censuses occurring before the referent yr. A sensitivity analysis was also performed to reduce the potential for misclassifying exposures caused by variations in exposure within an occupation. For this, an occupation was considered to have low MF exposure if the median of the measurements within that occupation was 0.10 µT or less, and the 3rd exposure quartile was lower than 0.17 µT. An occupation with high MF exposure was defined as a high exposure occupation if the median exposure was 0.25 µT or more and the first quartile was greater than 0.17 µT. This categorization served to increase the exposure contrast between occupations. For maximum values, cutoff points were 1.5, 2, and 3.5 µT. For the RC metric, 0.05 µT/4 sec, 0.07 µT/4sec, and 0.12 µT/4 sec were used. These cutoff points corresponded to the 10th, 50th, and 90th percentiles of the distribution among the controls. The proportion of time spent above 0.3 µT was analyzed using cutoff points following the 10th, 50th, 90th, and 95th percentiles, which represented 6, 10, 35, and 40% of the workday. Associations between various MF exposure metrics and breast cancer risk were assessed by logistic regression models in SAS version 8.2 software (SAS Institute, Inc., Cary, NC). Risk estimates, presented as odds ratios (ORs) and their 95% confidence intervals (CIs), were adjusted for potential confounding by socioeconomic status, age, referent yr, number of children, and age at first birth. Data on these parameters were obtained from the censuses, and from the multigeneration registry operated by Statistics Sweden. All ORs were close to unity regardless of exposure cutpoint or choice of MF exposure metric. For example, for all cases of breast cancer occurring in women
with GM exposures of 0.10-0.19, 0.20-0.29, and 0.30 µT or greater, the ORs adjusted for age, socioeconomic status, and referent yr were 1.01 (CI 0.96-1.06), 1.00 (CI 0.94-1.06), and 1.01 (CI 0.93-1.10), respectively. Data on estrogen receptor status of the tumor were available for about 64% of the cases. Risk estimates showed only minor differences for women diagnosed before age 50 yr or after, or having estrogen-positive or negative breast cancers. For example, in the highest exposure category (0.3 µT or more), the adjusted OR for postmenopausal women with estrogen-positive tumors was 1.01 (CI 0.88-1.16) while for premenopausal women it was 0.94 (CI 0.72-1.23). For estrogen-negative breast cancers, the corresponding ORs were 0.94 (CI 0.72-1.22) and 1.11 (CI 0.77-1.61). Comparison using occupations with extreme exposure contrast gave similar results. Having an occupation with exposures of 0.30 µT or more in at least 4 consecutive censuses prior to the referent yr (which corresponded to 15-20 yr of exposure) was associated with an adjusted OR of 1.05 (CI 0.81-1.37). No associations were found for MF exposures assessed as the RC metric or extreme values. The authors concluded that this study provide no evidence that women working in occupations with high MF exposures are at increased risk of breast cancer. The size of the study population also allowed for risk estimates with good precision in subgroups where previous studies have suggested an increased risk. The authors' previous study of occupational and residential EMF exposure and breast cancer risk (Forssen et al., Epidemiology 11:24-29, 2000) found a statistically insignificant but suggestive breast cancer risk increase in highly exposed premenopausal women with estrogen receptor-positive tumors using a job-exposure matrix based on measurements performed on male workers. In the present study, based a new job-exposure matrix measuring exposures of female workers, no evidence was found to support the hypothesis that MFs influence the risk of female breast cancer. This suggests that the previous indication of an elevated risk was most likely caused by random variation.

(29 Refs).

AUTHOR KEY WORDS: Breast neoplasms, Case-control studies, Electromagnetic Fields, Female, Receptors, Estrogen
E6:
Residential and Occupational Exposure to 50-Hz Magnetic Fields and Brain Tumours in Norway: A Population-Based Study.

Klaeboe, L.; Blaasaas, K. G.; Haldorsen, T.; Tynes, T.
The Cancer Registry of Norway, Montebello., Oslo, N-0310 Norway, e-mail: lars.klaeboe@kreftregisteret.no (L.K., T.H., T.T.); Norwegian Armed Forces Joint Medical Services, Osteras, Norway (K.G.B.); Norwegian Radiation Protection Authority, Osteras, Norway (T.T.)
*Int J Cancer* 115(1):137-141 2005
Funding: Res. Council of Norway

IVI SUMMARY: The authors examined associations between residential and occupational exposure to 50-Hz magnetic fields (MFs) and brain tumor incidence among Norwegian residents. The study was a population-based nested case-control study of the same cohort that was utilized in a previous study (Kliukiene et al., *Am J Epidemiol* 159:852-861, 2004) that examined associations between MF exposure and breast cancer. The cohort consisted of all adults (16 yr of age or older) who lived in a defined corridor around a high-voltage power line in Norway on November 1, 1980 or on January 1 of at least one of the years between 1986 and 1996. The width of the corridors varied from 40 m for 33-kV power lines to 300 m for 420-kV power lines. Cohort members were identified from records of Statistics Norway. Persons were included in the cohort the first yr they were registered as living within the corridors. The corridors around power lines were established using geographic information systems, and were chosen to be wide enough to include both exposed and unexposed residences. The Norwegian Mapping Authority provided coordinates of every residence linked to its address, and the Norwegian Water Resources and Energy Directorate provided coordinates of all power lines. Cases were identified by linking the cohort to the Norwegian Cancer Registry to identify all persons in whom brain tumors were diagnosed between January 1, 1980 and December 31, 1996. For each case, 2 matched controls were selected at random from the cohort. The controls were alive, free of brain tumor at the time of diagnosis of the case, and entered the cohort at the same time as the case. The controls were matched to the cases by age (+/- 5 yr), sex, and municipality of residence at the first time of entry into the cohort. This process yielded 454 cases and 908 controls. Fifty-one percent of both cases and controls were males. Residential histories of the subjects were obtained from Statistics Norway. Residential exposure to MFs was defined in terms of calculated values of MFs generated by power lines close to residences within a corridor. Statistics Norway provided residential information for cases and controls as far back as 1967, allowing exposure calculations from then to the year of diagnosis. Calculations of the MFs were performed using a computer program (Teslaw) developed at SINTEF Energy (Trondheim, Norway). The calculations took into account the height of the towers, the distance between phases, the ordering of phases, the distance between the power line and a house, and the average load on the power line during each year that a subject lived in the residence. Distance of a house to a power line was specifically defined as the distance from the inner corner of the house to the midpoint between the outer phases of the line. Underground cables were not taken into account because they were not considered significant sources of MFs. Changes in the configuration of the power lines were also taken into account. The period of time that a subject lived near a power line was calculated by combining his/her residential history with the year that the power line was built. Time-weighted average (TWA) residential MF exposures were used as the exposure metric and categorized by using cut points of 0.05 and 0.2 µT. TWA exposures used in the analyses were from 1 January, 1967 to the time of diagnosis and for the last 5 yr before diagnosis. Occupational MF exposures of cases and controls were assessed a priori using a method based on the expert judgment method described by Flynn et al. (*Appl Occup Environ Hyg* 6:141-145, 1991). Jobs were assigned a rank if they were judged to involve an exposure that was above the above background level (0.1 µT): a rank of 1 if the exposure was less than 4 hr/wk, a rank of 2 for exposures of 4 to 24 hr/wk, and a rank of 3 for exposures of greater than 24 hr/wk. Jobs were classified on the basis of occupational codes used in the 1960, 1970, 1980, and 1990 Norwegian censuses. Exposure follow-up was from January 1, 1955 to the date of diagnosis, and the potentially occupationally active period was defined as the age interval of 18-67 yr. Exposure categories were cumulated and multiplied by the number of years. For subjects who changed jobs between 2 censuses, the first job was cumulated until the midpoint between the 2 relevant censuses. The first and third quartiles in the controls, used as cutoff points, were 18 and 31 category-yr, respectively. For estimates of combined residential and occupational exposure, 3 exposure categories were used: residential exposure only, occupational exposure only, and residential plus occupational exposure. Only subjects who had information on exposures both at home and at work were included in this analysis. Subjects were considered not to be exposed if their residential exposure was less than 0.05 µT and their concomitant occupational
exposure was less than 18 category-yr. Subjects were considered to be highly exposed if their residential exposure was 0.2 µT or greater and their concomitant occupational exposure was 31 category-yr or greater. Educational level was coded as 1 = primary school, 2 = secondary school, and 3 = university or research degree, using information collected from the census closest in time to the yr of diagnosis. Type of residence was coded as either a single family home or apartment. Associations between MF exposure and brain tumor risk were assessed by computing odds ratios (ORs) utilizing conditional logistic regression models. The 2 upper residential TWA exposure categories (0.05-0.19 µT, and 0.20 µT or greater) showed elevated unadjusted ORs for all brain tumors combined of 1.6 (95% confidence interval (CI) 0.9-2.7) and 1.3 (CI 0.7-2.3), respectively. These ORs were only slightly altered by adjusting for educational level and type of residence; consequently, only unadjusted ORs were presented for the remaining analyses. Elevated ORs were seen for some tumor subtypes. For example, ORs for residential exposures of 0.05-0.19 µT and 0.20 µT or greater were associated with histologically verified meningioma risks of 3.0 (1.0-9.2, based on 8 cases) and 1.2 (CI 0.4-4.2, based on 4 cases), respectively. ORs were also elevated for MF exposures during the last 5 yr before diagnosis. For all brain tumors combined, exposures to 0.05-0.19 µT and 0.20 or greater µT yielded ORs of 1.3 (CI 0.7-2.2) and 1.6 (CI 1.0-2.5), respectively. No significant linear trends were observed for MF exposures during the entire follow-up period or for the last 5 yr before diagnosis. Analysis of continuous TWA residential MF exposures showed an increase in OR per µT of 1.0 (CI 0.6-1.7) for all brain tumors combined, and an OR per µT of 1.3 (CI 1.0-1.6) for the last 5 yr before diagnosis. Occupational MF exposure alone was not associated with brain tumor risk. An inverse association was actually observed for all brain tumors combined, the ORs being 0.8 (CI 0.5-1.2) for 18 to 30 category-yr and 0.6 (CI 0.3-9) for 31 category-yr or greater using the nonexposure (<18 category-yr) category as the reference. Combined high MF exposure both at home and at work was associated with an OR for all brain tumors combined of 1.0 (CI 0.4-27). The authors concluded that the main finding of this study was a moderately elevated brain tumor risk for residential exposure to MFs, evaluated as TWA exposures. The elevated risk was not statistically significant and showed no clear exposure-response pattern. The data, therefore, provide no clear evidence of an association between residential MF exposures and brain tumor risk. The results of the residential analysis are not consistent with the findings for occupational exposure, in which an inverse association was found. (26 Refs).

AUTHOR KEY WORDS: Electromagnetic fields, Brain tumor, Case-control study, Residential and occupational exposure
ABSTRACT:
OBJECTIVE: To examine mortality from cancer and non-malignant causes among a large cohort of UK electricity generation and transmission workers.

METHODS: The mortality experienced by a cohort of 83,923 employees of the former Central Electricity Generating Board of England and Wales was investigated for the period 1973-2002. All employees had worked for at least 6 months with some employment between 1973 and 1982. Standardized mortality ratios (SMRs) were used to assess mortality in the total cohort and in three sub-cohorts: power station workers, substation and transmission workers and workers at non-operational locations. These classifications were based on the place of work of the first known job.

RESULTS: Overall mortality was significantly below that expected, based on national rates [males: observed (Obs) 18,773, expected (Exp) 22,497.9, SMR 83; females: Obs 1122, Exp 1424.9, SMR 79]. Statistically significant deficits of deaths were also found for most of the major disease groupings. However, significant excesses of deaths were found in male power station workers for cancer of the pleura (Obs 129, Exp 30.3, SMR 426) and in male workers from non-operational locations for cancer of the brain (Obs 55, Exp 36.0, SMR 153). There was also a non-significant excess of deaths from cancer of the breast in male power station workers (Obs 10, Exp 5.3, SMR 190).

CONCLUSIONS: Mortality was exceptionally low for most causes of death but late health effects from earlier asbestos exposure were still in evidence.
E8: Clinical Study of Interference with Cardiac Pacemakers by a Magnetic Field at Power Line Frequencies.

Trigano, A.; Blandeau, O.; Souques, M.; Gernez, J. P.; Magne, I.
Dept. of Cardiology, Centre Hospitalier Universitaire Nord, 13915 cedex 20, Marseille, France, e-mail: alexandre.trigano@mail.ap-hm.fr (A.T., O.B.); Dept. of Medical Studies, Electricite de France EDF-Gaz de France, Paris (M.S.); Electricite de France Res. and Development, Electrical Laboratories, Electromagnetic Compatibility Group, Moret-sur-Loing, France (J.P.G., I.M.)

*J Am Coll Cardiol* 45(6):896-900 2005

Funding: Le Reseau de Transport de l'Electricite and Electricite de France, Dept. of Medical Studies, Paris, France

**IVI SUMMARY:** The authors performed a clinical study of the potential electromagnetic interference (EMI) risk from power-frequency magnetic fields (MFs) for patients with implanted cardiac pacemakers. A total of 250 tests were performed on 245 patients, 151 males, mean age 72.2 +/- 10.6 yr, who were undergoing routine ambulatory pacemaker follow-up at La Pitie-Salpetriere Hospital, University of Paris, France were included in the study. They had been implanted with a wide variety of pacemaker models, manufactured by Biotronik (6 tests, 4 models), Ela Medica (56 tests, 9 models), Guidant (43 tests, 5 models), Intermedics (4 tests, 3 models), Medtronic (67 tests, 19 models), Pacesetter (5 tests, 3 models), St. Jude (47 tests, 6 models), Sorin (5 tests, 4 models), Telecommunications (1 test), and Vitatron (16 tests, 6 models). The patients were exposed to a 50-Hz MF by walking through a gated system consisting of a pair of rectangular 120 x 140-cm Helmholtz coils spaced 80 cm apart mounted at chest level. The coils were energized by a programmable AC generator (model 6530, Chroma, Taipei-Hsien, Taiwan). Each coil consisted of 29 wires (turns) having a cross-sectional area of 1.53 mm². The strength of the MF in the exposure space was calculated using EFC 400 software (Wandel & Goltermann, Eningen, Germany). Field strength, calculated as the total flux density divided by the cross sectional area of the exposure volume, was monitored by a sensor attached to one of the gates at the level of the patient's chest. Ambient MFs in the room were measured by a 3-axis detector placed 3 m away from the system. The maximum flux density of the MF, measured at the center of the exposure volume where the field was homogeneous, was 100 µT (1 G). The electric field between the gates did not exceed 0.10 V/m. Each patient was instructed to walk through the system at a normal pace, once parallel and once perpendicular to the gates, then to stand for at least 20 sec inside the system. Three corresponding control measurements with the gate system deactivated were also obtained for each patient. Pacemaker function was assessed by monitoring the patients with a 12-lead electrocardiogram (ECG) using an independent computer-based ECG with an optical fiber connection, to ensure complete isolation of the patients from the computer. ECG recordings that were free of motion or 50-Hz artifacts were taken for analysis. In case of EMI, the MF produced by the system was ramped up and down to identify the lowest flux density causing the interference. Each pulse generator was interrogated after the tests. A total of 250 tests were performed because 5 patients had a second test after the pulse generator was replaced due to a depleted battery. EMI was detected in 4 of the 250 tests (1.6%). A switch to the asynchronous mode was recorded in 3 patients with pacemakers programmed to unipolar sensing (a Medtronic 731, Medtronic 7960, and a Guidant 1280 model). A sustained mode switch followed by symptomatic pacing inhibition was recorded in another patient implanted with a Medtronic 7960 pacemaker. The lowest flux density causing the interference was 45 µT. No interference was seen in 153 tests of pacemakers programmed for bipolar sensing, except for a single interaction with a specific capture monitoring algorithm detected in a St. Jude model 5376 unit. No pacemaker reprogramming was detected in any test. The authors concluded that the overall incidence of EMI induced by a power-frequency MF was very low in patients implanted with a wide range of conventionally programmed pacemaker models. Power-frequency MFs can cause a mode switch and pacing inhibition in patients with pacemakers programmed for unipolar sensing, but the risk appears negligible in patients with pacemakers programmed for bipolar sensing.

(7 Refs).
Magnetic Field Exposure and Long-Term Survival among Children with Leukaemia.

Foliart, D. E.; Pollock, B. H.; Mezri, G.; Iriye, R.; Silva, J. M.; Ebi, K. L.; Kheifets, L.; Link, M. P.; Kavet, R. Public Health Inst., 555 12th St, Oakland, CA 94607 (D.E.F.); 3470 Buskirk Ave, Pleasant Hill, CA 94523, e-mail: dfoliart@hospice.org (D.E.F.); Center for Epidemiology and Biostatistics, Univ. of Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, TX 78229 (B.H.P.); EPRI, 3412 Hillview Ave., Palo Alto, CA 94304 (G.M., R.K.); Enertech Consultants, 300 Orchard City Drive, Suite 132, Campbell, CA 95008 (R.I., J.M.S.); Exponent Health Sciences Group, 1800 Diagonal Rd., Suite 300, Alexandria, VA 22314 (K.L.E.); Dept. of Epidemiology, Sch. of Public Health, Univ. of California, Los Angeles, 650 Charles E Young Dr. South, Los Angeles, CA 90095 (L.K.); Dept. of Pediatrics, Stanford Univ. Sch. of Medicine, 300 Pasteur Dr., Stanford, CA 94305 (M.P.L.)

2006
Funding: EPRI; Electricite de France (EDF)

IVI SUMMARY: The authors examined associations between magnetic field (MF) exposure and long-term survival among children with leukemia. The purpose of the study was to test the hypothesis that, assuming that environmental exposure to MFs influences leukemia blast cells following tumor initiation, this should produce detectable effects on disease relapse and survival in newly diagnosed acute lymphoblastic leukemia (ALL) cases. A total of 482 children with ALL who were being treated under the auspices of the Pediatric Oncology Group (POG), a National Cancer Institute (NCI) sponsored consortium that represents approximately half of centers treating childhood cancer in North America, were recruited for the study. Recruited subjects met the following inclusion criteria: (1) diagnosed with B-precursor, T-cell, or B-cell ALL within the previous 12 wk, (2) 1-15 yr old, (3) enrolled in a POG treatment protocol at a participating center, and (4) had an adult family member who spoke English, Spanish, or French. Patients were issued EMDEX Lite meters to measure environmental MF exposures after receiving initial therapy, typically 4 wk after enrollment at a POG center, and while they were undergoing "consolidation" (intensified) therapy as an outpatient. The EMDEX meters, which had pictorial and written instructions (in English, Spanish, or French) were sent to the patients' families by mail and returned by mail. Personal, 24-hr MF exposures were monitored prospectively, with the first measurement taken shortly after enrollment, and later measurements taken at the beginning of the second and third years after enrollment using the protocol described by Foliart et al. (J Expo Anal Environ Epidemiol 12:441-447, 2002; Bioelectromagnetics 22:574-580, 2001). The study design involved having subject families make measurements and send back the EMDEX meters, but a substantial number of subjects found the magnetic field measurements too difficult to make. A higher percentage than expected (8% in the first year) lost or failed to return their meter, while another 5% (in the first year) returned the meter with invalid or no data recorded. This was attributed to the family stress and disruption that resulted from having a child diagnosed with leukemia. The number of patients who completed the monitoring protocol and returned EMDEX meters with usable data decreased over time. A total of 412 children completed the first monitoring, 304 completed the second monitoring, and 134 completed the third monitoring. Because mean time-weighted average (TWA, 0.11-0.13 µT) and geometric mean (GM, 0.073-0.082 µT) MF exposures were similar across the 3 monitoring years, and because of limited numbers of second and third measurements, only MF exposure data for first-year 24-hr monitoring periods were analyzed for this study. At the time of diagnosis, all children provided blood and bone marrow samples for cytogenetic analyses. For the most common immunophenotype (B-precursor ALL), children were enrolled in 1 of 3 POG protocols based on prognostic factors at diagnosis predicting low, standard, or high risk of treatment failure, as described by Borowitz et al. (Cancer Res 131:257-267, 1993). For children with B-precursor ALL enrolled before 2000, NCI risk group criteria were used to determine their risk status based on initial white blood cell counts and age at diagnosis, as described by Smith et al. (J Clin Oncol (letter) 15:680-681, 1996). In 2000, DNA Index and the presence of trisomies 4 and 10 were added to the risk stratification. The primary study outcome was event-free survival, assessed in 386 children with ALL and 361 with B-precursor ALL, in children identified from September 1996 to January 2001 and tracked through December 2004. Event-free survival was defined as the elapsed time from diagnosis to the date of last contact or to any of the following events: (1) failure to obtain a complete remission after induction therapy, (2) leukemia relapse, (3) development of a secondary malignancy, or (4) death from any cause. Kaplan-Meier statistics with log rank tests were used to examine associations between TWA MF exposure, stratified as <0.1, 0.1-0.19, 0.2-0.29, >0.3 µT), and outcome. Removal of a subject because of a bone marrow transplant was considered a censoring event. Multivariate analyses were conducted using the Cox proportional hazards technique to assess associations between MF exposure and outcome and covariates such as NCI risk group,
race/ethnicity, immunophenotype, and socioeconomic status (SES). Low SES was defined as annual family income <$40,000 and both parents with less than a college degree. Secondary regression analyses included assessments of clinical and cytogenetic covariates such as DNA index, platelet counts at diagnosis, evidence of central nervous system involvement at time of diagnosis, and trisomies 4 and 10, trisomy 21, and trisomy 8. Of 1672 potentially eligible children under treatment, 482 (29%) participated and personal 24-hr MF measurements were obtained from 412 participants. A total of 386 children with ALL and 361 with B-precursor ALL were included in the analysis of event-free survival and overall survival. Of the 386 children with ALL included in the analysis, 71% were less than 6 yr old, and boys slightly outnumbered girls (52 vs. 48%). Most children were white (72%) and 41% were classified as having low SES. The distribution by race/ethnicity was somewhat distorted among participants: 72% white children in the cohort vs. 61% in potentially eligible, 15% Hispanic children in the cohort vs. 21% in potentially eligible, and 7% African-American children in the cohort vs. 9% in potentially eligible. The initial MF monitoring session was completed within 2 mo following diagnosis for 48% of participants, and within 4 mo following diagnosis for 86%. The overall mean TWA MF exposure was 0.1 μT with a 95% percentile value of 0.3 μT. Only 19 children (5%) had a TWA exposure of 0.3 μT or greater. Fourteen children (4%) had a GM exposure of 0.3 μT or greater. A higher percentage of nonwhite than white children had TWA exposures of 0.3 μT or greater, 7.3 vs. 4.1% (odds ratio (OR) and 95% confidence interval (CI) of 1.8 (CI 0.70-4.77). The mean duration of follow-up was 5.07 yr. Seventy-three failure events occurred among all children, and 70 events occurred among the 361 children with B-precursor ALL. A total of 30 deaths occurred, of which 28 occurred among children with B-precursor ALL. In only 1 child was death the first failure event. For the other 29 deaths, the initial failure event was relapse in 25 and secondary malignancy in 4. Five failures were reported for children in the highest exposure group (0.3 μT or greater), 4 due to relapse and one due to secondary malignancy, and there were 4 deaths. Because of the small numbers, relationships between non-B-cell precursor ALL and MF exposure and survival were not analyzed. For event-free survival, Kaplan-Meier statistics and Cox proportional hazards analysis showed significant decreases in event-free survival for children with TWA or GM MF exposures of 0.3 μT or greater (log rank test p=0.054). Cox proportional hazards ratios (HRs) were calculated for TWA MF exposures. HRs were increased for children with B-cell precursor in the highest exposure category (0.3 μT or greater) for event-free survival in univariate analyses, HR = 1.66 (CI 0.66-4.18). In multivariate analysis, after adjusting for age at diagnosis, initial white blood cell counts, and SES, the event-free survival HR for children with B-cell precursor ALL in the highest TWA exposure category was 1.92 (CI 0.75-4.90). For overall survival, HRs were significantly elevated among children exposed at 0.3 μT or greater in both univariate and multivariate analyses, with OR of 3.39 (CI 1.14-10.06) and 4.53 (CI 1.49-13.76), based on 4 deaths. In the multivariate analysis, a marginal statistically significant trend (p=0.06) was seen between increasing TWA exposure category and deaths, although the number of deaths was small. Children in the higher NCI risk group were at an increased risk of poor outcome for both event-free and total survival. SES was not associated with outcome. No first order interaction terms were observed for the clinical or cytogenetic covariates. The authors concluded that these results indicate poorer survival among children with ALL exposed to higher levels of environmental MFs (0.3 μT or greater). However, clinical inferences are limited due to the small number of deaths, with results possibly being due to chance alone. The study was further limited by a small portion of the cohort who were in the highest TWA MF exposure category of 0.3 μT or greater (5% or 19 children); the low participation rate (a third of potentially eligible children); and usable measurement data only for the first year, which would provide inaccurate measurements for the 12% of children who moved during the extended follow-up period. Independent confirmation of the results is needed. Since this study was the first to look at relapse and survival, the results should be regarded only as hypothesis generating. (17 Refs).

AUTHOR KEY WORDS: Electromagnetic fields, Leukemia, Lymphoblastic leukemia, Acute childhood leukemia
Childhood Leukemia and Magnetic Fields in Japan: A Case-Control Study of Childhood Leukemia and Residential Power-Frequency Magnetic Fields in Japan

National Institute for Environmental Studies, Ibaraki, Japan. kabuto@nies.go.jp


2006

Funding: Special Coordination Funds for Promoting Science and Technology from the Ministry of Education, Culture, Sports, Science and Technology for 1999-2001

ABSTRACT: Residential power-frequency magnetic fields (MFs) were labeled as a possible human carcinogen by the International Agency for Research on Cancer panel. In response to great public concern, the World Health Organization urged that further epidemiologic studies be conducted in high-exposure areas such as Japan. We conducted a population-based case-control study, which covered areas inhabited by 54% of Japanese children. We analyzed 312 case children (0-15 years old) newly diagnosed with acute lymphoblastic leukemia (ALL) or acute myelocytic leukemia (AML) in 1999-2001 (2.3 years) and 603 controls matched for gender, age and residential area. Weekly mean MF level was determined for the child's bedroom. MF measurements in each set of a case and controls were carried out as closely in time as possible to control for seasonal variation. We evaluated the association using conditional logistic regression models. The odds ratios for children whose bedrooms had MF levels of 0.4 μT or higher compared with the reference category (MF levels below 0.1 μT) was 2.6 (95% CI = 0.76-8.6) for AML + ALL and 4.7 (1.15-19.0) for ALL only. Controlling for some possible confounding factors did not alter the results appreciably. Even an analysis in which selection bias was maximized did not fully explain the association. Most of the leukemia cases in the highest exposure category had MF levels far above 0.4 μT. Our results provided additional evidence that high MF exposure was associated with a higher risk of childhood leukemia, particularly of ALL.

AUTHOR KEY WORDS: residential magnetic fields, childhood leukemia, population-based, case-control study, Japan
E11:  
Individual Subject Sensitivity to Extremely Low Frequency Magnetic Fields.

Legros, A.; Beuter, A.  
Lawson Health Res. Inst., Dept. of Imaging, St. Joseph's Health Care, 268 Grosvenor St., London, Ont., Canada N6A 4V2, e-mail: alegros@lawsonimaging.ca (A.L.); Institut de Cognitique, Universite Victor Segalen Bordeaux 2, 146 Rue Leo Saignat, 33076 Bordeaux Cedex, France  
Neurotoxicology 27(4):534-546  
2006  
Funding: Hydro-Quebec

ABSTRACT: It is becoming important to specify the smallest effects of extremely low frequency (ELF) magnetic fields (MF) on human physiology. One difficulty is that some people seem more sensitive and more responsive than others to MF exposure. Consequently, within- and between-subject differences have to be taken into account when evaluating these effects. As shown in previous work, human postural tremor is sensitive to MF exposure. But data about individual responses have not been examined in detail. Thus, postural tremor of 24 subjects was evaluated under ELF MF "on" and "off" conditions in a double-blind real/sham exposure protocol. The direction of the tremor changes was analyzed individually for three tremor characteristics. Results showed that subjects with high amplitude tremor seem to be more responsive to MF exposure. MF had an instantaneous effect (between "on" and "off" conditions) and also a more delayed and persistent one (between real and sham conditions), but differences were small. Moreover, due to the within- and between-subject variability, no statistical analysis could be done. However, these results do not show any potentially harmful effect of domestic or industrial 50 Hz MF on humans. They provide a starting point to orient future studies and should be taken into account in the establishment of new exposure limits.  
(37 Refs).  
AUTHOR KEY WORDS: Postural tremor, ELF, Magnetic field, Individual differences
IVI SUMMARY: The authors presented an extensive review of epidemiologic research on the health effects of electromagnetic fields (EMFs) of various types. The review was organized into 3 major sections that covered epidemiologic studies investigating health effects of: (1) static magnetic fields (SMFs), (2) extremely low frequency (ELF) EMFs, and (3) radiofrequency (RF) fields. Each of the 3 sections were divided further into subsections that covered the topics: (1) sources of exposure to the fields, (2) general summary of the epidemiologic data, (3) epidemiologic studies investigating cancer, (4) epidemiologic studies investigating other (non-cancer) health outcomes, (5) limitations of the studies, (6) general summary of major reviews of health effects of the fields of interest, and (7) research needs. Typical sources of SMF exposure include employment in industries such as aluminum production and chloralkali plants in which workers are exposed to fields on the order of 4-50 mT (40-500 G), certain welding processes, and employment on electrified train systems operating from DC power supplies. Power sources for new train technology, such as magnetic levitation (MAGLEV) trains will be an important source of exposure when trains become operating in the future. Magnetic resonance imaging (MRI) systems used for diagnosis expose patients to field strengths as high as 2.5 T (25 kG), and new MRI machine are under development that will produce considerably higher exposures. MRI operators are occupationally exposed to SMFs up to about 5 mT. Acute effects of SMFs, such as nausea, vertigo, and visual phosphenes, can be induced while moving in fields stronger than about 2 T, while acute effects at field strengths below 2 T have not been reported. Few experimental animal or epidemiologic studies have investigated the long-term effects of exposure to SMFs, and therefore few reviews have included this type of exposure in their assessments. Most existing epidemiologic studies have focused on cancer risks. Most studies investigating cancer risks among aluminum production or chloralkali workers have focused on exposures other than SMFs, such as to polycyclic aromatic hydrocarbons, mercury, and asbestos, and consequently have poor, if any, assessment of exposures to SMFs. Results of these studies are inconsistent, reporting no pattern of cancer that could be clearly associated with exposure to SMFs. The situation is also complicated by the fact that aluminum and chloralkali workers are also exposed to time-varying MFs (mostly 50-100 Hz, 0.3-10 µT). There are a large number of studies on cancer risks among welders. None of these studies, however, estimated exposures of welders to SMFs, precluding an ability to distinguish between effects caused by welding fumes, SMFs, ELF EMFs, or RF fields. A few studies have examined EMF effects on reproductive outcomes among aluminum workers and MRI operators, but limitations in study design prevent any conclusions from being drawn. An evaluation made by the International Agency for Research on Cancer (IARC) of the carcinogenic potential of SMFs and ELF electric (EFs) and MFs concluded that there is inadequate evidence in humans for determining the carcinogenicity of static EFs or SMFs, and no relevant data from experimental animals is available. Static fields, therefore, were categorized as group 3, not classifiable as to their carcinogenicity to humans. Exposure to ELF EFs and MFs occurs during the production, transmission, and use of electric power. Early epidemiologic studies of residential MFs estimated exposures through wire codes. A more sophisticated method for assessing MF exposures was developed in which calculations were made of fields generated by nearby power lines on the basis of detailed information about the configuration of the lines and their historical current loads. New MF meters were gradually developed, making it possible to make spot measurements and later to assess personal or bedroom MF exposures over periods of 24 or 48 hr. Early occupational exposure assessment methods simply categorized certain occupational titles as "electrical occupations," while more recent studies have combined the use of systematic workplace measurements, individual job history descriptions, and the development of job exposure matrices. As a result of the evolution to more sophisticated exposure assessments, exposure misclassification is considered likely to have decreased over time. Research on long-term ELF EMF effects has focused on cancer, reproductive disorders, and neurodegenerative and cardiovascular diseases. In vitro studies on the possible carcinogenicity of EFs and MFs have investigated, under a wide range of exposure conditions, a number of processes in a number of cell lines and tissue cultures. ELF EMFs do not appear to initiate cancer; consequently, researchers have hypothesized that they may act as cancer promoters or stimulate cancer progression.
In vitro research on possible ELF EMF carcinogenicity has been plagued by a lack of consistency and reproducibility. Recent reviews have concluded that ELF MFs above 100 µT cause cellular effects, although possible mechanisms for these effects are unknown. The authors noted that, overall, a coherent picture of ELF EMF effects at the cellular level is lacking. Sporadic ELF EMF effects have been reported in some experimental animal studies; however, results have most often been negative. Of the approaches used to evaluate ELF EMFs as a potential health hazard, toxicologic experiments have provided the most consistently negative data. Epidemiologic studies of ELF EMF carcinogenicity have focused on either residential or occupational exposures, and only a few studies have looked at combined exposure sources. Data on adult cancer and residential ELF EMF exposures, including use of appliances, are sparse and show severe methodological limitations. Because earlier evidence suggested that residential ELF EMF exposure is not a risk factor for adult cancers and researchers expected that occupational studies would provide a better test of adult cancer hypotheses than residential studies, residential studies using the more sophisticated exposure assessment methods, such as long-term measurements and calculated fields, have focused on children, primarily with the endpoints of leukemia and brain tumors. A possible association between residential ELF EMF exposure and childhood leukemia was first proposed in 1979 using residential EMF exposures estimated by wire codes (Wertheimer and Leeper, Am J Epidemiol 109:273-284, 1979). Since then, a large number of increasingly sophisticated studies have examined this association. There have also been numerous comprehensive reviews, meta analyses, and pooled analyses. Two recent pooled analyses found a relative risk (RR) for childhood leukemia of 2 for residential ELF MF exposures above 0.4 µT (Ahlbom et al., Br J Cancer 83:692-698, 2000). The other found an RR of 1.7 for exposures above 0.3 µT (Greenland et al., Epidemiology 11:624-634, 2000). The childhood leukemia association is consistent and, in the authors' view, represented the strongest association in ELF EMF/cancer epidemiology. No consistent relationship has been seen in studies of childhood brain tumors or other cancers and residential ELF EMF exposures. These studies, however, have generally been smaller and of poorer quality, and a formal pooled analysis for brain cancer has not been done. Data on adult cancer and residential ELF EMF exposures have been largely been negative, but plagued with uncertain exposure assessments and other methodological difficulties. Occupational studies in the 1980s and early 1990s indicated a possible increased risk of leukemia, brain tumors, and male brain cancer with presumed exposure to ELF EMFs above average levels. Several large studies conducted in the later 1990s using improved methods for assessing occupational exposure and controlling for potential confounders found no consistent exposure-response relationships. In light of a hypothesis that EMFs can affect breast cancer by suppressing production of melatonin, concern extended to female breast cancer and occupational exposure. Although some earlier registry based studies provided limited support for a possible association between ELF EMF exposure and female breast cancer, the most recent large study that incorporated exposure measurements in female workers did not find an association (Forssen et al., Am J Epidemiol 161:250-259, 2005). Studies that investigated ELF EMF exposure as a risk factor for cardiovascular disease have produced inconsistent results, with the balance showing no association. Investigation of potential EMF effects on neurodegenerative diseases is still not well developed. The focus has been on Parkinson's disease (PD), Alzheimer's disease (AZD), and amyotrophic lateral sclerosis (ALS). Of the three, PD has received the least attention and no study has provided clear evidence of an association between PD and above-average exposure to ELF EMFs. The evidence related to AZD is more difficult to assess since early studies indicating that ELF EMF exposure is a significant risk factor for AZD have not been replicated by subsequent studies, or results have been inconsistent, leading to the conclusion that evidence for an association between ELF EMF exposure and increased risk of AZD is weak. More evidence is available for ALS, where a number of studies have suggested that employment in electrical occupations may increase the risk of ALS. Currently, the most interesting suggestion, in the authors' view, is that electric shock, rather than increased EMF exposure, may play a role in the development of ALS. Possible associations of ELF EF and MF exposure with human reproductive outcomes have been examined in a number of studies. Although some studies have reported adverse effects, more rigorous studies have generally not replicated these results. For example, studies investigating residential ELF EMF exposures and use of electric blankets have found no increase in adverse pregnancy outcomes, such as miscarriages or intrauterine growth retardation (Belanger et al., Epidemiology 9:36-42, 1998; Bracken et al., Epidemiology 6:263-270, 1995). Numerous national and international organizations have provided comprehensive reviews of the ELF EMF/health effects literature over the years. Conclusions have varied somewhat with time and the individuals involved, but in general most concluded that, while the evidence is not conclusive, the possibility of ELF EMFs being associated with adverse health effects could not be excluded and that epidemiologic studies of childhood leukemia provide the strongest association. The IARC has classified ELF MFs as a group 2B carcinogen, possibly carcinogenic to humans. There is currently very little ongoing work in ELF EMF epidemiology, and much of it relates to childhood leukemia. One interesting study is an examination of a newly proposed contact current hypothesis (Kavet and Zaffanello, Bioelectromagnetics 23:464-474, 2002). While there are many sources of RF
exposure, the most frequently discussed is exposures related to mobile telephones. Mobile phones typically operate on frequencies covering the range 450-2500 MHz. Other general population sources of RF exposure are radio and TV transmitters operating at frequencies between 200 kHz and 900 MHz. Occupational exposures include RF PVC welding machines, plasma etchers, and military and civilian radar systems. The main focus of the review was on RF exposures related to mobile phones. Exposures from mobile phones are concentrated in the part of the head closest to the handset and the antenna and decreases rapidly with distance from the antenna. Consequently, human exposure from mobile phone base stations are several orders of magnitude lower than from the phones and most of the research has focused on mobile phone use. There is no convincing evidence from experimental studies at the cell level that RF fields are carcinogenic or promote carcinogenic agents. Isolated findings of DNA damage have not been replicated, results on micronuclei induction have been contradictory, and the relevance of micronuclei induction for human health is unclear. There is some evidence that RF exposure induces expression of heat shock proteins; however, the few available studies are inconsistent. There have been sporadic reports of effects such as increases in gene expression or increased permeability of the blood-brain barrier, but most of these studies have not reported dose-response effects. Recent experimental animal studies have not provided evidence that RF radiation below guideline exposure levels promote the effects of known carcinogens. Epidemiologic studies of health effects related to RF exposure from mobile phones have primarily focused on cancer outcomes (mainly brain tumors), and a few studies have focused on other symptoms. Mobile phone technology is relatively new, and therefore the number of studies available for review is limited. Nine studies of mobile phone use and brain tumors have been published to date. Most have found no effects on brain tumor risk with the exception of a positive finding from a Finnish register-based case-control study (Auvinen et al., Epidemiology 13:356-359, 2002). This study reported an increased risk of glioma related to 1- or 2-yr use of analog phones, but the finding was not confirmed in a similar Danish cohort study using similar exposure assessments (Johansen et al., J Natl Cancer Inst 93:203-207, 2001), or in other case-control studies. The glioma incidence in Scandinavian countries where mobile phone use started relatively early (late 1980s) has not increased since the introduction of handheld mobile phones. There have been no studies of cancer risk related to mobile phone base stations. The few studies that have investigated cancer risks related to radio and TV transmitters have been of an ecological design, with distance from the transmitter being the exposure metric. No data on individual exposures or confounders have been provided. The studies have produced conflicting results, but generally do not support an association between RF transmitters and increased cancer risk, although they do not provide strong evidence against such an association. Occupational studies of RF exposure, conducted for more than 20 yr, have investigated a variety of occupations including radar technicians, radio and telegraph operators, workers employed in dielectric heat sealing, and workers in telecommunications manufacturing. The studies have a number of methodological weaknesses, especially with respect to exposure assessment. None of the studies made measurements of the RF exposures of the study subjects, and exposure classifications were often made on job title alone. No control or only limited control of confounding was attempted. Although some increased risks have been reported in some of the studies, there is no consistent evidence of risk increases for any cancer sites. The RF exposure frequencies studied in these studies have generally been different from those used in mobile telephone technology. Epidemiologic studies studying symptoms related to use of mobile phones or exposures from mobile phone base stations are all of cross sectional designs, which in the authors' view makes them of limited value for health risk assessments. The subjects themselves estimated their degree of exposure (such as difference to the nearest base station or the amount of mobile phone use) as well as the health outcome, and no attempt has been made to verify exposures or symptoms, which makes the information inadequate for assessing symptoms attributable to mobile phones or base stations. The literature on possible effects of RF exposure have been summarized and evaluated by a number of national organizations in recent years, such as the Royal Society of Canada, the Stewart Commission in the United Kingdom, and the Swedish Radiation Protection Agency. These reviews have more or less come to the same conclusion: existing scientific evidence does not give cause for concern, but the research has limitations since widespread use of mobile telephones has occurred for only a relatively short time. This means, in the authors’ view, that the possibility that RF exposures from mobile phones can cause adverse health effects remains unresolved, and continued research is needed. The authors concluded that the quality of studies investigating health effects of ELF EMFs has improved over time, especially with regard to exposure assessment. Current studies investigating the effects of RF exposure are comparable to the early generation of ELF EMF studies with respect to exposure assessment, but as knowledge advances about exposure distribution and determinants, RF research can be expected to follow the same track as ELF EMF research, with quality improving over time. The history of ELF EMF research also refutes accusations that epidemiology is a source of many false accusations. Such accusations are not warranted when good studies are conducted. There are indications that the association between ELF EMF exposure and childhood leukemia is causal, but lack of a known mechanism for such low energy fields having an effect and negative experimental animal data require explanation.
For some endpoints, such as cardiovascular disease and breast cancer, enough data exist to conclude that ELF EMF exposure is probably not a risk factor. For other health outcomes, the data are considerably weaker than for childhood leukemia. It may, therefore, be too early to discount any possible associations with ELF EMFs. The situation is different for RF fields. No convincing data suggestive of a health risk associated with RF exposure have been obtained. Research in this area is still immature, with respect to both the amount of available data and the quality of available studies. Thus, no conclusions about possible adverse health effects from RF exposure can be drawn yet.

(92 Refs).

AUTHOR KEY WORDS: Childhood leukemia, Electromagnetic fields, Epidemiology, Exposure assessment, Scientific development
ER2:
The Sensitivity of Children to Electromagnetic Fields.

Kheifets, L.; Repacholi, M.; Saunders, R.; van Deventer, E.
Dept. of Epidemiology, Univ. of California Sch. of Public Health, 73-284 CHS, 50 Charles E. Young Dr. S, Los Angeles, CA 90095-1772, e-mail: kheifets@ucla.edu (L.K.); Radiation and Environmental Health, WHO, Geneva, Switzerland (M.R., R.S., E.v.D.)

Pediatrics 116(2):e303-e313 (303-313) Electronic publication:
http://pediatrics.aappublications.org/cgi/content/full/116/2/e303, doi:10.1542/peds.2004-2541

2005

Funding: WHO, EPRI, European programs EMF-NET and COST281, Statens Stralskyddsinstitut of Sweden

IVI SUMMARY: The authors reviewed studies examining the sensitivity of children to electromagnetic fields (EMFs). The review was derived from discussions and recommendations made at an expert workshop convened by the World Health Organization in Istanbul, Turkey in June 2004 to evaluate the available information relevant to children's sensitivity to EMFs and to identify research needs. The review covered the following topics: (1) background information on the development of the embryo, fetus, and child, with a focus on development of the brain; (2) childhood susceptibility to environmental toxicants in general, (3) childhood diseases relevant to EMF exposure; (4) children's exposure to radiofrequency (RF) and extremely low frequency (ELF) EMFs, including residential ELF and RF field exposures and exposure to fields from cell phones; (5) assessment of risks to children from ELF and RF EMFs; (6) developing an EMF exposure policy for children and for pregnant women; and (7) recommendations for research in this area. Childhood leukemia and brain cancer are childhood diseases relevant to EMF exposure. Epidemiologic studies have provided consistent evidence of a risk of childhood leukemia associated with environmentally high levels of ELF magnetic fields (MFs) and the International Agency for Research on Cancer (IARC) has classified ELF MFs as a "possible human carcinogen" on this basis. Experimental laboratory studies in animals and cells, however, have provided no biological explanation for this effect. Leukemias represent the most common cancer to affect children, accounting for 25-35% of all childhood malignancies. As with most other malignancies, the mechanisms by which leukemia arises is considered likely to involve gene-environment interactions. Exposures acting before birth and early in life have long been thought to be important determinants of leukemia; however, evidence related to most of the exposures is limited and often contradictory. Ionizing radiation administered therapeutically at large doses is one of the few known risk factors for leukemia. The possibility that ELF or RF EMF exposures can increase the risk of brain cancer has also been investigated, and there is particular concern with respect to the use of cell phones and absorption of RF energy in the brain, although there is no convincing evidence suggesting any increased risk. CNS tumors account for approximately 20% of childhood cancers, where they occur in cells of mesodermal or embryonic origin (the majority being brainstem gliomas), but represent less than 2% of adult cancers, where they occur in epithelial tissues (predominantly in the cerebral hemispheres). The causes of central nervous system (CNS) cancers are largely unknown, although up to 5% may be explained by genetic predisposition, associated with disorders such as neurofibromatosis type I. Having a parent or sibling with a CNS tumor also increases the risk. Identifying environmental risk factors for CNS tumors has generally produced inconsistent results. Again, ionizing radiation given in therapeutic doses is one of the few known risk factors for CNS tumors. The authors noted that the workshop addressed the potential sensitivity of children to EMFs at all stages of development, from conception through to sexual maturity. The nature of any adverse health effect that results from exposure to an environmental toxicant depends not only on the timing and magnitude of the exposure but also on the mechanisms by which the toxicant interacts with the developing tissue or organ. Consequently, it is not possible to generalize about possible effects that might result from exposure to an agent presenting unknown risks to health by drawing parallels with other toxic agents, unless they are known to have very similar mechanisms of interaction. It is necessary, instead, to examine experimental and epidemiologic evidence by formulating and testing hypotheses on the basis of an examination of known and possible interaction mechanisms. With respect to the observed epidemiologic associations between environmental levels of MFs and childhood leukemia, the authors noted that there is no experimental evidence to support the view that this relationship is causal, or provide a scientific explanation if it is. Two hypotheses for the relationship were discussed at the workshop. The first is that the association of ELF MFs with childhood leukemia may result from the flow of electric current through the bone marrow after children come into contact with water fixtures or a stream of water in which a small voltage difference exists as a result of grounding residential electrical systems to metallic water pipes. Calculations have shown that potentially significant electric fields (EFs) over 100 mV/m may be induced in the bone marrow under these circumstances. The existence of these contact currents lends plausibility to the proposed
mechanism, but the action of such weak EFs in hematopoietic tissue (leading to leukemia) has not been investigated. A second hypothesis suggests that exposure to power MFs might increase the risk of childhood leukemia by disrupting nocturnal production of melatonin by the pineal gland. The authors noted that although the International Commission on Nonionizing Radiation Protection (ICNIRP) concluded that there is no convincing evidence for such an effect, subtle effects on melatonin physiology are not easily excluded. This issue remains unresolved. Although scientific uncertainty remains, WHO recommends that precautionary measures for protecting children from ELF MF exposure be adopted. For RF exposures, numerous studies have evaluated the developmental effects of RF fields on mammals, birds, and other nonmammalian species. These studies have shown clearly that RF fields are teratogenic at exposure levels that are high enough to cause significant increases in body temperature. There is no consistent evidence of effects occurring at nonthermal RF exposure levels. All experimental laboratory animal studies examining the potential carcinogenicity of RF fields in normal animals at SARs comparable to those produced by cell phones have reported negative results, although some controversy exists about carcinogenic effects of RF fields in a transgenic mouse model. Several ecological studies have examined cancer risk, including the risk of childhood leukemia, among people living near radio and TV broadcast towers. Often motivated by a preexisting cancer cluster, these studies were based only on distance from the RF source and frequently included only extremely small numbers of cases. As a result, these studies are considered uninformative. Few epidemiologic or experimental studies have examined possible effects of RF exposures in children. Because of the widespread use of cell phones among children and adolescents and relatively high exposures to the brain, research focusing on the potential effects of RF fields on the development of childhood brain tumors is warranted. The specific type of cell phone use among children (e.g., more frequent use of text messaging), their potential biological vulnerability, and longer lifetime exposure makes extrapolation from studies conducted among adults problematic. This scientific uncertainty can be addressed both through applying the precautionary principle, and through conducting additional research. The authors noted that participants at the workshop developed a research agenda that identifies studies considered to be high priority for assessing the potential vulnerability of children to ELF and RF fields. The agenda is described at the web site http://www.who.int/peh-emf/research/rf03/en/. Because of widespread use of cell phones and the relatively high exposure to the brain among children and adults, investigation of the potential effects of RF fields on cognition and the development of childhood brain tumors was considered particularly urgent.

(68 Refs).

AUTHOR KEY WORDS: Children, Environmental risk, Policies, Sensitive periods, Mobile phones, Electromagnetic fields, Power lines
Developing Policy in the Face of Scientific Uncertainty: Interpreting 0.3 \( \mu \text{T} \) or 0.4 \( \mu \text{T} \) Cutpoints from EMF Epidemiologic Studies.

Kheifets, L.; Sahl, J. D.; Shimkhada, R.; Repacholi, M. H.
Dept. of Epidemiology, UCLA Sch. of Public Health, Los Angeles, CA 90095-1772, e-mail: kheifets@ucla.edu

Risk Anal 25(4):927-935
2005

ABSTRACT: There has been considerable scientific effort to understand the potential link between exposures to power-frequency electric and magnetic fields (EMF) and the occurrence of cancer and other diseases. The combination of widespread exposures, established biological effects from acute, high-level exposures, and the possibility of leukemia in children from low-level, chronic exposures has made it both necessary and difficult to develop consistent public health policies. In this article we review the basis of both numeric standards and precautionary-based approaches. While we believe that policies regarding EMF should indeed be precautionary, this does not require or imply adoption of numeric exposure standards. We argue that cutpoints from epidemiologic studies, which are arbitrarily chosen, should not be used as the basis for making exposure limits due to a number of uncertainties. Establishment of arbitrary numeric exposure limits undermines the value of both the science-based numeric EMF exposure standards for acute exposures and precautionary approaches. The World Health Organization's draft Precautionary Framework provides guidance for establishing appropriate public health policies for power-frequency EMF.
Childhood Leukemia and EMF: Review of the Epidemiologic Evidence.

Kheifets, L.; Shimkhada, R.
Dept. of Epidemiology, UCLA Sch. of Public Health, 73-284 CHS, 650 Charles E. Young Drive South, Los Angeles, CA 90095-1772, e-mail: kheifets@ucla.edu (L.K., R.S.)

Bioelectromagnetics 26(Suppl 7):S51-S59 International EMF Project Workshop on Sensitivity of Children to EMF, Istanbul, Turkey, 9-10 June 2004

2005
Funding: EPRI

IVI SUMMARY: The authors reviewed the epidemiologic literature on electromagnetic field (EMF) exposure and childhood leukemia risk. Leukemia is one of the most common childhood cancers, comprising about a third of the total cancers for children under 15 yr, with standardized incidence rates of 3.5 per 100,000 per yr for females and 4.2/100,000/yr for males in the developed world, and 2.2/100,000/yr for females and 2.9/100,000/yr for males in the developing world. Consistent evidence has been obtained in epidemiologic studies that exposure to extremely low frequency (ELF) EMF is associated with a small increase in the risk for childhood leukemia, which was the basis of the International Agency for Research on Cancer (IARC) classification of ELF EMF as a "possible" or class 2B human carcinogen in 2002. There are several possible explanations for the observed association. Epidemiologic studies found significant increases in childhood leukemia associated with ELF magnetic field exposures averaging above about 0.3-0.4 μT. Analyses of factors that could have confounded the observed associations such as chance, selection bias, or misclassification indicated that the association was not likely to be explained away by misclassification, although the quantitative influence of selection bias could not be clearly determined. Lack of a known mechanism to explain how EMFs at such low energy levels could cause disease, especially since experimental animal studies have yielded negative results, detracts from the conclusion that the association between ELF EMF exposure and childhood leukemia is causal. There is little epidemiologic data on possible associations between radiofrequency (RF) EMF and childhood leukemia. A number of ecological studies or cluster investigations have looked at cancer risk, including risk of childhood leukemia, among people living near radio and TV broadcasting towers. Most of these studies used distance from the source as the exposure surrogate and included only a small number of cases. Consequently, these studies were regarded as being largely uninformative, producing inconsistent results that were limited by small sample size, lack of any information on exposures, and had short follow-up periods with only a limited ability to deal with potential confounders. The authors noted that, as a result of recent developments of technologies using RF radiation such as wireless communications, there is an emerging interest in exposure to RF sources and childhood leukemia. Studying possible associations between RF exposure and childhood leukemia presents unique methodological challenges because RF fields are harder to characterize than ELF fields, RF signals from new wireless technologies involve increasingly complex frequency and modulation patterns, and exposure assessment methodology for RF fields is still in its infancy. The authors noted that the ELF EMF/childhood leukemia association has been studied extensively and further studies of similar design are not likely to provide any new insights. Only studies that can substantially improve exposure assessments and/or identify highly exposed or susceptible subgroups will be informative. For RF fields, current exposure assessment is particularly weak for base stations and TV and radio towers. Improved exposure assessments and the development of RF exposure meters are considered critical steps to better capture exposure from these sources and to determine the feasibility of conducting epidemiologic studies of leukemia in children living near RF sources. It has been suggested that cell phones represent an important source of EMF exposure, particularly to bone marrow in the hands of children. If there is a high potential for exposure to the hand, the authors suggested that an epidemiologic study of leukemia among young cell phone users should be considered.

(54 Refs)

AUTHOR KEY WORDS: Epidemiology, Extremely low frequency EMF, Radio frequency, Cancer, Review
ABSTRACT: Widespread concerns about whether electric and magnetic fields (EMF) could adversely affect human health have been raised in epidemiologic studies reported since the 1980s. Possible EMF health effects have been widely publicized in the popular press since that time. We consider here three possible mechanisms of action of EMF on childhood leukemia. We identify the first as "magnetic fields": this hypothesis relates the average level of magnetic field to the incidence of childhood leukemia. We identify a second, recently proposed, mechanism as "contact current": this hypothesis relates the low voltage and consequent current that occurs on the domestic water pipe, due to U.S. grounding practices, as a source for exposure of children. The third hypothesis is that the relationship observed is spurious. Using a modified example taken from the work of Von Winterfeldt and Keeney, we use Decision Analysis to estimate the value of information for distinguishing between the three hypotheses. We believe that this improves on the usual process for deciding on research budgets. Depending on which hypothesis we favor a priori, the value of being informed ranges from US 101 dollars to US 233 dollars per "problem household." Since there could be as many as 2 million such households, the value of information for resolving this issue could approach half a billion dollars! We find that there is no value of information for finding the odds ratio given the contact current hypothesis. In writing this article, we have consciously kept the computations as simple as possible so as to engage the reader's attention and interest. In a penultimate section, we suggest numerous possible extensions for a group interested in discussing and deciding on the value of research on the relationship between magnetic fields and cancer.

AUTHOR KEY WORDS: Childhood leukemia, Decision analysis, EMF, Magnetic Fields, Value of information
ER6:  
Childhood Leukemia and Residential Magnetic Fields: Are Pooled Analyses More Valid than the Original Studies?

Elwood, J. M.  
Epidemiologist, 1 Rathdowne St., Carlton 3053 (Melbourne), Victoria, Australia, e-mail: melwood@ncci.org.au  
Bioelectromagnetics 27(2):112-118  
2006  
Funding: Energy Supply Assoc. of Australia

IVI SUMMARY: The reported association in epidemiologic studies between residential magnetic field (MF) exposure and childhood leukemia has been very important in influencing reviews of electromagnetic field (EMF) health effects by international groups and standards setting organizations such as the International Agency for Research on Cancer (IARC), the UK Advisory Group on Nonionizing Radiation (AGNIA), and the UK National Radiological Protection Board (NRPB). Claims for an association are usually based on 2 published pooled analyses (Ahlbom et al., Br J Cancer 83:692-698, 2000; Greenland et al., Epidemiology 11:624-634, 2000), which are usually given much more weight than results of individual studies included in the analyses. The author (1) described the Ahlbom et al. (2000) and Greenland et al. (2000) analyses, (2) considered the advantages of pooled analyses vs. analysis of original studies in interpreting risks, and (3) discussed the issue of whether pooled analyses are more valid than the original studies. The pooled analysis by Ahlbom et al. (2000) used data from 5 studies that included measurements of magnetic fields (MFs) in the child's home, and from 4 studies from Scandinavian countries, which estimated residential MF exposures from calculations based on wiring configurations, proximity to electrical distribution systems, and data on line loads. Four of the studies that had included MF measurements were the largest and most detailed studies, conducted in the US (Linet et al., N Engl J Med 337:1-7, 1997), Canada (McBride et al., Am J Epidemiol 149:831-842, 1999), and the UK (UK Childhood Cancer Study Investigators, Lancet 354:1925-1931, 1999). Studies using MF exposures based on calculated fields did not include contributions from wiring and electrical appliances within the home, except for one study that included spot measurements for some subjects (Feychtling and Ahlbom, Am J Epidemiol 138:467-481, 1993). The Ahlbom et al. combined analysis included 3,247 children with leukemia and 10,400 controls. In the pooled analysis, the average exposure during the year prior to diagnosis for cases and at the corresponding age for controls was estimated. When there were measurements, MF values based on 24- or 48-hr measurements in the bedroom or elsewhere in the home of the child, before or at the time of diagnosis and at an equivalent time for the control children, was used to compute a geometric mean (GM) exposure. For studies using calculated fields, the estimate made for a home was based on its position in relation to power lines and other sources. Exposure categories in the pooled analyses were based on resulting MF exposure estimates. For the Ahlbom et al. combined analysis, the reference group was children with average exposures less than 1 mG, and the exposure categories were 1 to <1 mG, 2 to <4 mG, and 4 mG or higher. The pooled analysis showed no significantly increased leukemia risk for exposures to MFs of 1 to <2 mG or 2 to <4 mG, odds ratios (ORs) being 1.08 (95% confidence interval (CI) 0.89-1.31) and 1.11 (CI 0.84-1.47). The highest exposure category, 4 mG or greater, showed a significantly increased risk characterized by an OR of 2.00 (CI 1.27-3.13). A continuous exposure analysis was also performed, yielding an OR of 1.15 (CI 1.04-1.27) per 2 mG increase in exposure. Statistical assessment of the consistency of the study results based on the continuous analysis showed no significant heterogeneity. The increased risk seen in the 4-mG and greater category was based on 6 studies that included a total of 44 cases and 62 controls in this exposure category. The pooled analysis by Greenland et al. (2000) included 12 case-control studies, of which 7 were in the Ahlbom et al. pooled analysis. However, it had fewer subjects, 2,656 cases and 7,084 controls, since the larger UK study was not included. The remaining 4 studies not included in the Ahlbom et al. analysis were small older studies that relied only on wire codes for exposure assessment. The exposure metric chosen was the best approximation to a time-weighted average exposure up to 3 mo before diagnosis. Greenland et al. preferred calculated historical MFs or averages of multiple measurements to spot measurements. Greenland et al. also used slightly different exposure categories from Ahlbom et al.: up to 1 mG (reference), >1 to 2 mG, >2 to 3 mG, and >3 mG. The 2 lower exposure categories (>1 to 2 mG and >2 to 3 mG) indicated no significant increase in leukemia risk, ORs being 1.01 (CI 0.84-1.21) and 1.06 (CI 0.78-1.44), respectively. The OR for the highest exposure category (>3 mG) indicated a significantly increased risk, OR=1.68 (CI 1.23-2.31) based on 99 cases and 130 controls. The average MF exposure in the >3 mG category was 5.8 mG. For several studies, results for the exposure categories in the pooled analyses differed substantially from comparable results reported in the individual study and were interpreted differently. For example, the McBride et al. (1999) study included 399 Canadian children with any type of leukemia and 399 controls. MF exposures were
assessed by having the child wear a meter in a small backpack for 48 hr, placing it in the child's bedroom at night, and from measurements made in the home. Exposure categories used were: <1 (reference), 1 to <2 mG, 2 to <3 mG, 3 to <4 mG, 4 to <5 mG, and 5 mG or greater. There was no evidence in the McBride et al. (1999) study of any increased risk for exposures above 4 mG or even above 5 mG, the ORs for these categories, based on the 48-hr average exposures, being 0.44 (CI 0.11-1.80) and 0.89 (CI 0.24-3.36), respectively. By contrast, in the pooled analysis of Ahlborn et al., personal (backpack) measurements were not used, and 24-hr bedroom measurements were used instead (to be consistent with other studies). The resulting OR for the highest (>4 mG) exposure category for the McBride et al. data was 1.55 (CI 0.65-3.68). The pooled analysis of Greenland et al. used personal monitoring results, but defined different cut points for exposure categories. The resulting analysis indicated an OR of 1.42 (CI 0.63-3.21) for their highest (>3 mG) exposure category for the McBride et al. data. The original McBride et al. (1999) study, therefore, indicated no substantial or significantly increased ORs in the higher exposure categories and no dose-response trend, but data from that study contributed to the increased risk estimate in the two pooled analyses. Linet et al. (1997) and the UK CCS (1999) studies also concluded that their results did not support the hypothesis that leukemia is increased by MF exposure. Of the studies that contributed data to the highest exposure group in the Ahlbom et al. pooled analysis, only 2 of the original studies, Feychting and Ahlbom (1993) and a German study by Michaelis et al. (Cancer Causes Control 8:167-174, 1997) and (Epidemiology 9:92-94, 1998), interpreted their data as suggesting an association between residential MF exposure and childhood leukemia. Feychting and Ahlbom (1993) reported an OR of 2.70 (CI 1.00-6.30) in the main analysis and an OR of 3.80 (CI 1.40-9.30) in the highest exposure category (>2 mG). Michaelis et al. reported ORs of 2.30 with CIs of (0.70-14.90) and (0.80-6.70) in the main analysis of their 2 papers. Only the results of the Feychting and Ahlbom (1993) study represented a statistically significant risk. The author noted that a major advantage of a pooled analysis is that it provides greater numbers in the high exposure categories, although the numbers are still quite small. To obtain these higher numbers, however, the investigators used different inclusion criteria and categorizations of data than those originally reported. Cases and controls were carefully matched in the original studies, but in the pooled analysis any matching was ignored and other methods were used to adjust for age and socioeconomic status. In the case of the Ahlbom et al. (2000) analysis, risk estimate results for the Canadian (McBride et al., 1999) and US (Linet et al., 1997) study data were substantially higher than in the original papers, and these studies contributed 68% of the cases in the highest exposure group. In the Greenland et al. (2000) analysis, the Canadian study was again higher than in the original paper and the UK study was not included in the analysis. One reason why these studies show the greatest discrepancies is that they have the most extensive exposure measurements, and these could not be used in a pooled analysis that depends on exposure assessments that are common to all studies. The author suggested it would be reasonable to give the results of studies such as the McBride et al. (1999) study greater weight because they use arguably the best measures of exposure. Pooled analyses ignore or downplay studies with more detailed exposure measurements. This does not mean, in the author's view, that pooled analyses are inherently flawed or have been done poorly. Both the Ahlbom et al. and Greenland et al. analyses involved the leading investigators of the major individual studies. Both pooled analyses, however, emphasized the uncertainty of the results and showed that different ways of analysis can produce quite different results, especially for the high exposure groups. The consensus view of expert panels, as reflected in reports of the IARC, AGNiR, NRPP and similar groups, is that the results of pooled analyses give a more valid result than individual studies. This consensus view is consistent with many assessment systems in which meta-analyses and pooled analyses are rated as having greater validity than single studies. However, the author cautioned, meta-analyses techniques were developed primarily for randomized trials of medical treatments in which there are often many small studies, which apart from their size, are judged to be of comparable methodological quality. By combining data, meta-analyses overcome the problems of small numbers. Meta-analyses of observational studies present greater problems, as issues that affect validity in observational studies include response bias, confounding, and limitations of exposure assessment, which are usually greater issues than chance variation. The author concluded that while it is widely assumed that an association between childhood leukemia and MF exposure has definitely been shown, there are doubts as to whether the association is causal. It would be helpful in these discussions to give more consideration to results of large individual studies that use the best individual exposure assessment measurements.

(23 Refs).

AUTHOR KEY WORDS: Exposure measures, Meta-analysis, ELF, Leukemia, Cut-off levels
ER7:
Leukemia Attributable to Residential Magnetic Fields: Results from Analyses Allowing for Study Biases.

Greenland, S.; Kheifets, L.
Dept. of Epidemiology and Dept. of Statistics, Univ. of California, Los Angeles, CA 90095-1772, e-mail: lesdomes@ucla.edu. (S.G.); Dept. of Statistics, Univ. of California, Los Angeles, CA 90095-1772 (L.K.)
Risk Anal 26(2):471-482
2006
Funding: EPRI

ABSTRACT: Nearly every epidemiologic study of residential magnetic fields and childhood leukemia has exhibited a positive association. Nonetheless, because these studies suffer from various methodologic limitations and there is no known plausible mechanism of action, it remains uncertain as to how much, if any, of these associations are causal. Furthermore, because the observed associations are small and involve only the highest and most infrequent levels of exposure, it is believed that the public health impact of an effect would be small. We present some formal analyses of the impact of power-frequency residential magnetic-field exposure (as measured by attributable fractions), accounting for our uncertainties about study biases as well as uncertainties about exposure distribution. These analyses support the idea that the public health impact of residential fields is likely to be limited, but both no impact and a substantial impact remain possibilities in light of the available data.

(55 Refs)
AUTHOR KEY WORDS: Bayesian methods, Epidemiology, Leukemia, Magnetic fields, Risk analysis
**ABSTRACT**: During the past 25 years concern has been raised about the possible health effects of extremely low frequency (ELF) electric and magnetic fields (EMFs), particularly regarding childhood leukemia. Comparison of changes in electricity consumption (a surrogate for exposure) to changes in childhood-leukemia rates, known as ecologic correlation, have been used to argue both for and against the association between magnetic fields and childhood leukemia. In this paper we explore what can be learned from such an ecologic approach. We first examine separately the evidence on trends in exposure to EMFs and on trends in leukemia rates, and then compare the two. Both incidence rates and exposures have increased, but there are so many approximations and assumptions involved in connecting the two trends that we cannot regard the ecologic evidence as providing any meaningful evidence for or against a causal link.
Selection Bias and its Implications for Case-Control Studies: A Case Study of Magnetic Field Exposure and Childhood Leukaemia.

Mezei, G.; Kheifets, L.
Environment Dept., EPRI, 3412 Hillview Ave., Palo Alto, CA 94303, e-mail: gmezei@epri.com (G.M.); Dept. of Epidemiology, UCLA Sch. of Public Health, Los Angeles, CA (L.K.)

Int J Epidemiol 35(2):397-406

2006

Funding: EPRI.

ABSTRACT: Based on the epidemiological association between residential exposure to extremely low frequency-magnetic fields (ELF-MF) and childhood leukaemia, the International Agency for Research on Cancer classified ELF-MF as a possible human carcinogen. Since clear supportive laboratory evidence is lacking and biophysical plausibility of carcinogenicity of MFs is questioned, a causal relationship between childhood leukaemia and magnetic field exposure is not established. Among the alternative explanations, selection bias in epidemiological studies of MFs seems to be the most plausible hypothesis. In reviewing the epidemiological literature on ELF-MF exposure and childhood leukaemia, we found evidence both for and against the existence of selection bias. To evaluate the potential for selection bias, we examined the relationship of socioeconomic status to subject participation and exposure to MFs. We find that, often, reporting of selection processes in itself is biased and incomplete, making the interpretation and evaluation of a potential for bias difficult. However, if present, such a bias would have wide implications for case-control studies in general. We call for better reporting and for evaluation of the potential for selection bias in all case-control studies, as well as, for the development of novel methods in control selection and recruitment.

(41 Refs)

AUTHOR KEY WORDS: Epidemiological methods, Selection bias, Childhood leukaemia, Extremely low frequency-magnetic fields
Animal Studies

A1:
Evaluating DNA Damage in Rodent Brain after Acute 60 Hz Magnetic-Field Exposure.

McNamee, J. P.; Bellier, P. V.; Chauhan, V.; Gajda, G. B.; Lemay, E.; Thansandote, A.
Consumer and Clinical Radiation Protection Bureau, Product Safety Programme, Health Canada, 775 Brookfield Rd., PL 6303B, Ottawa, Ontario, K1A 1C1, Canada, e-mail: james_mcnamee@hc-sc.gc.ca (J.P.McN.)

Radiat Res 164(6):791-797
2005

ABSTRACT: In recent years, numerous studies have reported a weak association between 60 Hz magnetic-field exposure and the incidence of certain cancers. To date, no mechanism to explain these findings has been identified. The objective of the current study was to investigate whether acute magnetic-field exposure could elicit DNA damage within brain cells from both whole brain and cerebellar homogenates from adult rats, adult mice and immature mice. Rodents were exposed to a 60 Hz magnetic field (0, 0.1, 1 or 2 mT) for 2 h. Then, at 0, 2 and 4 h after exposure, animals were killed humanely, their brains were rapidly removed and homogenized, and cells were cast into agarose gels for processing by the alkaline comet assay. Four parameters (tail ratio, tail moment, comet length and tail length) were used to assess DNA damage for each comet. For each species, a significant increase in DNA damage was detected by each of the four parameters in the positive control (2 Gy x rays) relative to the concurrent nonirradiated negative and sham controls. However, none of the four parameters detected a significant increase in DNA damage in brain cell homogenates from any magnetic-field exposure (0 – 2 mT) at any time after exposure. The dose-response and time-course data from the multiple animal groups tested in this study provide no evidence of magnetic-field-induced DNA damage.

(30 Refs).
**A2: Histological Characteristics of Cutaneous and Thyroid Mast Cell Populations in Male Rats Exposed to Power-frequency Electromagnetic Fields.**

**Rajkovic, V.; Matavulj, M.; Johansson, O.**
Dept. of Biology, Faculty of Sciences, Trg Dositerja Obradovica 2, 21000 Novi Sad, Serbia and Montenegro, e-mail: vesna.rajkovic@ib.ns.ac.yu (V.R., M.M.); Experimental Dermatology Unit, Dept. of Neuroscience, Karolinska Inst., Stockholm, Sweden (O.J.)

*Int J Radiat Biol* 81(7):491-499

**2005**

Funding: Cancer och Allergifonden and the Karolinska Institute

**IVI SUMMARY:** The authors examined the effects of extremely low frequency electromagnetic field (ELF EMF) exposure on the morphological and histological characteristics of cutaneous and thyroid mast cells in rats. Twenty-four 2-mo-old male Wistar rats were exposed (12 animals) or sham exposed (12 animals) to a 50-Hz EMF 4 hr/day, 7 days/wk, for 1 mo. The EMF was produced by a single solenoid coil (Electronic Equipment Factory "Novkabel," Novi Sad, Serbia and Montenegro) that was energized by 50-Hz, 220-V, 10-A current, stepped down via an autotransformer to a voltage of 100 V. Rats were exposed in cages placed on both sides of the solenoid at an approximate distance of 12 cm. The EMF was oriented horizontally with respect to the cages and was inhomogeneous, decaying in intensity horizontally along the cages. The intensity of the field, measured with an AC milligaussmeter (model 42B-1, Monitor Industries, Boulder, CO) and ELF electric field (EF) meter (HI-3607, Holaday Industries) varied from 300 μT and 160 V/m on the side of the cages nearest the solenoid to 100 μT and 54 V/m on the opposite side. The ambient 50-Hz EMF in the laboratory was 0.2 μT and 2.9 V/m. The average strength of the geomagnetic field (GMF) in the laboratory, measured with a tesla/gaussmeter (model 4048, F.W. Bell, Orlando, FL) was 40 μT. Rats were killed after the last exposure and samples of skin from the interscapular region, the thyroid gland with adjacent parts of the trachea, and surrounding connective tissue were harvested. All samples were fixed in 4% paraformaldehyde and 14% picric acid at 4 C, then processed for 14-um thick frozen sections used for toluidine staining or indirect immunohistochemical analysis. The sections were assayed for mast cells, eosinophils, or nerve fibers in the skin and mast cells in the thyroid samples using the indirect immunofluorescence technique described by Johansson et al. (Arch Dermatol Res 292:371-378, 2000). Toluidine blue stained skin and thyroid sections stained according to the immunohistochemistry protocol were used for quantitative analysis of mast cells, eosinophils, and nerve fibers. Skin sections were analyzed starting from the epidermal-dermal junction and thyroid sections from the middle of the lobe (facing the trachea) to the periphery. Analysis of toluidine blue stained sections was performed using a multipurpose stereological grid M42 that was placed in the ocular of a Reichert light microscope. Additionally, histamine- and serotonin-containing eosinophils, eosinophil cationic protein- (ECP-) labeled eosinophils, and protein gene product 9.5- (PGP 9.5-) labeled nerve fibers were estimated using a stereological technique that employed a custom-designed microscope frame in the ocular of a fluorescence microscope. Total mast cell numerical (Nvm) and volume (Vvm) densities were determined using this technique. Nvm and Vvm densities were also determined for 3 types of mast cells: (1) type A, compact mast cells with abundant cytoplasmic granules; (2) type B, mast cells characterized by numerous cytoplasmic extensions that are indicative of the beginning of degranulation; and type C, degranulated mast cells with extruded granules in the intercellular space. All analyses were performed using blind-coded samples and were tested statistically by the nonparametric Mann-Whitney U test. Histological (toluidine blue staining) and stereological analysis of skin samples indicated an increased incidence of mast cells with decreased metachromasia and cytoplasmic processes in the papillary dermis of exposed animals and an increase in the number of mast cell granules present in surrounding connective tissue. These changes were indicative of mast cell degranulation. Only solitary, darker stained cells were observed in skin samples from control animals. Degranulated mast cells in exposed rats were frequently seen in close proximity to blood vessels. No significant differences in any stereological parameters were seen between skin samples from exposed and control animals. Solitary histamine-positive mast cells with decreased cell volume and weak fluorescence were observed in the papillary dermis of exposed animals. In 6 of 12 exposed rats, large mast cells arising in lines toward the epidermis were found; however, these were seen only in 2 of 12 control animals. There were no significant differences in values of the stereological parameters between histamine positive mast cells between exposed and control animals. The distribution density of PGP 9.5-positive nerve fibers in the epidermis and dermis of exposed rats was greater than in the controls, but none of the differences were statistically significant. Groups or solitary immunolabeled eosinophils (visualized as ECP-positive cells) were found in the dermis of exposed rats. Only diffusely scattered...
immunolabeled eosinophils were seen in control animals. Differences in the number of ECP-positive cells between exposed and control rats, however, were not statistically significant. In the thyroid gland, mast cells in exposed rats showed weak metachromatic staining with toluidine blue. These cells were found in interfollicular connective tissue in close proximity to blood vessels. Toluidine blue stained mast cells in thyroid tissue samples from control animals were usually observed adjacent to follicular cells. Stereological analysis showed an increased Nvm and Vvm of type A mast cells in thyroid tissues from exposed rats compared to control animals. These differences were statistically significant. No other significant differences in stereological parameters between mast cells from exposed and control animals were observed. A number of degranulated histamine containing mast cells, including released granules and degranulated cells in the thyroid interfollicular space, were seen adjacent to blood vessels in exposed animals. There were, however, no significant differences in the value of any stereological parameters of histamine positive mast cells between exposed and control rats. Mast cells exhibiting bright serotonin fluorescence were seen in both exposed and control rats. Occasional mast cells with decreased fluorescence or reduced volume, indicating degranulation, were seen in thyroid tissues from exposed animals. The number of serotonin-positive mast cells in the exposed group, however, did not differ significantly from the control group. The authors concluded that exposure of male rats to ELF EMFs can cause certain specific changes in the morphology, distribution, and number of cutaneous and thyroid mast cells. The possible effects of these changes on other tissue structures or cells in the skin and thyroid gland are unknown, however, and warrant further investigation. (31 Refs). AUTHOR KEY WORDS: Cutaneous mast cells, Thyroid mast cells, Electromagnetic fields, Stereology
Oxidative DNA Damage in Rats Exposed to Extremely Low Frequency Electro Magnetic Fields.

Yokus, B.; Cakir, D. U.; Akdag, M. Z.; Sert, C.; Mete, N.
Dept. of Biochemistry, Faculty of Veterinary, Dicle Univ., 21280 Diyarbakir, Turkey, e-mail: beyokus@dicle.edu.tr (B.Y.); Dept. of Biochemistry, Faculty of Medicine, Dicle Univ., 21280, Diyarbakir, Turkey (D.U.C., N.M.); Dept. of Biophysic, Faculty of Medicine, Dicle Univ., 21280, Diyarbakir, Turkey (M.Z.A.); Dept. of Biophysic, Faculty of Medicine, Harran Univ., 21280 Sanliurfa, Turkey (C.S.)

2005

IVI SUMMARY: The authors examined the potential of extremely low frequency (ELF) magnetic fields (MFs) to produce oxidative DNA damage in rats. Forty-eight 2-mo-old female Wistar rats were divided into 4 groups of 12 animals each. Two groups were exposed to a 0.97-mT, 50-Hz MF for either 50 or 100 days. The other 2 groups were sham exposed for the same periods of time. For exposure/sham exposure, rats were housed in 17 x 17 x 25-cm methacrylate cages. The MF was produced by a custom-designed system that consisted of 2 pairs of 25-cm diameter Helmholtz coils, each with 225 turns of 1.0-mm diameter insulated soft copper wire. Coil pairs were oriented vertically and horizontally and separated by a distance of 25 cm. The coils were driven by 50-Hz, 0.65-A current produced by an AC power supply (DAYM, Turkey). This produced a mean flux density of 0.97 +/- 0.136 mT, determined from measurements made at 15 points in one of the methacrylate cages using a digit teslameter (PHYWE 209101074, Germany). No differences in temperature were measured in the coils between actual exposure and sham exposure. Ambient MFs, measured with a cell sensor (Cell Sensor EMF detection meter, Tec Health Corp, USA), varied from 0.1 (the lower limit of the meter sensitivity) to 0.2 µT. Rats were killed after the MF exposure/sham exposure period, cardiac blood was collected, plasma was separated, and leukocytes were harvested from the blood samples. The plasma was analyzed for thiobarbituric acid-reactive substances (TBARS), as a marker of lipid peroxidation, using the spectrophotometric procedure described by Ohkawa et al. (Anal Biochem 95:351-358, 1979). DNA was isolated from the leukocytes and analyzed for 8-hydroxy-2'-deoxyguanosine (8OHdG) adducts, one of the predominant forms of DNA lesions induced by HO reaction with the C8 of guanine, used as a marker of oxidative DNA damage. The 8OHdG assay was a modification of the liquid chromatography assay described by Kasai (Mut Res 387:147-163, 1997). Data were tested statistically by the independent sample t-test and linear regression analysis. Exposure to the 50-Hz MF significantly increased the level of 8OHdG adducts compared to sham exposure at both 50 days exposure (from 3.02 +/- 0.63 to 4.39 +/- 0.88 8OHdG/dG.10(5) ratio, p<0.001) and 100 days (from 3.46 +/- 0.38 to 5.29 +/- 1.16 8OHdG/dG.10(5) ratio, p<0.001). TBARS was also increased compared to sham exposure at both 50 days exposure (from 19.59 +/- 2.27 to 26.37 +/- 4.44 nmol/ml, p<0.001) and 100 days exposure (from 19.96 +/- 1.64 to 33.03 +/- 8.42 nmol/ml, p<0.001). The level of TBARS and 8OHdG adducts after 100 days of sham exposure did not differ significantly from those measured after 50 days of exposure. Linear logistic regression analysis showed that the level of 8OHdG adducts normalized to the concentration of deoxyguanosine (8OHdG/dG ratio) was significantly positively correlated with the level of TBARS in rats that had been exposed to the MF for 50 days, but no correlation between the 8OHdG/dG ratio and TBARS was seen in rats exposed to the field for 100 days. The authors concluded that ELF MFs can induce oxidative DNA damage and lipid peroxidation. The extent of DNA damage and level of lipid peroxidation depends on exposure time. The observed exposure time dependence may have important health implications, as long-term ELF EMF exposure may cause cumulative oxidative DNA damage.

AUTHOR KEY WORDS: DNA damage, Magnetic field, 8-Hydroxy-2'-Deoxyguanosine, 8-Oxoguanine, Thiobarbituric acid, TBARS
Effects of Extremely Low-Frequency Magnetic Fields in the Brain of Rats.

Inst. for Biological Res. Sinisa Stankovic, Bulevar Despota Stefana 142, 11000 Beograd, Serbia and Montenegro, e-mail: aka950@yahoo.com (A.J.)
Brain Res Bull 68(5):355-360
2006
Funding: Ministry of Science and Environmental Protection of Republic of Serbia, Contract No. 1636.

ABSTRACT: An extremely low-frequency magnetic field (50 Hz, 0.5 mT) was used to investigate its possible effect on the brain of adult male Wistar rats following a 7-day exposure. The control rats were sham-exposed. Superoxide dismutase activities and production of superoxide radicals, lipid peroxidation, and nitric oxide were examined in the frontal cortex, striatum, basal forebrain, hippocampus, brainstem, and cerebellum. Significantly increased superoxide radical contents were registered in all the structures examined. Production of nitric oxide, which can oppose superoxide radical activities, was significantly increased in some structures: the frontal cortex, basal forebrain, hippocampus, and brainstem. Augmentation of lipid peroxidation was also observed, with significance only in the basal forebrain and frontal cortex, in spite of the significantly increased superoxide dismutase activities and nitric oxide production in the basal forebrain, and increased production of nitric oxide in the frontal cortex. The results obtained indicate that a 7-day exposure to extremely low-frequency magnetic field can be harmful to the brain, especially to the basal forebrain and frontal cortex due to development of lipid peroxidation. Also, high production of superoxide anion in all regions may compromise nitric oxide signaling processes, due to nitric oxide consumption in the reaction with the superoxide radical.

(45 Refs).
AUTHOR KEY WORDS: Extremely low-frequency magnetic field, Brain, Nitric oxide, Lipid peroxidation, Superoxide radical, Rats.
50 Hz Magnetic Fields of 1 mT [10,000 mG] Do Not Promote Lymphoma Development in AKR/J Mice.

Sommer, A. M.; Lerchl, A.
Sch. of Engineering and Science, International Univ. Bremen, Res. II, Campus Ring 6, D-28759, Bremen, Germany, e-mail: a.lerchl@iu-bremen.de (A.L.)
Radiat Res 165(3):343-349
2006
Funding: Beeinflussung der spontanen Leukamierate bei AKR-Mausen durch niederfrequente Magnetfelder.

ABSTRACT: Some epidemiological studies suggest that exposure to power-frequency magnetic fields increases the risk of leukemia, especially in children with high residential exposures. In contrast, most animal studies did not find a correlation between magnetic-field exposure and hematopoietic diseases. The present study was performed to investigate whether chronic, high-level (1 mT) magnetic-field exposure had an influence on lymphoma development in a mouse strain that is genetically predisposed to thymic lymphoblastic lymphoma. Three groups of 160 unrestrained female AKR/J mice were sham-exposed or exposed to sinusoidal 50 Hz magnetic fields beginning at the age of 12 weeks for 32 weeks, 7 days per week, either for 24 h per day or only during nighttime (12 h). Exposure was carried out in a blind design. Exposure did not affect survival time, body weight, lymphoma development or hematological parameters. The resulting data do not support the hypothesis that exposure to sinusoidal 50 Hz magnetic fields is a significant risk factor for hematopoietic diseases, even at this relatively high exposure level.
(44 Refs).
Mechanism + in vitro Studies

M1:

Bodega, G.; Forcada, I.; Suarez, I.; Fernandez, B.

Environ Res 98(3):355-362
2005

IVI SUMMARY: The authors examined the effects of exposure to sinusoidal 50 Hz magnetic fields (MFs) and combined sinusoidal and static magnetic fields (SMFs) of the same flux density (1 mT) on cytoskeletal proteins, stress protein, and proliferation of rat astrocytes. Primary cultures of astroglial cells harvested from the cerebral hemisphere of PO-P1 Wistar rats by mechanical dissociation and were grown to confluence in 25-cm2 flasks containing DMEM supplemented with 12% fetal bovine serum (FBS), 100-U/ml penicillin and streptomycin, and 2.5-ug/ml fungizone at 37 C under a 5% CO2 atmosphere. After about 20 days this procedure yielded a culture enriched to greater than 95% astrocytes. The astrocytes were exposed for 1, 2, or 4 hr to a 50-Hz MF; a DC SMF; or to a combined 50-Hz and DC MF, each field having a flux density of 1 mT. The MFs were produced by a pair of coils connected to a 50-Hz and/or static power supply located outside the incubator. Measurements made with a Hall probe indicated that the MFs were uniform to within 5% inside the exposure volume. The ambient static MFs in the incubator (other than the geomagnetic field) had an intensity of less than 0.6 \( \mu T \), as measured by a model 4080 Teslameter (F.W. Bell). Control astrocyte cultures were sham exposed by placing them in the incubator with the coil not activated. The effects of the exposures on expression of heat shock protein (hsp) 25, hsp60, hsp70, actin, and glial fibrillary acidic protein (GFAP) were assessed by Western blotting techniques. Protein concentrations were measured using the Bradford microassay procedure. Changes in expression of hsp25, hsp60, and hsp70 were used as indicators of the effects of MF exposure on stress protein. Changes in expression of actin and GFAP were used as indicators of MF exposure on cytoskeletal protein expression. All experiments were repeated in triplicate and data were tested statistically by Student's t test. In an initial experiment, astroglial astrocytes cultured with or without added FBS were exposed to the 1-mT DC for 1 hr and effects on the expression of hsp25, hsp60, hsp70, actin, and GFAP were measured. No significant differences in the level of expression of hsp25, hsp60, hsp70, actin, or GFAP between exposed and sham exposed cells were seen. Serum-deprived astrocytes generally showed lower levels of expression of all proteins than cells cultured in the presence of FBS. Consequently, subsequent experiments were performed using serum-deprived astrocytes. Exposure of astrocytes in FBS-free medium to the DC MF, 50-Hz MF, and the combined DC/50-Hz field for 1 hr did not produce any significant changes in expression of any of the proteins compared to sham exposure. Expression of hsp25, hsp60, hsp70, and GFAP following exposure to the combined DC/50-Hz field, however, showed a greater standard deviation (SD) than exposure to the DC or 50-Hz field alone. Exposure to the combined MF for longer periods (2 or 4 hr) did not significantly alter the level of expression of the 3 hsps, actin, or GFAP. To assess possible effects on cell proliferation, 2 million astrocytes were plated in two 75-cm2 flasks. Starting 24 hr later, a 16-cm2 area of one flask was exposed continuously for 11 days to the DC/50-Hz MF directed perpendicular to the base of the flask. A second 16-cm2 area was used as the sham exposure area. A 16-cm2 area in the second flask was used as an untreated control area. At the end of the 11-day experimental period, the percentage of each 16-cm2 area covered by astrocytes was determined by examination under an optical microscope using a X20 objective lens. Twelve different points on each 16-cm2 surface were counted in the analysis. Exposure to the combined DC/50-Hz MF did not significantly affect astrocyte proliferation. There were no structural differences (size and morphology) observed between exposed, sham-exposed, and control cells. A positive control experiment was conducted for hsp expression by heating astrocyte cultures to 42 C for 45 min. A negative control experiment was conducted for GFAP and actin expression by incubating astrocytes with 5-mM ammonium chloride for 4 days. Heat shocking astrocytes by heating them to 42 C for 45 min caused a significant increase in the level of expression of hsp25, hsp60, and hsp70. Treatment with 4-mM ammonium chloride for 4 days significantly reduced the level of expression of GFAP and actin. The authors concluded that exposure to 1-mT 50-Hz, DC, or combined MFs has no significant effects on stress responses, cytoskeletal protein levels, or proliferation of astroglial cells in culture. (57 Refs)

AUTHOR KEY WORDS: Heat shock proteins, Actin, GFAP, Magnetic field, Astrocyte
M2:
Genotoxic Effects of Extremely Low Frequency (ELF) Magnetic Fields (MF) Evaluated by the Tradescantia-Micronucleus Assay.

Fatigoni, C.; Dominici, L.; Moretti, M.; Villarini, M.; Monarca, S.
e-mail: Massimo.moretti@unipg.it (M.M., C.F., L.D., M.V., S.M.)
Environ Toxicol 20(6):585-591
2005

IVI SUMMARY: The authors examined the feasibility of using the Tradescantia-micronucleus (Trad-MN) bioassay to detect genotoxic effects from extremely low frequency (ELF) magnetic fields (MFs). The Trad-MN bioassay, described by Ma et al. (Mutat Res 310:221-230, 1994), was originally developed to detect chromosome damaging effects of a range of environmentally relevant pollutants in water, air, and soil. It was first used to study the clastogenic effects of 1,2-dibromoethane and later was validated with well-known mutagens, such as ethylmethane sulfonate, sodium azide, and cyclohexylamine. Tradescantia is a succulent plant genus that contains such common houseplants as Tradescantia fluminensis (Wandering Jew) and Tradescantia virginiana (Virginia Spiderwort). In this study, Tradescantia (clone No. 4430, a hybrid of T. hirsutiflora and T. subcaulis) inflorescences were exposed or sham exposed to a test 50-Hz, 1-mT p-p MF for 1, 6, or 24 hr to assess possible effects on micronucleus frequency. The MF was generated by a pair of 16.5-cm O.D., 6-cm thick 1000-turn bifilar Helmholtz coils arranged in parallel 12 cm apart. The coils were fed by a digital power supply with a quartz crystal oscillator (3T Srl, Bevagna, Italy). Current was passed through both wires in parallel to generate the 1-mT field or in anti-parallel directions to produce a sham exposure condition. The MF in the active exposure volume during sham exposure was 2.05 µT, as measured by an EFA-300 Field Analyzer (Narda GmbH, Pfullingren, Germany). The homogeneity of the MF in the exposure volume during active exposure was +/- 1.0%. The ambient MF in the system, measured when the coils were turned off, was 0.073 µT. Temperature measurements indicated that the exposure system produced no significant heating during the experiment, the temperature averaging 37.0 +/- 0.3 C. Young Tradescantia inflorescences on a 10 to 15-cm long stem containing 8 to 10 buds in a cluster in groups of 15 were grown in 100-ml of Hoagland's solution, as described by Ma (Trad-MN test for environmental clastogens. In: In Vitro Toxicity Testing of Environmental Agents, Current and Future Possibilities. Part A. Survey of Test System. New York, Plenum, p. 191-214, 1983). The cuttings were grown under controlled conditions with a light/dark photoperiod of 16:8 hr, using an artificial light. For MF exposure/sham exposure, cuttings were arranged in the exposure system with the buds placed at the point of maximum MF strength and uniformity. After the end of the 1, 6 or 24-hr experimental period, cuttings were allowed to recover for at least 6 hr. Aeration was controlled to avoid possible oxygen depletion in Hoagland's solution. Positive and negative control experiments were also run. As a positive control, Tradescantia cuttings were incubated in 0.2-mM sodium azide in Hoagland's solution for 6 hr, rinsed with distilled water, and then returned to fresh Hoagland's solution and allowed to recover for 24 hr. As a negative control, additional plant cuttings were maintained in Hoagland's solution for 30 hr. After appropriate recovery times, MF exposed and sham exposed and positive and negative Tradescantia cuttings were fixed in 3:1 ethanol/acetic acid for 24 hr and stored in 70% ethanol. Anthers at an adequate stage of development were dissected out and early tetrads of meiotic microspore mother cells were stained with aceto-carmine stain (2% carmine in 45% acetic acid). Coded slides were prepared and scored for micronuclei (MN) under optical microscopy at 400 X magnification. The number of MN in approximately 300 early tetrads was counted in each of 5 slides per experimental group. MN data were tested statistically using the nonparametric Mann Whitney U test. Within each sequences of assays (MF exposed or sham exposed inflorescences), MN frequencies were tested statistically by ANOVA followed by Dunnett's multiple comparison test. Tradescantia inflorescences exposed to the MF for 1, 6, and 24 hr all had significantly higher MN frequencies than the corresponding sham exposed inflorescences with individual differences at p<0.001 and F-test (ANOVA) p<0.0001. MN frequencies (1-mT exposed vs. sham) were 12.1 +/- 1.0 vs. 5.2 +/- 1.0 MN/100 tetrads for a 1 hr exposure, 14.7 +/- 1.1 vs. 6.5 +/- 0.8 MN/100 tetrads for a 6 hr exposure, and 24.5 +/- 2.1 vs. 7.7 +/- 0.4 MN/100 tetrads for a 24 hr exposure. The mean MN frequency of the positive and negative controls was 24.2 +/- 3.8 and 5.5 +/- 0.5 MN/100 tetrads, respectively. Regression analysis of the time-response relationships of the MN frequency of MF exposed fluorescences showed a statistically significant linear trend with increasing exposure time, the regression coefficient being 0.835 (p<0.01 at 1 hr, p<0.001 at 6 and 24 hr). The authors concluded that a 1-mT 50-Hz MF is genotoxic in the Trad-MN bioassay, and that this assay may be suitable for detecting genotoxicity of ELF MFs under field conditions. (59 Refs).

AUTHOR KEY WORDS: Extremely low frequency magnetic fields, ELF-EMF, Tradescantia-micronucleus assay, Trad-MN test, Genotoxicity
IVI SUMMARY: The authors examined possible cell type specificity in the genotoxic response of mammalian cells to exposure to an intermittent extremely low frequency (ELF) magnetic field (MF). This was a follow-up to a previous study which found that exposure of human diploid fibroblasts to an intermittent 50-Hz MF caused significant increases in DNA single-strand breaks (SSBs) and double-strand breaks (DSBs), as assessed by alkaline and neutral comet assays (Ivancsits et al., Mut Res 519:1-13, 2002; Int Arch Occup Environ Health 76:431-436, 2003). The purpose of the present study was to determine whether intermittent ELF MF exposure causes similar effects in cell types other than human fibroblasts. Human melanocytes, SV-40 transformed rat GFSH-R17 granulosa cells, human skeletal muscle cells, human lymphocytes, human monocytes, as well as human diploid fibroblasts were exposed to a 50-Hz, 1-mT intermittent MF (5 min on/10 min off) for 1 to 24 hr. The melanocytes were obtained from a 3-yr-old male. Skeletal muscle cells, obtained from a 63-yr-old male, were received from Promocell (a commercial cell culture supplier in Heidelberg Germany). The monocytes were harvested from a healthy 31-yr old female donor and lymphocytes were obtained from a healthy 27-yr old female donor. Both were collected by Ficoll Paque gradient centrifugation of venous blood samples. Fibroblasts were obtained from a healthy 6-yr-old male donor. All cells were cultured in Dulbecco's modified Eagle's medium with appropriate supplements (antibiotics, 10-25% fetal bovine serum, glutamine, HEPES buffer). The MF exposure system, constructed by the ITiS Foundation (Foundation for Information Technologies in Society, Zurich, Switzerland), consisted of two 4-coil bifilar wound systems (2 coils with 56 windings, 2 coils with 50 windings), each of which was placed inside a mu-metal box. Current in the bifilar coils could be switched parallel for active exposure or anti-parallel for sham exposure. One system was used for active MF exposure and the other for sham exposure. The residual MF in the sham exposure chamber was at least 150 times (43 dB) lower than the applied field in the active exposure chamber. The chambers were not insulated from the geomagnetic field. Both systems were placed inside a commercial incubator (BBD 6220, Kendro, Vienna, Austria) that maintained constant environmental conditions (37 C, 5% CO2, 95% relative humidity). Temperature and magnetic flux density were monitored continuously. Differences in temperature between exposure and sham exposure chambers never exceeded 0.3 C. To enable blind exposures, a computer randomly determined which chamber was used for active and which was used for sham exposure. Cells were exposed to the MF 24 hr after seeding in 35-mm Petri dishes, typically at a density of 2 x 10(5) cells/3 ml. Lymphocytes were studied with or without stimulation with 1% phytohemagglutinin (PHA). Genotoxicity was assessed by determining DNA SSBs and DSBs using the alkaline and neutral comet assays, respectively, performed according to the procedure of Singh et al. (Exp Cell Res 175:184-191, 1988). MF-exposed and sham-exposed cells were processed in parallel. Results were reported in a series of figures showing average comet tail factor (%) values without error bars for each culture type as a function of hours of exposure. Each experiment was performed in duplicate by the same investigator. Exposure to the intermittent MF caused significant increases in the frequency of DNA SSBs and DSBs in rat granulosa cells, human fibroblasts, and human melanocytes. The magnitude of the response was greater in fibroblasts and rat granulosa cells than in melanocytes, peaking somewhat earlier in fibroblasts (around 15 hr) than in granulosa cells (around 19 hr). Exposure to the MF produced no detectable DNA strand breakage in human lymphocytes (with or without PHA stimulation), monocytes, or skeletal muscle cells, as characterized by a constant tail factor values over the 0-24 hr time period. The authors concluded that induction of DNA strand breaks in mammalian cells by exposure to an intermittent ELF EMF depends on the specific cell type. Three types of cells responded to the MF: human melanocytes, human fibroblasts, and transformed rat granulosa cells. Three other cell types were not affected by the field: human lymphocytes, monocytes, and skeletal muscle cells. These results also emphasize the importance of considering the type of cell being studied when investigating genotoxic effects of ELF EMFs in vitro. (28 Refs).

AUTHOR KEY WORDS: ELF-EMF exposure, Comet assay, Different cell types
M4:
Contact Current Hypothesis: Summary of Results to Date.

Kavet R.
Electric Power Research Institute (EPRI), Palo Alto, California 94303, USA.
kavet@epri.com
Bioelectromagnetics. Suppl 7:S75-85.
2005

ABSTRACT: Research conducted over the past 5 years has addressed the hypothesis that the reported association between residential magnetic fields and childhood leukemia may be explained by exposure to contact current. The use of multi-grounded neutrals in electrical distribution and residential electrical wiring systems in the United States results in a voltage on a residence's water line relative to earth that in turn creates a voltage between the water fixtures of a bathtub, sink, or shower and the drain, if the latter is made of conductive material. A bathing child may thus be exposed to contact current upon manual contact with the faucet, spout, or water stream. Dosimetry modeling indicates that modest and realistically anticipated currents (10’s of µA) can produce electric fields in bone marrow (100’s of mV/m) sufficient to overcome questions of biophysical plausibility. Both measurements in two regions of the United States and computer modeling of typical single-residence US neighborhoods indicate that residences with average magnetic fields in the high tail of the magnetic field distribution are more likely than residences with lower fields to also have higher contact voltage. The association of residential magnetic fields with contact voltage, the dosimetry results, and the indication from a behavioral survey that children tend to engage in behavior that results in exposure all support the hypothesis. Further research is needed to characterize electrical systems in other nations to determine whether contact current exposure occurs and whether it is associated with residential magnetic fields.
M5: Combined Exposure of ELF Magnetic Fields and X-rays Increased Mutant Yields Compared with X-rays Alone in pTN89 Plasmids.

Koyama S, Nakahara T, Sakurai T, Komatsubara Y, Isozumi Y, Miyakoshi J.

Department of Radiological Technology, School of Health Sciences, Faculty of Medicine, Hirosaki University, Japan.


ABSTRACT: We have examined mutations in the supF gene carried by pTN89 plasmids in Escherichia coli (E. coli) to examine the effects of extremely low frequency magnetic fields (ELFMFs) and/or X-rays to the plasmids. The plasmids were subjected to sham exposure or exposed to an ELFMF (5 mT), with or without X-ray irradiation (10 Gy). For the combined treatments, exposure to the ELFMF was immediately before or after X-ray irradiation. The mutant fractions were 0.94x10(-5) for X-rays alone, 1.58x10(-5) for an ELFMF followed by X-rays, and 3.64x10(-5) for X-rays followed by an ELFMF. Increased mutant fraction was not detected following exposure to a magnetic field alone, or after sham exposure. The mutant fraction for X-rays followed by an ELFMF was significantly higher than those of other treatments. Sequence analysis of the supF mutant plasmids revealed that base substitutions were dominant on exposure to X-rays alone and X-rays plus an ELFMF. Several types of deletions were detected in only the combined treatments, but not with X-rays alone. We could not find any mutant colonies in sham irradiated and an ELFMF alone treatment, but exposure to ELFMFs immediately before or after X-ray irradiation may enhance the mutations. Our results indicate that an ELFMF increases mutation and alters the spectrum of mutations.
M6:
Effects of ELF Magnetic Fields on Protein Expression Profile of Human Breast Cancer Cell MCF7.

Li, H.; Zeng, Q.; Weng, Y.; Lu, D.; Jiang, H.; Xu, Z.
Bioelectromagnetics Lab., Zhejiang Univ., Hangzhou 310031, China
2005

ABSTRACT: Extremely Low Frequency Magnetic Fields (ELF MF) has been considered as a "possible human carcinogen" by International Agency for Research on Cancer (IARC) while credible mechanisms of its carcinogenicity remain unknown. In this study, a proteomics approach was employed to investigate the changes of protein expression profile induced by ELF MF in human breast cancer cell line MCF7, in order to determine ELF MF-responsive proteins. MCF7 cells were exposed to 50 Hz, 0.4 mT ELF MF for 24 h and the changes of protein profile were examined using two dimensional electrophoresis. Up to 6 spots have been statistically significantly altered (their expression levels were changed at least 5 fold up or down) compared with sham-exposed group. 19 ones were only detected in exposure group while 19 ones were missing. Three proteins were identified by LC-IT Tandem MS as RNA binding protein regulatory subunit, Proteasome subunit beta type 7 precursor and Translationally Controlled Tumor Protein. Our finding showed that 50 Hz, 0.4 mT ELF MF alternates the protein profile of MCF7 cell and may affect many physiological functions of normal cell and 2-DE coupled with MS is a promising approach to elucidating cellular effects of electromagnetic fields.
Extremely Low Frequency Electromagnetic Fields Do Not Affect DNA Damage and Gene Expression Profiles of Yeast and Human Lymphocytes.

Dept. of Pharmacology, Univ. of Florence, Viale Pieraccini 6, 50139, Florence, Italy, e-mail: cristina.luceri@unifi.it (C.L., C.D., L.G., P.D.); Dept. of Statistics, Univ. of Florence, Florence, Italy (M.B., F.A., M.P., A.B.); Inst. for Applied Physics, Nello Carrara, Natl. Res. Council, Florence, Italy (D.A., L.P.); Transfusion Unit, Meyer Hosp., Florence, Italy (F.B.)

2005

Funding: MAP (Italian Ministry for Productive Activities)

IVI SUMMARY: The authors examined the genotoxic potential of extremely low frequency (ELF) electromagnetic fields (EMFs) in yeast cells and human lymphocytes. Cultures of yeast cells (Saccharomyces cerevisiae, strain DBY 747) and lymphocytes isolated from buffy coats of blood samples collected from 18 healthy donors, 20-50 yr old, were exposed for 18 hr to 50-Hz magnetic fields (MFs) with flux densities of 1, 10, or 100 µT. The yeast cells were grown in 1% yeast extract/2% peptone/2% glucose (YPD) medium at a density of 1.6 x 10(7) cells/ml. The lymphocytes were collected and purified using the Lymphoprep protocol (Axis-Shield, Oslo, Norway) and were suspended in RPMI 1640 medium supplemented with 100,000-U/l penicillin G, 100-mg/l streptomycin sulfate, 10% heat inactivated fetal calf serum, and 2-mM L-glutamine at a density of 1 x 10(6) cells/ml. MFs were produced by the "HC-50" exposure system, developed at IFAC-CNR (Institute for Applied Physics "Nello Carrara," Italian National Research Council, Florence, Italy). The system consisted of a pair of parallel Helmholtz coils connected in series. The coils had a diameter of 40.6 cm and were fabricated with 16 turns of 0.5-mm thick enameled copper wire. The separation distance between the coils was 20.3 cm. The coil system was driven by an adjustable power supply unit that could produce 50-Hz MFs with flux densities of 1 to up to 150 µT. The uniformity of the field, within 1% for the exposure volume, was confirmed with an EMDEX II meter. For experiments with yeast cells, cells were grown in a water bath with the water temperature set at 30 C. The bath was inserted into the Helmholtz coil system, but the motor operating the water bath was placed more than 2 m away from the incubator to avoid any effect of the EMF from the motor on the cells. Unexposed yeast cells were grown in a different water bath placed in a part of the laboratory where the ambient MF was below 0.1 µT. For experiments with lymphocytes, each lymphocyte sample was divided into 2 aliquots, one for exposure to the MF at the desired flux density and the other to be sham exposed. Temperature measurements made in the standard cell incubators with a precision thermocouple connected to an electronic temperature monitor found that the temperature in the area where the cells were placed was maintained at 37 +/- 0.5 C. The ambient MF in the incubators was 1 µT. To determine if a 1-µT MF was able to affect gene expression or was genotoxic to lymphocytes, a low-exposure control incubator system was created to eliminate this MF. Flasks containing lymphocytes were maintained at 37 C in air using 2 water baths that were placed in separate areas of the laboratory where the background MF was below 0.1 µT (at least 2 m away from any electrical equipment). The temperature in each water bath was monitored using the precision thermocouple/monitoring system as before. Genotoxicity was assessed by measuring induction of DNA damage using the comet assay, as described by Giovannelli et al. (Mutat Res 538:71-80, 2003). The effects of the MFs on gene expression were evaluated by constructing gene expression profiles of MF-exposed and sham-exposed lymphocytes and yeast cells and examining these using DNA microarray analysis utilizing a library containing 6212 oligonucleotides for yeast cell analysis, and a library of 13,971 oligonucleotides for lymphocyte analysis. Comet data were tested statistically by 1-way ANOVA. Gene expression data obtained for yeast cells were tested statistically by the statistical analysis of microarray technique, described by Tusher et al. (Proc Natl Acad Sci U S A 98:5116-5121, 2001). The lymphocyte gene expression data were tested statistically using the Bayesian method, as proposed by Loenst jedt and Speed (Stat Sin 12:31-46, 2002). In both analyses, a p value of 5% was considered to indicate a statistically significant effect. In the preliminary experiments to assess the effects of low-level (0.1 or 1-µT) MF exposure on induction of DNA damage in human lymphocytes, the baseline level of DNA strand breaks measured at 1 µT was slightly, but significant, higher in cells kept in the water bath (3.19 +/- 0.14 breaks/10(10) Da DNA) than cells kept in an incubator at 1-µT ambient MF (1.29 +/- 0.11 breaks/10(10) Da DNA), but was only slightly higher than cells in the water bath exposed to a 1-µT MF (2.76 +/- 0.11 breaks/10(10) Da DNA). Cell viability was greater than 99% for lymphocytes maintained in both condition. The baseline level of oxidized DNA bases, also used as a measure of DNA damage, measured at 1 µT was greater for cells maintained in the incubator.
than for cells maintained in the water bath. Exposure of cells to 10 and 100-μT 50-Hz MFs did not significantly increase the level of DNA damage (measured either as strand breaks or oxidized bases) relative to the 1-μT MF exposures: there were 0.86 +/- 0.06 breaks/10(10) Da DNA in cells in the incubator exposed to 10 μT, and 1.41 +/- 0.09 breaks/10(10) Da DNA in cells in the incubator exposed to 100 μT. Analysis of gene expression in lymphocytes indicated that just 1 gene was downregulated by exposure at 100 μT. One gene was downregulated, and 2 genes were upregulated after exposure to the 10-μT field. No genes were up or downregulated by exposure to the 1-μT field. Analysis of yeast cells showed that exposure to the 100-, 10-, and 1-μT MFs resulted in 2, 15, and 2 genes being differentially expressed compared to sham exposure. Most of these genes were downregulated, but 1 gene, the SPS100 gene that is involved in sporulation, was consistently upregulated by exposure at all 3 MF intensities. With a P value of 5%, none of the genes, however, were considered to be significantly up or downregulated, suggesting that the observed effects may reflect "experimental noise." The authors concluded that 1- to 100-μT ELF MFs do not induce DNA damage or alter gene expression in yeast cells and human lymphocytes. The fact that no significant variation in gene expression or consistent pattern of DNA damage was observed in these experiments supports the suggestion that EMFs at these frequencies and intensities apparently do not affect eukaryotic cell physiology. (34 Refs).

Scarfi, M. R.; Sannino, A.; Perrotta, A.; Sarti, M.; Mesirca, P.; Bersani, F.
CNR-Inst. for Electromagnetic Sensing of Environment (IREA), Via Diocleziano, 328-80124 Naples, Italy, e-mail: scarfi.mr@cnr.it (M.R.S., A.S., A.P., M.S.); Dept. of Physics, Univ. of Bologna, 41027 Bologna, Italy (P.M., F.B.)
Radiat Res 164(3):270-276
2005

Funding: EU Commission "quality of life and management of living resources" Program Grant No. QLK4-CT-1999-01574; Italian Ministry of Univ. and Scientific Res.

IVI SUMMARY: The authors examined the potential genotoxicity of intermittent extremely low frequency (ELF) electromagnetic fields (EMFs) in human fibroblast cultures. The purpose of the study was to verify results reported by Ivancsits et al. (Mutat Res 519:1-13, 2002; Int Arch Occup Environ Health 76:431-436, 2003; Mech Ageing Dev 124:847-850, 2003) indicating that intermittent exposure of human diploid fibroblasts (ES-1 cells) and other cell types to 50-Hz intermittent EMFs caused a significant induction of DNA damage, whereas continuous exposure to a sinusoidal field did not produce any genotoxic effects. ES-1 fibroblasts obtained from a 6-yr old male were exposed to the same intermittent 50-Hz fields using the same experimental conditions, procedures, and type of exposure as used in the Ivancsits et al. studies. The field consisted of a sinusoidal 50-Hz, 1-mT rms (10-G) magnetic field (MF) switched on and off (5 min on, 10 min off) during exposures of 15 or 24 hr. The field was produced by the system described by Schuderer et al. (Bioelectromagnetics 25:582-591, 2004). The system consisted of two 4-coaxial square coil arrays (20 cm edge length) arranged horizontally and, thus, parallel to the surface of the cell cultures. The coil systems were enclosed in mu-metal boxes to minimize stray currents. The vertical distances from the center to the inner and outer coils were 3 and 9 cm, respectively, a configuration that had been optimized to achieve maximum field uniformity, better than 1% within a region of approximately 12 x 12 x 20 cm. The coils were wound using a pair of parallel wires (inner coils 50 turns and outer coils 56 turns), so that current could be directed to flow in either the same or the opposite direction, the former producing an exposure condition and the latter a sham exposure condition. Both systems were placed inside a commercial CO2 incubator, which maintained a humidified 5% CO2 atmosphere at 37 C. The experimental setup was controlled by a personal computer which randomly decided which coil system would be used for exposure and which would be used for sham exposure. For exposure, ES-1 cells were cultured in DMEM supplemented with 10% fetal calf serum, 20-mM HEPES buffer, 2-mM L-glutamine, 100-IU/ml penicillin, and 100-ug/ml streptomycin. Induction of DNA damage was assessed, as in the Ivancsits et al. studies, using the alkaline comet assay. The Ivancsits et al. studies were extended in this study by also exposing ES-1 cells to a 1-mT MF made up of a 50-Hz basic frequency plus its harmonics (termed a power line MF, MF-PI) and evaluating DNA damage using the cytogenetics block micronucleus (MN) assay. The MF-PI signal corresponded to the maximum accepted distortion for low to medium voltage power systems, as described by the International Electronic Commission (Limits-Assessment of emission limits for disturbing loads in medium and high-voltage power systems. In: Electromagnetic Compatibility (EMC), Part 3.6, IEC technical report IEC 61000, Standards Australia International, Sydney, 1996). Additional ES-1 cells were treated with 25- to 100-uM hydrogen peroxide (H2O2) and 0.005- to 0.025-ng/ml mitomycin C (MMC) for 30 min as positive controls for the comet and MN assays, respectively. Data were tested statistically by ANOVA, Tukey's honestly significant differences test, and the 2-tailed paired Student's t test. None of the EMF exposures caused any significant increases in DNA damage, assessed by either the comet assay or the MN test, compared to sham exposure. For example, in the 24 hr exposure, intermittent MF exposure produced no increase in tail factor (3.5 +/- 0.2 vs. 3.6 +/- 0.3 in sham), tail moment (0.35 +/- 0.06 vs. 0.4 +/- 0.1), percentage DNA (1.2 +/- 0.2 vs. 1.4 +/- 0.4), or comet moment (1.0 +/- 0.1 vs. 1.1 +/- 0.1); and 9.0 +/- 0.6 vs. 9.3 +/- 0.8 micronuclei per 2000 binucleated cells. [These parameters were not specifically defined in the paper; tail factor indicates the amount of DNA in the tail, whereas tail moment is a product of tail length and the fraction of total DNA in the tail, which incorporates a measure of both the smallest detectable size of migrating DNA, reflected in the comet tail length, and the number of relaxed or broken pieces, represented by the intensity of DNA in the tail]. As expected, H2O2 and MMC caused significant increases in DNA damage as assessed by both assays (e.g., H2O2 values for the 4 comet assay parameters were 37.0, 31.7, 10.35, and 12.55 and the MMC exposure induced 40 +/- 4 micronuclei per 2000 binucleated cells). The authors concluded that these results do not support the view that intermittent exposures to 50-Hz MFs induce genotoxic effects nor do they confirm the results reported by Ivancsits et al. The failure to replicate the results of the Ivancsits et al. studies cannot be readily explained at the present time since efforts were...
made to exactly replicate the exposure conditions. The authors noted a few methodological differences, such as use of image analysis software rather than classification by eye to categorize DNA damage in the comet tail factor analysis and a low and consistent background micronuclei count in the ES-1 cells used in their experiments, but indicated that these differences should have increased the reliability of their results. They could find no obvious errors in the experiments of either group, and suggested it would be worth an additional effort to understand the reason for the discrepancy in results, especially since Ivancsits et al. reported consistent results using several genotoxic assays (comet assay results, chromosomal aberrations, and micronuclei), and other groups have reported positive results with different systems that conflict with largely negative results reported by other groups.

(27 Refs).
Chromosomal Damage in Human Diploid Fibroblasts by Intermittent Exposure to Extremely Low-Frequency Electromagnetic Fields.

Winker, R.; Ivancsits, S.; Pilger, A.; Adlkofer, F.; Rudiger, H. W.
Div. of Occupational Medicine, Medical Univ. of Vienna, Wahringer Gurtel 18-20, Vienna A-1090, e-mail: robert.winker@meduniwien.ac.at Austria (R.W., S.I., A.P., H.W.R.); Foundation Verum, Pettenkoferstr. 33, D-80336 Muenchen, Germany (F.A.)

Mutat Res 585(1-2):43-49

2005

Funding: European Union under the programme "Quality of Life and Management of Living Resources," Key Action 4 "Environment and Health":QLK4-CT-1999-01574

IVI SUMMARY: The authors examined the potential of intermittent extremely low frequency (ELF) magnetic fields (MFs) to induce chromosome damage in human fibroblasts. Diploid fibroblasts harvested from a skin biopsy obtained from a healthy 6-yr-old male were cultured in DMEM supplemented with 10% fetal calf serum, 20-mM HEPES buffer, 40-ug/ml neomycin, 2-mM L-glutamine, 100-IU/ml penicillin, and 100-ug/ml streptomycin. Cells were exposed for 2 to 24 hr to an intermittent 50-Hz, 1-mT (10-G), MF characterized by "on" periods of 5 min and "off" periods of 10 min. The MF was produced by two bifilar 4-coil systems (2 coils with 56 windings, 2 coils with 50 windings) each of which was placed inside a mu-metal box that reduced background AC MFs and the static geomagnetic field. Current in the bifilar coils could be switched parallel for active field exposure or nonparallel for sham exposure. Both coil systems were placed inside a commercial incubator (BBD 6220, Kendro, Vienna) maintained a 37°C under a humid 5% CO2 atmosphere. The temperature difference between active exposure and sham exposure incubators did not exceed 0.3°C. A computerized control system randomly determined which system was used for exposure and sham exposure, producing blinded conditions for experiment. At the end of the experimental periods, fibroblasts were scored for micronuclei (MN) and chromosomal aberrations (CAs). The fibroblasts were analyzed for MN using the assay described by Fenech and Morley (Mutat Res 203:339-345, 1985) and Fenech (Mutat Res 285:35-44, 1993). Cells were trapped at metaphase using a cytochalasin B block, treated with hypotonic KCl solution, fixed with methanol/aqua bidest, stained with 4',6-diamidino-2-phenylindole, and 2000 binucleated cells/sample were scored under fluorescent microscopy. CAs were assayed by scoring 10,000 (5000 exposed, 5000 sham exposed) fibroblasts trapped at metaphase with colcemid and stained with 4% GIEMSA prepared in Sorenson's buffer. The following types of CAs were scored: gaps, breaks, rings, dicentrics, and acentric fragments. The data were tested statistically by the chi-squared test or the independent Student's t-test. Exposure to the MF produced a time-dependent increase in MN frequency that became statistically significant after 10 hr (p<0.05). After approximately 15 hr of exposure, the MN frequency plateaued at a level of about 3 times the control value. Induction of CAs by the MF was examined after 15 hr of exposure, the time point that showed the strongest increase in MN frequency and DNA damage in a previous study that used the Comet assay to assess DNA damage after exposure to the intermittent MF (Ivancsitis et al., Mech Ageing Dev 124:847-850, 2003). Exposure to the MF for 15 hr produced significant increases in the frequency of all 5 types of CAs. The most pronounced effects were seen in chromosome gaps (increased from 5.5 +/- 0.7 to 23.4 +/- 1%, p<0.001) chromosome breaks (increased from 1.3 +/- 0.3 to 2.2 +/- 0.3%, p=0.0015), dicentric chromosomes (increased from 0.06 +/- 0.05 to 0.4 +/- 0.1%, p<0.001), and acentric fragments (increased from 0.02 +/- 0.04 to 0.3 +/- 0.07%, p<0.001). There was a marginal increase in ring chromosomes (increased from none to 0.1 +/- 0.07%, p=0.0133). The authors concluded that these results provide clear evidence that intermittent ELF EMFs are genotoxic and clastogenic. These effects must occur via an indirect mechanism since ELF EMFs are not strong enough to directly break chemical bonds in DNA.

(45 Refs).

AUTHOR KEY WORDS: ELF-EMF, Intermittent exposure, Micronuclei, Chromosomal aberrations
The authors examined the potential for extremely low frequency (ELF) magnetic fields (MFs) to induce cell proliferation and DNA damage in several types of mammalian cells: embryonic lung fibroblasts (WI-38 cells), human leukemia cells (HL-60 cells), and rat fibroblasts (Rat-1 cells). WI-38 cells were selected to represent a normal cell line, HL-60 cells a neoplastic cell line, and Rat-1 cells an immortalized cell line. The 3 cell types were maintained in their specific culture media at 37°C under a 5% CO2 atmosphere in a tissue culture incubator. WI-38 cells were cultured in Eagle Basal Medium supplemented with 10% fetal calf serum (FCS) and 1-mM sodium pyruvate. HL-60 cells were grown in RPMI 1640 medium supplemented with 10% FCS. Rat-1 cells were grown in EMEM medium supplemented with 10% FCS. Cells were exposed to 50-Hz MFs at flux densities of 0.5, 0.75, or 1.0-mT, produced by the solenoid system described by Grassi et al. (Cell Calcium 35:307-315, 2004). Exposure times varied from 3 to 72 hr. For exposure, the cells were placed in culture dishes that were held in a Plexiglas cylinder, and the cylinder was inserted into the solenoid within an incubator. Control cell cultures were placed in the same incubator, but kept outside the solenoid. A thermometer probe placed in exposed and control cell culture dishes revealed no significant changes in temperature during an experiment. Cell proliferative activity was assessed at 24-hr intervals by counting cells using an automatic Coulter counter. DNA damage was determined by analyzing cells for the presence of 8-hydroxydeoguanosine (8-OHdG) adducts using the immunohistochemical technique described by Yarbrough et al. (Cancer Res 56:683-688, 1996) and DNA single-strand breaks (SSBs) were determined by single-cell microgel electrophoresis using the basic procedure described by Singh et al. (Exp Cell Res 175:184-191, 1988). In experiments where the effects of antioxidant treatment were investigated, 10-uM DL-alpha-tocopherol (vitamin E) in tetrahydrofuran or 96% ethanol was added to the cells. All experimental data were tested statistically by multifactorial 2-way ANOVA and Tukey's Honestly Significant Difference test. In an initial experiment, the 3 cell types were exposed to 0.5, 0.75, or 1.0-mT MFs for up to 72 hr to examine effects on cell proliferation rates. At 1-mT, proliferation of the 3 cell types was increased in a time-dependent manner. Increases in proliferation became statistically significant (p<0.05) after 48-hr of exposure. At 72 hr the proliferation rate had increased by 20-30% in all cells. Smaller increases in proliferation rate were induced by exposure to the 0.5 and 0.75-mT fields. After 48-hr exposure to the 0.75-mT field, the average cell number increase for the 3 cell types was 15-20%. Since effects of MF exposure were dose dependent, all subsequent experiments were performed using the 1-mT, 50-Hz MF to maximize any observed effects. To confirm results obtained by cell counts, HL-60, Rat-1, and WI-38 cells were exposed to the 1-mT, 50-Hz MF for up to 72 hr and time-related changes in the cell cycle distribution were measured at 12, 24, 48, and 72 hr by cytofluorimetric analysis. Representative data obtained with Rat-1 cells showed that after 12 hr of exposure the percentage of S-phase cells had significantly increased relative to control values (38.8% in exposed, 31.5% in controls, p<0.05). The increase was also significant at 48 hr (34.3 vs. 27.5%, p<0.05). By 72 hr, the percentage of cells in S phase was decreased by 30% (17.0 vs. 24.0), suggesting that exposed cells had reached confluence earlier than control cells. Similar results were obtained with HL-60 and WI-38 cells. In experiments to quantify DNA damage by measuring SSBs, the 3 cell types were exposed to 0.5-, 0.75-, and 1-mT MFs for up to 72 hr. At baseline, the level of SSBs in HL-60 cells was significantly higher than in Rat-1 and WI-38 cells, as would be expected for a hyperdiploid neoplastic cell line. Regardless of baseline levels of DNA damage, exposure to the fields caused a dose-dependent increase in SSBs, with 2 peaks occurring after 24 and 72 hr of exposure. Repair of DNA damage was also investigated in Rat-1 and HL-60 cells. After a 24-hr recovery period following exposure to the 1-mT MF, 92% of the SSBs induced in Rat-1 cells had been repaired vs. only 44% in HL-60 cells. This finding was not considered surprising, as neoplastic cells are known to be deficient in DNA damage repair. Pretreatment with 10-uM vitamin E prevented the stimulatory effect of the 1-mT MF on cell proliferation in all 3 cell types when measured after 24-hr exposure. After 48-hr exposure, the inhibitory effect was
seen in Rat-1 and WI-38 cells, but not in HL-60 cells. After 72-hr of MF exposure, vitamin E inhibited cell proliferation only in WI-38 cells. Similar effects on induction of SSBs were seen in cells pretreated with vitamin E. Effects were more persistent in Rat-1 and WI-38 than in HL-60 cell. When 8-OHdG levels were used as a marker of DNA damage, exposure to the 1-mT 50-Hz MF for 24, 48, or 72 hr significantly increased levels of 8-OHdG adducts, with the peak response occurring after 24 and 72 hr exposure. Pretreatment with 10-uM vitamin E inhibited formation of 8-OHdG adducts by about 50% throughout the period of MF exposure. To assess a possible role of reactive oxygen species (ROS) in MF-induced DNA damage and proliferation, Rat-1 cells preloaded with dichlorodihydrofluorescein diacetate (DCF), a marker for intracellular ROS, were exposed to the 1-mT, 50-Hz MF for 3 or 24 hr. Increases in intracellular fluorescence were measured a commercial assay kit, Cytofluor 2300/2350 (Millipore, Billerica, MA). An 18% increase in intracellular fluorescence was seen after 3 hr of MF exposure and it persisted for 24 hr. Pretreatment with 10-uM vitamin E almost completely prevented the increase in DCF fluorescence at 3 hr and reduced the level of fluorescence by approximately 50% at 24 hr. In a final experiment to examine possible changes in expression of proteins involved in redox-mediated signaling, Rat-1 cells were exposed to the 1-mT, 50-Hz MF for 3, 6, 12, 24, or 36 hr and Western blotting was used to follow changes in expression of p65 and p50 proteins related to NF(kappa)B (NFkB), and the I(kappa)B(alph) (IkBa) subunit. Exposure to the MF caused significant increases in the level of expression of p65 and p50 after 6, 12, and 24 hr. The level of expression of the IkBa subunit tended to decrease after 6 to 24 hr of exposure. The p65/IkBa ratio, used as an indicator of NFkB activity, increased significantly after 6-24 hr of exposure with the maximum response after 6 hr of exposure. Pretreatment with 10-uM vitamin E did not affect p65 expression in either MF-exposed or control cells. Vitamin E pretreatment always abolished the MF-induced increase in the p65/IkBa ratio, indicating that redox-mediated signals are involved in the cell proliferative responses to ELF MF exposure. The authors concluded that ELF MFs affect cellular proliferation and DNA damage in normal and transformed (or tumor) cells through the actions of free radical species. Because normal and transformed/tumor cells have very different proliferation rates, these results emphasize the importance of continued research aimed at characterizing the role of ELF EMFs in carcinogenesis and tumor progression.

(49 Refs).

AUTHOR KEY WORDS: 8-OHdG, Single strand break, Cell cycle, DCF, NF(kappa)B, I(kappa)B, alpha-Tocopherol
Increased Levels of Inducible HSP70 in Cells Exposed to Electromagnetic Fields.

Sezione di Patologia Molecolare ed Immunologia, Dipartimento di Medicina Sperimentale, Universita degli Studi di Parma, Parma 43100, Italy, e-mail: roberta.alfieri@unipr.it (R.R.A.)
Radiat Res 165(1):95-104
2006
Funding: Universita degli Studi di Parma; MUIR.

ABSTRACT: Because reports in the literature on the effects of electromagnetic fields (EMFs) on expression of the 70-kDa heat-shock protein (HSP70) are somewhat contradictory, we studied the influence of low-frequency EMFs on the accumulation of inducible HSP70 in several cell models. Some of the cell types tested showed increased levels of HSP70 protein when exposed for 24 hr to 50 Hz, 680 µT EMFs. In endothelial cells, EMFs alone induced only a poor and transient activation of the heat-shock transcription factor 1 (HSF1); however, neither the level of HSP70 mRNA nor the synthesis of HSP70 appeared to be altered significantly. Accordingly, transfection experiments involving HSP70 promoter showed that gene transcription was not affected. We also noted a marked reduction in proteasome activities in cell extracts exposed to EMFs. Interestingly, the heat-shock-induced levels of HSP70 mRNA and protein were increased by a concomitant weak stressor like EMFs. Taken together, our results indicate that in EMF-exposed endothelial cells, HSP70 gene transcription and translation are unaffected; however, EMFs alone promoted accumulation of the inducible HSP70 protein, probably by increasing its stability, and it enhanced accumulation and translation of the heat-induced HSP70 mRNA when applied in concert with heat shock. (43 Refs).
M12:
Exposure to AC and DC Magnetic Fields Induces Changes in 5-HT1B Receptor Binding Parameters in Rat Brain Membranes.

Espinosa, J. M.; Liberti, M.; Lagroye, I.; Veyret, B.
Bioelectromagnetics Lab., Ecole Pratique des Hautes Etudes, Pessac, France, e-mail: b.veyret@enscpb.fr (B.V.)
Bioelectromagnetics 27(5):414-422
2006
Funding: EDF/RTE, France.

ABSTRACT: The binding properties of the G-protein coupled receptor (GPCR) serotonin 5-HT1B receptor were studied under exposure to AC (50 and 400 Hz) and DC magnetic fields (MF) in rat brain membranes. This was an attempt at replicating the positive findings of Massot et al. In saturation experiments using [3H]5-HT, 1-h exposures at 1.1 mTrms 50 Hz caused statistically significant increases in both the KD and Bmax binding parameters, from 1.74 +/- 0.3 to 4.51 +/- 0.86 nM and from 1428 +/- 205 to 2137 +/- 399 CPM, respectively, in good agreement with previous results. Exposure of the membranes at 400 Hz 0.675 mTrms did not elicit a larger increase in KD in spite of a much larger induced current density. DC fields (1.1 and 11 mT) had a lesser effect compared to AC fields at low values of KDsham, but decreased the affinity at higher values of KDsham. Modeling of the receptor-ligand-G protein interactions using the extended ternary complex model yielded good fits for all our data and that of Massot et al., showing that the AC field may act by decreasing the ability of the G-protein to alter the ligand-receptor affinity. The hypothesis is that the bipolar nature of the AC field explains the different nature of the effects observed with AC and DC exposures. These findings constitute one of the few documented pieces of evidence for cell-free effects of DC and extremely low frequency (ELF) AC MFs in the mT range.

AUTHOR KEY WORDS: Binding, Ligand, G-protein, Coupled receptors, Rat brain membranes, Extended ternary complex model
M13:
Alteration in Cellular Functions in Mouse Macrophages after Exposure to 50 Hz Magnetic Fields.

Frahm, J.; Lantow, M.; Lupke, M.; Weiss, D. G.; Simko, M.
Dept. of Cell Biology and Biosystems Technology, Unit of Environmental Physiology, Univ. of Rostock, Albert-Einstein-Strasse 3. D-18057 Rostock, Germany, e-mail: myrtill.simko@biologie.uni-rostock.de (M.S.)
J Cell Biochem 98: "in press"
2006

ABSTRACT: The aim of the present study is to investigate whether extremely low frequency electromagnetic fields (ELF-EMF) affect certain cellular functions and immunologic parameters of mouse macrophages. In this study, the influence of 50 Hz magnetic fields (MF) at 1.0 mT was investigated on the phagocytic activity and on the interleukin-1beta (IL-1beta) production in differentiated macrophages. MF-exposure led to an increased phagocytic activity after 45 min, shown as a 1.6-fold increased uptake of latex beads in MF-exposed cells compared to controls. We also demonstrate an increased IL-1beta release in macrophages after 24 h exposure (1.0 mT MF). Time-dependent IL-1beta formation was significantly increased already after 4 h and reached a maximum of 12.3-fold increase after 24 h compared to controls. Another aspect of this study was to examine the genotoxic capacity of 1.0 mT MF by analyzing the micronucleus (MN) formation in long-term (12, 24, and 48 h) exposed macrophages. Our data show no significant differences in MN formation or irregular mitotic activities in exposed cells. Furthermore, the effects of different flux densities (ranging from 0.05 up to 1.0 mT for 45 min) of 50 Hz MF was tested on free radical formation as an endpoint of cell activation in mouse macrophage precursor cells. All tested flux densities significantly stimulated the formation of free radicals. Here, we demonstrate the capacity of ELF-EMF to stimulate physiological cell functions in mouse macrophages shown by the significantly elevated phagocytic activity, free radical release, and IL-1beta production suggesting the cell activation capacity of ELF-EMF in the absence of any genotoxic effects.
M14:
Chromatid Damage in Human Lymphocytes is Not Affected by 50 Hz Electromagnetic Fields.

Hone, P.; Lloyd, D.; Szluinska, M.; Edwards, A.
Health Protection Agency, Radiation Protection Div., Chilton, Didcot OX11 0RQ, UK
2006

ABSTRACT: Cultured human blood lymphocytes were exposed during the S/G2 phases of the cell cycle to continuous extremely low frequency (50 Hz) electromagnetic fields of 0.23, 0.47 or 0.7 mT either alone or immediately after an acute exposure to 1.0 Gy of gamma rays. The ionising radiation, as expected, induced chromosomal aberrations of the chromatid-type observed at the next metaphase. The field applied alone did not induce chromosomal damage nor did it modify the frequency of aberrations caused by the gamma rays.
M15:
Effects of Sinusoidal Magnetic Field Observed on Cell Proliferation, Ion Concentration, and Osmolarity in Two Human Cancer Cell Lines.

Huang, L.; Dong, L.; Chen, Y.; Qu, H.; Xiao, D.
Dept. of Electrical Engineering, Shanghai Jiaotong Univ., Huashan Rd. 1954, Shanghai, 200030 China, e-mail: dmxiao@sjtu.edu.cn (D.X., L.H.); Sch. of Pharmacy, Shanghai Jiaotong Univ., Shanghai, China (L.D., Y.C., H.Q.)
Electromagn Biol Med 25(2):113-126
2006
Funding: Natl. Natural Sci. Foundation of China, Grant No. 50477007

ABSTRACT: Low frequency magnetic fields have previously been shown to affect cell functions. In this article, the effects of 20 mT, 50 Hz sinusoidal magnetic field on cell proliferation, ion concentration, and osmolarity in two human cancer cell lines (HL-60 and SK-Hep-1) were investigated. Inhibition of cell growth was observed. On the other hand, the exposure also increased the Na+, K+ ion concentration and osmolarity in cell supernatant compared to the control group. To our knowledge, this is the first study on cancer cells where magnetic fields affect osmolarity in cell supernatant. In addition, a model of cells exposed to the oscillating magnetic field is described as well as the characteristics of ions in and out of cells. The experimental data appears to be consistent with the theoretical analysis. The results are also discussed in terms of the relationships among cell growth, ion concentration, and osmolarity. Magnetic field inhibitions of cell growth in vitro may relate to changes in cell ion concentration and osmolarity.
(39 Refs).
M16:
Effects on Apoptosis and Reactive Oxygen Species Formation by Jurkat Cells Exposed to 50 Hz Electromagnetic Fields.

Palumbo, R.; Capasso, D.; Brescia, F.; Mita, P.; Sarti, M.; Bersani, F.; Scarfi, M. R.
CNR-Inst. for Electromagnetic Sensing of Environment, Via Diocleziano, 328-80124 Naples, Italy. e-mail: scarfi.mr@irea.cnr.it (M.R.S., F.B., P.M., M.S.); CNR-Inst. of Biostructure and Bioimaging, Naples, Italy (R.P., D.C.); Istituto Nazionale di Biotecnologie e Biosistemi at the Dept. of Physics, Univ. of Bologna, Italy (F.B.)
Bioelectromagnetics 27(2):159-162
2006
Funding: ISPESL "Studio degli effetti dei campi elettromagnetici su cellule dell'organismo umano e su singole componenti cellulari" Grant No. B81/ML/02

IVI SUMMARY: The authors examined the capability of an intermittent extremely low frequency (ELF) magnetic field (MF) to induce apoptosis and formation of oxygen radicals (reactive oxygen species (ROS)) in human leukemia cells. Jurkat cells, a human T-leukemic cell line, were grown for 2 days in RPMI 1640 medium supplemented with 10% heat-inactivated fetal calf serum, 1% L-glutamine, and 0.5% of a penicillin/streptomycin cocktail. They were then seeded at a density of 2-3 x 10(5) cells/ml into culture plates and exposed to an intermittent 50-Hz 1-mT rms MF (5 min on/10 min off) for 1 hr (corresponding to 4 on/off cycles). The MF was produced by a system designed and constructed by IT'IS-foundation (Zurich, Switzerland), as described by Schuderer et al. (Bioelectromagnetics 25:582-591, 2004). The system consisted of 4 coaxial square coils (20 cm edge length) placed horizontally, each of which was housed inside a mu-metal box. The configuration of the coils was such that the field was directed perpendicular to the cell culture plates. The coils were wound using pairs of parallel coils (inner coils made up of 50 turns, outer coils, made up of 56 turns). Current flowing in the same direction in the coil pairs produced active MF exposure, while current flowing in the opposite direction produced sham exposure by inducing MFs of opposite phase that canceled each other. Both active and sham coil systems were housed in the same commercial CO2 incubator (Heraeus 6000). A personal computer randomly decided in a blinded manner which coil system would be used for active MF exposure and which would be used for sham exposure. The computer codes were not decoded by IT'IS Foundation until all analyses had been completed at the end of the experiment. Formation of ROS was assessed by measuring the oxygen radical-mediated oxidation of 2',7'-dichlorofluorescein diacetate to dichlorofluorescein using the spectrofluorimetric procedure described by Zeni et al. (Toxicology Letters 147:79-85, 2004). As a positive control, one culture of Jurkat cells was treated with 500-uM hydrogen peroxide (H2O2) for 1 hr. To evaluate apoptosis, changes in caspase-3 activity were assessed by stimulating Jurkat cells with 50-ng/ml anti-Fas, and then measuring caspase-3 catalyzed production of amino-4-trifluoromethyl coumarin (AFC) from carbobenzoxy-Asp-Glu-Val-Asp-7-amino-4-trifluoromethyl coumarin using the procedure described by Russo et al. (Oncogene 22:3330-3342, 2003). Results were normalized to protein concentrations, determined using the Bio-Rad protein microassay. Data were tested statistically by the 2-tailed paired Student's t-test. MF exposure did not significantly increase the level of ROS production. Only a 5.8% increase in oxygen radical formation was measured in exposed Jurkat cells compared to sham exposed cells. Treatment with the positive control (500-uM H2O2) produced a statistically significant 63% in ROS production. MF exposure caused a slight but significant 16% increase in spontaneous apoptosis in Jurkat cells (i.e., cells not treated with anti-Fas) compared to sham exposure, as indicated by an increase in caspase-3 activity (from 0.13 +/- 0.02 to 0.15 +/- 0.01 nM AFC/min/ug protein, p<0.05). Treatment with 50-ng/ml anti-Fas caused a 4-fold increase in Jurkat cell apoptosis. Exposure to the MF for 1 hr reduced the level of anti-Fas-induced apoptosis by 22% compared to sham exposure (caspase-3 activity reduced from 0.60 +/- 0.06 nM AFC/min/ug protein in sham-exposed cells to 0.47 +/- 0.04 nM AFC/min/ug protein, p<0.05). The authors concluded that exposure to an intermittent ELF MF can reduce apoptosis in response to anti-Fas stimulation in jurkat cells, and that the mechanism does not increased generation of ROS.
(18 Refs).
AUTHOR KEY WORDS: ELF fields, T-leukemia cells, ROS formation, Apoptosis
Extremely Low Frequency (ELF) Magnetic Fields and Apoptosis: A Review.

Santini, M. T.; Ferrante, A.; Rainaldi, G.; Indovina, P.; Indovina, P. L.
Dipartimento di Ematologia, Oncologia e Medicina Molecolare, Istituto Superiore di Sanita, Rome, Italy, e-mail: santini@iss.it; (M.T.S., A.F., P.I.); Istituto Nazionale per la Fisica della Materia, Unità di Napoli, Complesso Universitario Monte S. Angelo, Naples, Italy (G.R.); Dipartimento di Scienze, Fisiche, Università di Napoli Federico II, Complesso Universitario Monte S. Angelo, Naples, Italy (P.L.I.)
2005

IVI SUMMARY: The authors reviewed the literature on extremely low frequency (ELF) magnetic field (MF) exposure and apoptosis. The review covered the following major topics: (1) major characteristics of the apoptosis process, (2) selected studies investigating apoptosis induced by ELF MFs, and (3) possible effects of MFs on cells and mechanisms of induction of apoptosis. The term "apoptosis" was first used in 1972 to describe an alternative type of cell death different from necrosis. Apoptosis is characterized by DNA fragmentation, chromatin condensation, membrane blebbing, cell shrinkage, and formation of apoptotic bodies (membrane enclosed vesicles). Necrosis, on the other hand, involves cell swelling followed by rupture in which the cellular contents are released, thereby eliciting an inflammatory response. Biochemical events that lead to apoptosis are mediated by a family of cysteine proteases called caspases, which can be irreversibly activated, either autcatalytically or by enzymes with similar specificity. Caspases inactivate proteins involved in DNA repair, DNA replication, and mRNA splicing. They destroy nuclear lamina, which results in chromatin condensation, cleave cytoskeletal proteins such as gelsolin and a number of intermediate filament proteins, and play a role in the degradation of focal adhesion kinase. Caspases also cleave proteins of the B cell leukemia-2 (Bcl-2) cell family and produce fragments that can activate the apoptotic process. Apoptosis is closely related to the cell cycle. Although a cell can enter apoptosis at any phase in the cell cycle, the G1 checkpoint is considered especially important for apoptosis. When a cell reaches the G1 checkpoint, it can either enter S phase or, if there is any evidence of damage, initiate the apoptotic process. One of the principal apoptotic regulators is the family of endogenous Bcl-2 oncoproteins whose members possess both pro- and anti-apoptotic activity. The fine control of these proteins induces or prevents apoptosis in cells. Bcl-2 and Bcl-X(L) are considered the 2 most important anti-apoptotic proteins, while the Bcl-2-associated x protein (Bax) represents the major pro-apoptotic member of the Bcl-2 family. It is thought that these proteins mediate the formation of homo- and hetero-dimers, which, once formed in particular combinations, may result in cellular life or death. Blood cells in general and human lymphocytes in particular have frequently been used in studies of the effects of ELF MFs on cells because of possible association between exposure to ELF MFs and leukemia in epidemiologic studies. For example, in a study of human lymphocytes exposed to 80- and 800-µT, 50-Hz MFs and treated with 0, 5, 10, or 15-ng/ml vinblastine, a known aneugen, it was found that the MFs augmented the apoptotic effects of vinblastine (Verheyen et al., Bioelectromagnetics 24:160-164, 2003). Exposure to the 800-µT field alone, however, appeared to promote cell proliferation. Pre-exposure of HL-60 cells, a human promyelocytic leukemia cell line, its retinoic acid receptor-alpha mutant (HL-60R), and human Burkitt lymphoma Raji cells to a 60-Hz, 0.15-mT sinusoidal MF for 4 to 24 hr prior to their being heated in a 43 C water bath for 60 min protected against apoptosis induced by heating at 43 C. This protection was observed after 12 hr of MF exposure and lasted for up to 48 hr (Robison et al., Bioelectromagnetics 23:106-112, 2002). Many studies investigating apoptosis induced by ELF MFs have been conducted on cells taken from exposed mice. For example, testicular germ cell apoptosis was studied by histological examination, the TUNEL assay, and flow cytometry in germ cells taken from adult male BALB/c mice that had been exposed continuously to a 60-Hz 0.1 or 0.5-mT MF for 8 wk. Exposure to the fields did not significantly affect body and testicular weights of the mice; however, a significant increase in the number of dying germ cells was observed in seminiferous tubules in exposed mice (Lee et al., Asian J Androl 6:29-34, 2004). Although the mechanisms underlying the observed apoptotic effects are not completely understood, results seem to suggest that ELF MFs may trigger germ cell death by altering the endocrinological environment and by inhibiting the hypothalamic-pituitary-gonadal axis. To explain effects of MFs in cells, 3 models have been proposed: the ion cyclotron resonance (ICR) model, the quantum mechanical interaction (quantum model), and the forced vibration (FV) model. The ICR, quantum, and FV models postulate that a cell membrane (e.g., plasma, mitochondrial, or endoplasmic reticulum) has free ions present inside the cell or organelle, and on the outside. An ELF MF acts on these ions, especially calcium ions (Ca++), and induces false signals, possibly through the phosphoinositol cycle.
According to the ICR model, movement of free ions is perturbed by MFs of appropriate frequencies (cyclotron frequency), leading to disruptions of normal cell behavior. In the quantum model, MFs interact with biologically active ions, especially Ca++, that are bound to channel proteins and alter the opening and closing of ion channels. Ionic homeostasis is therefore altered, leading to disruption of cell functions. The FV model proposes that an ELF MF produces an oscillating force on free ions on both sides of the plasma membrane and causes ions to move across the membrane through transmembrane proteins. The external oscillating force induces a forced vibration on each free ion. When the amplitude of each ion's forced vibration reaches some critical value, the oscillating ions give a false signal for gating electrically or mechanically sensitive channels. This leads to disruption of the electrochemical balance of the membrane, and ultimately of cellular function. Since the amplitude of the forced vibration is inversely proportional to the frequency of the MF, low-frequency fields appear more bioactive than high-frequency fields. Based on available data, the authors proposed a model to explain how ELF MFs could affect apoptotic processes in cells. An ELF MF acting on Ca++ could induce variations in ionic homeostasis via one of the physical models (ICR, quantum, or FV). This leads to a perturbation of intracellular Ca++ levels ([Ca++]i), which in turn leads to an increase in mitochondrial Ca++ levels, followed by a release of Ca++ from the endoplasmic reticulum via activated inositol-1,4,5-triphosphate channels, a process postulated to be controlled by Bcl-2, which itself is localized in the endoplasmic reticulum. This chain of events triggers the apoptotic cascade. The induced perturbations in [Ca++]i result in the release of cytochrome c from mitochondria, activation of caspase 9 and, consequently, of the effector caspases 3, 6, and 7, and finally cell death through apoptosis.

(94 Refs).

AUTHOR KEY WORDS: Sinusoidal magnetic fields (50 Hz), Apoptosis, Calcium ion
Controversial Cytogenetic Observations in Mammalian Somatic Cells Exposed to Extremely Low Frequency Electromagnetic Radiation: A Review and Future Research Recommendations.

Vijayalaxmi; Obe, G.
Dept. of Radiation Oncology, Univ. of Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, TX 78229, e-mail: vijay@uthscsa.edu (V.); Dept. of Genetics, Univ. of Duisburg-Essen, Essen, Germany (G.O.)
Bioelectromagnetics 26(5):412-430
2005
Funding: Forschungsstelle fur Elektropathologie, Munich, Germany

IVI SUMMARY: The authors reviewed studies published in peer reviewed scientific journals during the years 1990-2003 that investigated cytogenetic effects of extremely low frequency (ELF) electromagnetic fields (EMFs) in mammalian cells. The studies used animals, rodent and human somatic cell lines, and freshly collected human lymphocytes exposed in vivo and in vitro to ELF magnetic fields (MFs), electric fields (EFs), or EMFs to assess the potential genotoxicity of the exposure using cytogenetic endpoints such as DNA strand breaks, chromosomal aberrations, micronuclei, and sister chromatid exchanges (SCEs). A total of 63 peer-reviewed scientific reports were identified and included in the review. Among all 63 studies, conclusions reported in 29 studies (46% of the total) did not indicate any cytogenetic damage produced by ELF MF, EF, or EMF exposure compared with sham exposed and/or unexposed cells. Fourteen studies (22%) suggested an increase in cytogenetic damage in exposed cells. Results from the remaining 20 studies (32%) were inconclusive. Twenty-three studies investigated effects of combined exposure to ELF MF, EF, or EMF in combination with a known genotoxic mutagen. Of these, results from 10 studies did not identify any cytogenetic effect, 1 yielded evidence of a genotoxic effect, and the remaining 12 combination exposure studies produced inconclusive results. Most of the studies that indicated no genotoxic effects described the EF, MF, and/or EMF exposure conditions and experimental protocols in sufficient detail so that the results could be verified by independent researchers. Most of the studies reporting positive effects could not be replicated. The authors noted that the majority of reviewed studies used a wide range of EMF exposure variables and experimental protocols, thereby making it almost impossible to directly compare results obtained by different investigators and independent researchers. The authors suggested a number of possible causes for the discrepant findings. Historically, there has been a 10% incidence of sporadic and non-reproducible positive results in micronuclei assays in vivo studies in rodents. With in vitro studies, changes in the osmolarity or pH of the medium during treatment/exposure have been shown to alter the incidence of chromosomal aberrations, micronuclei, and SCEs. Unless appropriate statistical procedures to consider the multiple observations tested are used, analysis of results obtained from multiple genotoxic endpoints could have misidentified and reported as a "significant effect" positive results that were, in fact, due to random chance. The authors concluded that the preponderance of data thus far available in the literature shows that ELF EMF exposure itself is not genotoxic to mammalian cells. Research, however, should be continued to resolve the "controversial" (positive) findings reported in some of the studies. Data obtained from a well-coordinated multicenter collaborative study with adequate statistical power will be needed to identify factors contributing to the controversial findings. Such studies will probably require ELF EMF exposures using flux densities in the 1-10 mT range conducted in a single laboratory with validated dosimetry. Multiple cytogenetic endpoints (e.g., chromosome aberrations, micronuclei, SCEs) and multiple cell types of human origin (e.g., blood lymphocytes, fibroblasts, tumor cells) should be examined. It may also be desirable to examine cells with different genetic backgrounds.

AUTHOR KEY WORDS: ELF, DNA Strand breaks, Chromosomal aberrations, Micronuclei, Sister chromatid exchanges, Electric fields, Magnetic fields
ABSTRACT: Comparatively high exposures to power-frequency electric and magnetic fields produce established biological effects that are explained by accepted mechanisms and that form the basis of exposure guidelines. Lower exposures to magnetic fields (< 1 µT average in the home) are classified as "possibly carcinogenic" on the basis of epidemiological studies of childhood leukemia. This classification takes into consideration largely negative laboratory data. Lack of biophysical mechanisms operating at such low levels also argues against causality. We survey around 20 biophysical mechanisms that have been proposed to explain effects at such low levels, with particular emphasis on plausibility: the principle that to produce biological effects, a mechanism must produce a "signal" larger than the "noise" that exists naturally. Some of the mechanisms are impossible, and some require specific conditions for which there is limited or no evidence as to their existence in a way that would make them relevant to human exposure. Others are predicted to become plausible above some level of field. We conclude that effects below 5 µT are implausible. At about 50 µT, no specific mechanism has been identified, but the basic problem of implausibility is removed. Above about 500 µT, there are established or likely effects from accepted mechanisms. The absence of a plausible biophysical mechanism at lower fields cannot be taken as proof that health effects of environmental electric and magnetic fields are impossible. Nevertheless, it is a relevant consideration in assessing the overall evidence on these fields.