# Symposium 2000:
# Low frequency EMF,
# Visible Light,
# Melatonin and Cancer

# Abstracts of papers



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# Abstracts

## Historical Account of the Research Related to EMF, Melatonin and Cancer


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There are several questions that must be answered when research related to the biological effects and potential health consequences of electromagnetic field (EMF) exposures are evaluated. The tenets of the melatonin hypothesis rely on the fact that artificially generated EMF suppress the product of endogenous melatonin and this reduction increases the likelihood of cancer. The two questions that must be answered are: Do EMF exposures to which humans are exposed significantly attenuate nocturnal melatonin levels and, if they do, does the experimental evidence support a relationship between melatonin and cancer? The first question has been extremely difficult to

answer. Research efforts, mostly performed using experimental animals, carried out over the last 20 years have failed to provide a definitive answer to this question. Studies using humans have yielded equally ambiguous results. Over the course of the 20 year period the exposure systems have been elegantly refined and the measurement techniques for melatonin and its metabolites have been perfected. Many of the studies were jointly conducted by biologists and biophysicists with great attention being paid to every known detail. Yet, despite these concentrated efforts, the role (if any) of EMF in altering the production and/or release of melatonin remains undefined. This has proved frustrating to the scientists performing the studies and to the regulators who were depending on this information to recommend exposure limits. The second question, i. e., is there an association between melatonin and cancer is somewhat easier to answer. Data from a very large number of studies over many years have shown that melatonin has at least two mechanisms by which it can reduce cancer incidence and/or growth. First, as a direct free radical scavenger and antioxidant, melatonin is now known to protect nuclear DNA from oxidative damage. In doing so, it reduces the incidence of mutations and the likelihood of cancer. The free radical scavenging actions of melatonin are known to be receptor independent. Secondly, melatonin also is known to inhibit the growth of a diverse type of already established tumors; this action is believed to involve membrane receptors for melatonin on the cells in question. Some of the mechanisms by which melatonin reduces cancer growth have been identified and include the inhibition of fatty acid uptake by cancer cells which depend on these growth factors for their livelihood. Thus, while melatonin is now accepted as an oncostatic agent, it remains to be determined whether EMF exposures actually reduce melatonin synthesis or action to levels that an increased cancer incidence would be a consequence.

## The Melatonin Hypothesis: Circadian Disruption and Breast Cancer

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Breast cancer incidence and mortality are much higher in industrialized societies than in developing societies, and the reasons for these differences are not well understood. One idea that is receiving wide attention is the possible role of environmental exposures in inducing ’endocrine disruption’. Environmental exposures that disrupt human circadian hormone rhythms (i.e., ’circadian disruption’) may be an important example of endocrine disruption. The daily cycle of melatonin concentration in the blood is one of the signature aspects of circadian biology; blood melatonin level follows the solar cycle of terrestrial illumination and is high at night and low during the day. It can be acutely suppressed by bright artificial light in the middle of the night. Melatonin plays a critical role in reproduction among seasonally breeding mammals, and has been shown to reduce chemically-induced mammary tumorigenesis in rats. Low nocturnal circulating melatonin may be related directly to risk of breast cancer, or may be related through its impact on estrogen, or both.

Among the most profound environmental consequences of electrification of societies is exposure to light at night, and to light during the day of a different character than sunlight. We have come in our evolutionary past from an environment with dark nights and bright, full spectrum days to an environment with lighted nights in homes during sleep and dim, spectrum-restricted "days" inside buildings where most people now work. Indeed, the "built environment" is the predominant environment in the industrialized world. Since the vast majority of people in industrialized societies work in buildings, and virtually all people sleep in buildings, the long-term health effect of the indoor lighted environment deserves attention, particularly in terms of chronic disruption of melatonin rhythms.

The effect of light on pineal function in humans has several features that are relevant to potential long-term health effects: 1) the effect of light at night (LAN) is qualitatively similar to the effect in other mammals in that sufficient intensity of nocturnal illumination completely suppresses melatonin production, 2) some people are much more sensitive to LAN than others, 3) limited evidence supports blue-green (~500nm) LAN as most effective in reducing melatonin production, 4) there appears to be a dose-response to LAN; the brighter the light the greater the reduction in nocturnal circulating melatonin, 5) light quality during the day appears to affect night time melatonin production as well as the human circadian pacemaker, and 6) women may be more sensitive to the suppressive effects of LAN than men.

## Electric Components - Missing Link between EMF and Cancer?

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We are examining the possibility that electric field interactions with known carcinogens in air pollution could explain the observed association between high voltage powerlines and childhood leukemia. I will review two recent papers describing separate mechanisms by which increased exposure to airborne pollution (in the form of aerosol-sized particles) occurs near high voltage powerlines(1,2). Powerline cables can ionise the air creating so-called corona ions. These nucleate ultrafine aerosols which subsequently attach themselves to larger pollutant aerosol particles in the air. The latter may be carried considerable distances from the powerline by the wind. A powerline current loss of 0.1 mA per metre corresponds to $6.25 \times 10^{14}$ ions per metre per second potentially emitted into the atmosphere. Measurements of corona ions were made near 132 kV and other powerlines(1). Analysis suggests that at head height, typically 20% of pollutant aerosols either become charged or carry excess electric charge. On average the effect extended to 200 metres downwind of powerlines. In one case, the effect extended more than 500 metres from a 275 kV line.

Childhood leukemia is known to be associated with traffic pollution. When inhaled electrically charged aerosols are more likely to be deposited in the lung compared with neutral aerosols. Thereafter they may pass into the bloodstream reaching body organs generally, including bone marrow. Near powerlines increased lung deposition of inhaled electrically charged pollutants is expected. This phenomenon could explain the observed associations between proximity to high voltage powerlines and childhood leukemia, even though the association with powerline magnetic fields appears weak. The phenomenon also suggests that further research should be undertaken to ascertain whether other cancers such as lung cancer or non-cancer illnesses are associated with living near high voltage powerlines. Separately, we have modelled the increased deposition of pollutant aerosols on the human head under high voltage powerlines and have measured the effect experimentally using model heads exposed in a variety of weather conditions(2). Both the theoretical analysis and the experimental measurements show that the deposition of radon decay product marker aerosols on models of the human head under powerlines is increased 1.5 to 3-fold compared to control heads placed away from the powerline. We estimate that the radiation dose to the skin from radon decay product aerosols is increased 1.2 to 2-fold for a person spending 10% of time outdoors under powerlines, and that in some cases doses to the basal layer of the skin could exceed the International Commission on Radiological Protection’s limit for members of the public of 50 milli-sieverts per year. This finding suggests that there might be an increased risk of skin cancer in living under high voltage powerlines.

1. Fews AP, DL Henshaw, RJ Wilding, PA Keitch: Corona ions from powerlines and increased exposure to pollutant aerosols. International Journal of Radiation Biology 75 (1999) 1523 - 1531 (2)Fews AP, DL Henshaw, PA Keitch, JJ Close, RJ Wilding: Increased exposure to pollutant aerosols under high voltage powerlines. International Journal of Radiation Biology 75 (1999) 1505 - 1521

## Light Effects on Melatonin

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It has been hypothesized that increased risk of breast cancer in industrialized countries is partially due to increased exposure to electromagnetic fields and light at night which reduces melatonin production.(1) To assess this hypothesis, it is fundamentally important to understand how the human eye transduces light stimuli for melatonin regulation. In both animals and humans, more light is required to activate the circadian and neuroendocrine systems than to stimulate the visual system. Specifically, it is often thought that bright light of at least 2500 lux is needed to phase shift the rhythm or acutely suppress melatonin secretion from the human pineal gland. When exposure of the human eye is carefully controlled, however, illuminances as low as 5 - 17 lux of monochromatic green light or 100 lux of broadband white light can produce significant suppression of melatonin in normal human volunteers.(2) To understand how these lower illuminances can regulate pineal melatonin secretion, it is necessary to examine the ocular physiology that mediates this photic effect. In humans, factors which can significantly alter the amount and spectral quality of light reaching the retina include: 1) gaze behavior relative to a light source, 2) the age of the ocular lens, and 3) pupillary dilation. Once a light stimulus reaches the retina, physiology within the retina and within the circadian system determines the capacity of the stimulus to alter melatonin synthesis. This physiology includes: 1) the sensitivity of the operative photopigments and photoreceptors, 2) location of these photoreceptors within the retina, 3) the ability of the circadian system to integrate photic stimuli spatially and temporally and 4) the state of photoreceptor adaptation. Given the increasing exposure of citizens to light during the night in industrialized countries it is useful from both a scientific as well as a clinical perspective to elucidate the specific photosensory physiology in the eye which mediates melatonin regulation. This work was supported by the following grants: NIH RO1NS36590; FDA #785346, NASA #NAGW 1196, and the Philadelphia Chapter of the Illuminating Engineering Society.

1. Stevens RG, S Davis: The melatonin hypothesis: electric power and breast cancer. Environmental Health Perspectives 104 (1996) 135 - 140
2. Brainard GC, MD Rollag, JP Hanifin: Photic regulation of melatonin in humans: ocular and neural signal transduction. Journal of Biological Rhythms 12 (1997) 537 - 546

## Melatonin and Cancer: Experimental and Clinical Aspects

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Surgical removal of the pineal gland (pinealectomy) in experimental animals stimulates primary tumour growth as well as metastatic spread whereas administration of pineal extracts inhibits the malignant process. Pinealectomy also accelerates cell division in a number of normal tissues. These findings point to an important role of the pineal gland in the regulation of normal and abnormal growth leading to the question whether this phenomenon can be attributed to melatonin alone or not. Since the administration of melatonin to tumour-bearing animals is not inhibitory in all cases whereas pinealectomy stimulates such tumours it is clear that the pineal control of cell growth in some cases is exerted independent of melatonin. The inhibitory action of melatonin is most pronounced in case of those tumours that are controlled by neuroendocrine mechanisms involving prolactin as well as the estrogen response system. In this case the presence of membrane and/or nuclear melatonin receptors is an indispensable prerequisite. In addition, the pineal hormone inhibits liver tumours via a melatonin receptor-mediated effect on the metabolism of unsaturated fatty acids. Due to its stimulatory action on immune cells it is likely that melatonin may inhibit tumour growth via this system which at the same time explains why experimental leukemias are aggravated by melatonin administration and inhibited by pinealectomy.

These divergent effects of melatonin on different types of malignancy illustrate an apparently fundamental effect on cellular proliferation. Therefore it is of considerable interest to study melatonin and its biosynthesis in patients or in tumour-bearing animals. The current results show that circulating nocturnal melatonin undergoes dynamic changes during different phases of malignancy being low during localized primary tumour growth in patients with breast, endometrial, prostate, lung or stomach cancer and normal or elevated when recidives or metastases arise in them. According to our clinical studies, the depression of melatonin cannot be attributed to an enhanced hepatic degradation of 6-sulfatoxymelatonin, its main metabolite. Studies on tumour-bearing animals show that the biosynthesis and secretion of pineal melatonin is normal leading to the assumption that melatonin may rather be trapped and/or degraded by cancer cells. The summarized findings indicate an important but at the same time complex role of melatonin in the neuroimmunoendocrine control of malignancy probably constituting a central part of the link between the pineal gland and cancer.

## Reduced Cancer Incidence among the Blind in Sweden

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Melatonin is a hormone primarily produced by the pineal gland at night, which is suppressed by exposure to light. Experimental studies have indicated that melatonin may protect against cancer development, and different mechanisms for this effect have been suggested. Reduced melatonin levels increase the level of circulating estrogen, which would increase susceptibility to sex hormone related cancers. Furthermore, an oncostatic effect of melatonin has been demonstrated. Some studies have indicated an effect of melatonin on the immune system, and it has also been suggested that melatonin may act as a potent antioxidant, which means that melatonin would have a protective effect against cancer development in general. The majority of totally blind people, with no light perception, have a free running melatonin cycle, with a period slightly exceeding 24 hours, and melatonin is never suppressed by light exposure.

The aim of this study was to test the hypothesis that totally blind people have a decreased cancer incidence. We identified a cohort of 1,567 totally blind and 13,292 severely visually impaired subjects. In the severely visually impaired, but not blind people we did not hypothesize a decreased

risk of cancer development. We assumed that, because they perceive light, they would have a melatonin cycle similar to sighted people. We obtained information about cancer incidence from the Swedish Cancer Registry. A total of 136 cancer cases were identified in the totally blind cohort, and 1,709 in the visually impaired cohort. We calculated standardized incidence ratios based on the number of person years and national age, sex, and calendar year specific incidence rates.

The results of the study showed that totally blind people had a lower incidence of all cancers combined (SIR=0.69; 95% CI 0.59-0.82). The risk reduction was observed in both men and women, and was equally pronounced in hormone dependent tumors as in other types of cancer. For specific cancer sites, the number of cases was too small to allow firm conclusions. Apart from gender, age, and time period, we had no information about potential confounding factors. Separate analyses of smoking related cancers and cancers not related to smoking indicate that difference in smoking habits between blind and sighted people can not explain the findings. In severely visually impaired, SIR was 0.95 (95% CI 0.91-1.00).

The findings support the hypothesis that blind people have a lower cancer incidence. However, other explanations than the higher melatonin exposure must also be considered.

## Visual Impairment and Cancer in Finland

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In persons with intact vision, pineal secretion of melatonin is highest early in the morning and reduces following exposure to light. Melatonin may possess anticarcinogenic properties, so that increased exposures to light-at-night may decrease nocturnal melatonin secretion and thus contribute to the observed increases in breast cancer incidence rates. It has been reasoned that women who are profoundly blind, and therefore not susceptible to light-at-night, should have a reduced risk of breast cancer compared with those with intact vision. On the other hand, few studies have investigated life-styles of visually impaired persons. The objectives of this study were to investigate cancer risk patterns in persons with visual impairments, and in particular to explore the hypothesis that women with visual impairment may have decreased breast cancer risk. Altogether 17,557 such persons (65% women) were identified from the Finnish Register of Visual Impairment, and followed up for cancer through the Finnish Cancer Registry in 1983-95. The degree of visual impairments ranged from moderate low vision with visual acuity less than 0.3, into total blindness with no perception of light. The standardized incidence ratios (SIR) and 95% confidence intervals (CI) were calculated by primary site and degree of visual impairment, based on average cancer incidence rates in general Finnish population.

The overall cancer risk was increased by 15% (1255 cancers observed versus 1093 expected; SIR 1.15; 95% CI 1.09-1.21). Excesses were observed in both sexes in cancers of the liver (SIR 1.76; 95% CI 1.19-2.51) and lung (1.48; 1.26-1.72); in females in cancers of stomach (1.50; 1.17-1.88), colorectum (1.3, 1.1-1.6); and in males in cancers of the kidney (1.77; 1.13-2.62), eye (5.76; 1.87-13.44) and perhaps skin melanoma (1.75; 0.93-2.99). Contrary to most other cancers, a statistically significant decrease (P=0.04 for trend) was observed for breast cancer risk by increasing degree of visual impairment.

Cancer incidence among the visually impaired tended to be increased for most cancer types; attention should be paid to lifestyles perhaps underlying the observed risk increases. The statistically significant decrease in breast cancer risk by increasing degree of visual impairment suggests a dose-response relationship between visible light and breast cancer risk.

## Winter Darkness in the Arctic - Cancer in the Light of the Melatonin Hypothesis

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The melatonin hypothesis states that excess exposure to environmental light may contribute to breast cancer risks via impaired pineal secretion of melatonin.(1, 2) A corollary, not considered previously, is that a net annual increase in oncostatic melatonin would be expected in persons experiencing deficits of daylight during long winter days. Hormone-dependent cancers should therefore occur less frequently in people who reside north, rather than south, of the Arctic circle. We have reviewed descriptive epidemiologic data on cancer incidence during 1960 and 1988 in Greenland, northern Alaska, and the northern part of the Canadian mainland. They show a pattern of uniformly low risks for hormone-dependent cancer consistent with our prediction. SMRs or SIRs ranged between 0.2 and 0.5 for breast cancer, were 0.9 or less for cancer of the ovary and 0.3 or less for cancer of the corpus uteri, and ranged between 0.1 and 0.7 for prostate cancer. However, tobacco, alcohol and diet related cancer risks were high. The latter observations suggest that the low incidence of hormone-dependent cancers is unlikely to be explicable simply in terms of indigenous nutritional and life-style factors. Moreover, the available literature on genetic, reproductive, and environmental risk factors provides no obvious clues to the observed cancer patterns. We note also that melatonin concentrations in volunteers who live in the arctic part of Norway and in northern Finland have been reported as high during the dark season (November-January), when light intensity is low. This too is consistent with our prediction.

Conspicuous deficits in particular cancers in the Arctic have been noted previously. However, this has not been discussed in relation to a possible melatonin-related prophylactic effect. We conclude that research into diurnal, nocturnal and annual melatonin patterns, and analytic epidemiologic studies of the low-risk populations in the Arctic, might provide new insights into hormone-dependent carcinogenesis.

1. Cohen M, M Lippman, B Chabner: Role of pineal gland in etiology and treatment of breast cancer. Lancet 10 (1978) 814 - 816
2. Stevens RG: Electric power use and breast cancer: a hypothesis. American Journal of Epidemiology 125 (1987) 556 - 561

## Laboratory Studies on Magnetic Fields, Melatonin and Cancer

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A subject for controversy for 20 years has been the question of whether exposure to magnetic fields

(MFs) poses any health risk. The strongest evidence for health effects comes from associations observed in human populations between exposure to power-line frequency (50 or 60 Hertz) MFs and cancer, particularly childhood leukemia. In 1987, Stevens presented a hypothesis that use of electric power may increase the risk of breast cancer. This hypothesis was based on a number of experimental reports indicating an effect of light and powerline-frequency (50 or 60 Hertz) electric fields on pineal melatonin production, and on the relationship of melatonin to mammary (breast) carcinogenesis. However, at the time when this hypothesis was presented it was not known whether 50/60-Hertz magnetic fields (MF) affect pineal melatonin production in experimental animals and/or humans. Furthermore there was no experimental evidence for increased breast cancer development or growth in response to MF exposure. This prompted us to carry out a series of experiments designed expressly to test the "melatonin hypothesis" of MF-promoted breast cancer development and growth in female rats.

In this series of experiments, which was started shortly after the publication of Stevens in 1987, we studied whether 50-Hertz MFs of low flux density (1-100 mTesla; mT) enhance tumor development or growth in the DMBA (7,12-dimethylbenz(a)anthracene) model of breast cancer in female rats. The dosing protocol of the chemical carcinogen DMBA chosen for the MF experiments (i.e., intragastric application of 4x5 mg DMBA per rat with intervals of one week between each application) induced palpable mammary tumors in about 40-60 % of sham-exposed control animals within 3 months after application. For the MF experiments, groups of 36-99 rats were exposed to a 50-Hertz MF for 24 h/day 7 days/week for 13 weeks; control groups were sham-exposed under the same environmental conditions as the MF-exposed rats. Four flux densities were studied in a total of 660 rats (including sham-exposed controls): 0.3-1 mT, 10 mT, 50 mT, and 100 mT. Already 8 weeks after DMBA application, MF-exposed rats exhibited significantly more palpable tumors than sham-exposed animals in the experiments with 50 and 100 mT. At necropsy, i.e., at the end of the 13 weeks period of MF-exposure, incidence of grossly recorded (i.e., macroscopically visible) mammary tumors was significantly enhanced in the experiment with 50 mT (25.5 % above control) and 100 mT (50% above control). No increase in mammary tumors was seen in the experiment with 0.3-1 mT, while a 10% (non-significant) increase was determined in the experiment with 10 mT. Linear regression analysis of the data from the 4 experiments indicated a highly significant linear relation between flux density and increase in number of grossly recorded mammary tumors at time of autopsy. A replication of the experiment with 100 mT again resulted in a significant increase in tumor incidence in MF-exposed rats. Furthermore, in a more recent experiment with a lower dose of DMBA (10 mg per rat) but longer duration of MF exposure (27 weeks) we again found a significant increase in mammary cancer growth in MF exposed rats. Collectively, the data demonstrate that long-term MF exposure of DMBA-treated female rats promotes the growth of mammary tumors in a highly dose-related fashion, thus substantiating the melatonin hypothesis.

## Problems in Replication of Experimental Studies

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A long-standing hallmark for wide acceptance of scientific study results has been the replication of the original work in other laboratories. Such confirming research provides a basis for establishing the validity of the initial findings. In the event that replication of results is not obtained, the challenge is then to determine the reasons for differing results. A strong benefit in replication efforts is attained when there is communication or even scientific and personnel exchange between the original and replicating laboratories. There are a number of key issues that are critical in study

replication efforts:

Experimental Approach - Providing the initial work is described in adequate detail, any attempt at replication should follow the same experimental design.

Environment - In both in vitro and in vivo replications careful attention should be given to environmental factors such as: temperature; timing, quantity and quality of lighting; comparability of exposure systems.

Reagents and Other Consumables - Large differences in responses can be due to feed content (for animals) and media composition (for cells). Methodology - Cell cycling and sampling times are important variables that can directly impact replication success. In addition, proper controls (positive and negative) will aid in interpretation of results (either in support or refutation of the original results). Statistical Analysis and Data Interpretation - Initial analyses should replicate the approach used in the original work. In some cases, additional or enhanced statistical treatment may benefit the interpretation of results.

As an example of the challenges of replication, studies have been conducted wherein animals treated with DMBA were exposed to extremely low frequency magnetic fields. Dr Löscher has described the original studies showing an increase in mammary carcinogenesis in animals exposed to the fields. An attempt at replication was conducted in a separate laboratory (Battelle Northwest Laboratories). Results obtained in the Battelle experiments did not replicate those obtained in the original studies. Potential mitigating factors between the two studies will be explored for possible explanations to the differing results.

## Extremely Low Frequency Magnetic Fields (b=100µt) Affect the Microvesicle Velocity and Expression of Adhesion Molecule CD44s in Rat Astrocytes

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Introduction: The effect of extremely low frequency magnetic fields (MF) was examined in rat astrocytes looking at parameters which were found to be indicators of cell stress. The velocity of intracellular vesicle transport reflects the overall metabolic situation in acute experiments.

In case of environmental stress like hypoxia, cells react with a downregulation of prolonged adhesion molecules. Since adhesion molecules play an important role in tumor metastasis and inflammation, we tested the changes in expression of the adhesion molecule CD44s after MF.

Material and methods: CD44s in rat astrocytes were examined by means of immunohistochemistry, flow cytometry and laserscanning microscopy. Primary cultures of rat astrocytes were exposed to MF (f=50 Hz) in a gased humide incubator for different periods (T=1.5d, 3d, 7d) and different field strengths (B=100/200 µT). The vesicle velocity was analyzed by video enhanced microscopy in combination with a perfusable cell chamber. We have tested the MF-effect, the effect of heat shock (37°C/45°C) and the combination of both. The velocity of microvesicles was measured using a public domain image processing software (NIH Scion image 1.61). Results: After exposure of

astrocytes to MF (T=1h) the velocity of microvesicles in astrocytes increased to 128% (number of vesicles =175, 95% confidence interval) of the untreated control group. Fifteen minutes after HS (45 °C, 10 min) the microvesicles showed a 69% higher averaged velocity than the untreated control (number of vesicles=125, 95% confidence interval). Combination of HS and MF led to a 75% increase in velocity (number of vesicles=110, 95% confidence interval).

We have found a reversible MF-effect on CD44s, which depends on dose and time. The expression of the adhesion molecule CD44s in astrocytes decreased after a 7d-exposure to 63% (200 µT) and to 67% (100 µT) of the expression in none exposed cells (control). The downregulation of CD44s could be seen after 36 h (-18%) and was reversible after 5d. Changes of the surface (glass flasks) leads to an stronger downregulation after MF-exposure (-30%) in comparison to the downregulation on perspex flasks.

Discussion: The increased microvesicle velocity of the exposed cells compared to the untreated control group might be a stress response of the cell. Possibly, it is a sign of intensified intracellular traffic to adjust the metabolic needs of the cell organelles.

There is a controversial discussion about MF and their role as a promotor for neoplastic diseases. Different authors found that a higher expression of CD44s is combined with a higher invasiveness of gliomas. And therapeutic suppression of CD44 expression in gliomas had also been tested. Whether the downregulation of CD44s is combined with an upregulation of alternatively spliced tumor-related CD44-variants in rat astrocytes must be proven in future experiments.

## Meta-Analysis of EMF-Studies: Breast Cancer

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In 1987, Stevens suggested that extremely low-frequency EMFs (ELF-EMFs) and visible light at night (LAN) may increase the long-term risk of breast cancer.(1) This was followed by publication of 21 reports that focussed specifically on breast cancer as a possible hazard associated with EMF. 22 other papers on EMF published between 1983 and 2000 included cancer of the breast as one of several cancer endpoints. Stevens' hypothesis for a melatonin-mediated effect of electric power on breast cancer risks, although as yet unsubstantiated, provides a biological rationale for the interpretation of any association between breast cancer and EMF as reflecting a cause and effect phenomenon.

This paper reviews the publications that include information about possible associations between exposure to electric and magnetic fields (EMF), at work or at home, and risks of breast cancer in women and men. The data are grouped in relation to gender of study subjects, type of study, geographical location, and method used to assess exposure, with corresponding precision-weighted estimates of pooled relative risks (RR). Chi squared statistics are used to assess the degree to which differences between studies, within subgroups, may be attributable simply to sampling variability.

The pooled RR from 24 studies in women, for which estimation of relative risk associated with exposure was possible, was 1.12 (95% CI: 1.09, 1.15), but variations between the contributing results are not easily attributable to chance (P=0.0365). A fairly homogeneous increased risk was found for men based on 15 studies (pooled RR of 1.37, with 95% confidence limits of 1.11, 1.71, homogeneity P-value=0.1101). However, in both genders, results from individual studies are very

variable and, in part, contradictory.

Interpretation of these results is bedevilled by two problems. First, the questionable specificity of the reported exposure assessments to the EMF ranges of interest. Second, the possibility that the generic "breast cancer" description of the putative end-point may have obscured a more specific effect dependent on the menopausal and/or estrogen receptor status of the individuals studied. Future research should therefore include ELF-EMF and light in occupational and residential settings. Moreover, menopausal status and/or estrogen receptor status should be assessed when classifying the disease in women and men, respectively.

1. Stevens RG: Electric power use and breast cancer: a hypothesis. American Journal of Epidemiology 125 (1987) 556 - 561

## Meta-Analyses of EMF-Studies: Leukemia and Brain Cancer

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The issue of a possible relation between weak, extremely low frequency magnetic fields (EMF) and cancer remains controversial despite two decades of intense experimental and epidemiological research. There is no established biophysical mechanism that would explain such a relation. The epidemiological data that have been assembled since the original publication are indicative for some cancer sites, but not strong enough for firm conclusions without additional support from experimental mechanistic results. There is a general agreement that the epidemiological data provide strongest support for childhood leukemia. The purpose of this presentation is to review recent epidemiological studies. Later studies have mainly focused on childhood leukemia and this will therefore also be the focus of this review. The three studies, all published during 1999 will be discussed. Because of the high costs and long times required for further studies, there has been an increasing interest in utilizing available data as best as possible. Thus, EMF and cancer has been the topic of several meta-analyses. Some of these are based on the results from individual studies as published in the respective reports, while others have been based upon raw data from the various studies. Both types will be reviewed and discussed.

## German Case-Control Study of Childhood Leukemia and Residential Magnetic Fields

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Background: From 1993 to 1997 we conducted an epidemiological study on childhood leukemia and residential magnetic fields in the Northwestern part of Germany (Lower Saxony) and Berlin. Since the results were inconclusive, in 1998, the EMF-study was expanded to be an ongoing nationwide case-control study on childhood acute leukemia. Recently, international studies on this topic were combined in several meta-analyses, showing a consistent very small risk increase at exposures above .2µT.

Methods: In our studies, measurements over 24 hours of the residential 50 Hz-magnetic field were conducted in the child's bedroom and in a second room in the home where the child lived longest before the date of diagnosis. Spot measurements were conducted to identify sources of average magnetic fields exceeding .2µT. Furthermore, we collected information on the type of the building, the neighbourhood traffic density, the degree of urbanization, and on power lines, underground wiring, transformers, and substations proximate to the child's home.

Results: In our previous study, 24h-measurements were performed for 176 cases and 414 controls. The percentage of exposed subjects (median magnetic field greater than or equal 2µT) was only 2.9%. Odds ratios revealed a statistically nonsignificant increase (OR=2.3, 95%-CI: 0.8-6.7) based on nine leukemia cases (5.1%) and eight controls (1.9%) in the high exposure group. Stronger associations were observed for younger children and for those being exposed to stronger magnetic fields during the night. Only 3 of 17 median magnetic fields above .2µT were caused by high-voltage power lines. In our recent nationwide study which involved more than 1,800 participants, median magnetic fields above .2µT were even less frequent, indicating a prevalence of 1.4%. We found strong evidence for an association between magnetic fields and the type of the residence with higher magnetic fields in apartment buildings. There was also an association between magnetic fields and family net income and proxies for high traffic density. The measurement data will be linked with the data from the leukemia study in the near future.

Conclusions: If our risk analyses will show an association between childhood leukemia and stronger magnetic fields, we expect that only a small fraction of childhood leukemia cases can be explained by exposure to stronger residential magnetic fields. This is mainly due to the low prevalence of magnetic fields above .2µT in German residences.

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