

# Electromagnetic Fields and Cells

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**Abstract** There is strong public interest in the possibility of health effects associated with exposure to extremely low frequency (elf) electromagnetic (EM) fields. Epidemiological studies suggest a probable, but controversial, link between exposure to elf EM fields and increased incidence of some cancers in both children and adults. There are hundreds of scientific studies that have tested the effects of elf EM fields on cells and whole animals. A growing number of reports show that exposure to elf EM fields can produce a large array of effects on cells. Of interest is an increase in specific transcripts in cultured cells exposed to EM fields. The interaction mechanism with cells, however, remains elusive. Evidence is presented for a model based on cell surface interactions with EM fields. © 1993 Wiley-Liss, Inc.

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## HEALTH RISKS FROM EXPOSURE TO ELECTROMAGNETIC FIELDS?

There is increasing public interest in possible health effects associated with exposure to extremely low frequency (elf) electromagnetic (EM) fields. Concern has escalated, in part, as the result of media coverage of epidemiological studies which suggest a probable, but controversial, link between exposure to EM fields and an increased incidence of some cancers in both children and adults. Public awareness has led to the inclusion of exposure to elf EM fields as part of a growing series of environmental exposures related to "quality of life" in the industrial world.

Electromagnetic fields are produced when electric current flows through an electrical conductor such as a power line. Most human exposures are to elf EM fields (normally defined as less than 200–300 Hz), which are present in both residential and work place environments. Although EM fields are usually associated with high-voltage power lines and power stations, they are also produced by any electric-powered device and exposure occurs, for example, from

the routine use of common household and work place appliances such as video display terminals, TVs, hair dryers, and cellular phones.

More than 50 epidemiological studies have tested risk in specific populations exposed to elf EM fields (reviewed in Nair et al., 1989; EPA/600/6-90/005A, 1990), with wide differences in statistical interpretation of the results. The interpretation of risk is compounded by the fact that many of the studies were carried out in urban and/or work place environments where there are multiple factors that could predispose the subjects to cancer. Some risk ratios can apparently be traced directly related to EM field exposure and tend to be greater than unity (clustered around 1.2–1.5, although higher risk factors have been reported) [reviewed in Information Ventures (EPRI)]. There is no specificity with respect to cancer type or site associated with EM field exposure, but positive risk factors have been associated with leukemia, lymphoma, melanoma, lung cancer, and other malignancies. The most persuasive evidence is from studies of male electrical workers who are more likely to have certain forms of cancer, including an unusual incidence of breast cancer, which occurs about six times that of the normal incidence in men (Matanoski et al., 1991).

An association between elf EM field exposure and malignancy cannot rest solely on epidemiological data, however. Other criteria are re-

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quired. First, there must be unequivocal data that cell function is affected by elf EM fields. The evidence for effect on cell function is rapidly accumulating, but a direct relationship between field conditions and time of exposure relative to the observed effects is still lacking. Second, the association of EM field with malignancy requires that the functions affected experimentally must be those that are associated, at least in part, with factors known to be changed during the course of transformation/and or immortality of cells.

There are hundreds of basic scientific studies that have tested the effects of elf EM fields on cells and whole animals. Some studies have observed no effect, but a growing number of reports shows that exposure to elf EM fields can produce an amazing array of effects. A few examples of diversity of response to EM fields include: altered rate of cell growth (Liboff et al., 1984; Takahashi et al., 1986), suppression of T-lymphocyte cytotoxicity (Lyle et al., 1991), increases in the growth-related enzyme ornithine decarboxylase (Byus, et al., 1988), altered quantities of RNA transcripts and proteins (Goodman and Henderson, 1988, 1991a; Phillips et al., 1991a,b; Czerska et al., 1991), altered cell surface properties (Marron et al., 1988), effects on development (Delgado et al., 1982) and nerve regeneration (Sisken et al., 1989). EM fields have also been shown to slow the pineal secretion of melatonin (reviewed in Wilson, et al., 1989). Of interest are studies that show modulation of calcium and other ion flow across cell membranes (reviewed in Nair et al., 1989, Adey and Sheppard, 1987), since such alterations suggest a route for cell regulation in the presence of elf EM fields.

On the basis of present data, most scientists agree that elf EM fields interact with cells, but there is scientific uncertainty as to mechanism of interaction, and obvious concern over whether the effects that have been observed would be detrimental to health. The experimental induction of tumorigenesis can require a long time period, as well as repeated exposures to the promoting substance. There is presently no direct laboratory evidence that relates exposure of whole animals to elf EM fields and propensity to cancer, although some animal studies are suggestive. In cell studies, the largest proportion of research has been done on transformed, rather than "normal cells."

It has been proposed that EM fields do not initiate cancer, but rather, may promote cancer

that has been initiated by other causes; that is, the role of EM fields would be one involved in co-carcinogenesis or augmentation of preexisting transformation features. Changes normally associated with tumor initiation, such as chromosomal anomalies, DNA crosslinks, or changes in DNA repair, are not observed in cells exposed to EM fields (see for example, Reese et al., 1988; Rosenthal and Obe, 1989). Exposure of cells to EM fields, however, does accelerate tumorigenesis in experimental animals that are also exposed to carcinogens (reviewed in Nair et al., 1989). Other effects observed following EM field exposures could support the hypothesis that co-carcinogenesis is induced. These include modifications in growth rates of tumor cells (Phillips et al., 1986) and increases in the level of the enzyme ornithine decarboxylase (ODC) that are similar to the changes produced by exposure to the tumor promoter 12-o-tetradecanoyl-phorbol-13 acetate (TPA) (Byus et al., 1988).

Our laboratories, as well as other laboratories, have shown that levels of some RNA transcripts are increased in cells exposed to elf EM fields (reviewed in Goodman and Henderson, 1990; Goodman et al., 1991a). The effect of elf EM fields on transcripts is probably at the transcriptional level (Goodman et al., 1983; 1992a; Phillips et al., 1991a). The initial evidence came from our analysis of transcription autoradiograms of dipteran salivary gland cells. Isolated salivary glands were exposed to 60-Hz sinusoidal and other waveform signals in the elf EM field range. Short exposures (<60 min) cause a change from the expected pattern of transcription over specific regions of salivary gland chromosomes (see Goodman et al., 1992a,b). The analysis of transcription autoradiograms indicates either a direct or indirect influence of elf EM fields on transcription per se rather than, for example, an increase in RNA stability, or the release of RNA storage forms. The presence of increased transcript levels in cells exposed to EM fields has been confirmed in reports by Czerska et al. (1991) in PHA-stimulated lymphocytes and Daudi cells, and by Phillips et al. (1991a,b) in CEM-CM3 human T-lymphoblastoid cells. Nuclear run-off analysis was used to assess changes in transcription by Phillips et al. (1991a, 1991b). Increased transcription was observed for the genes encoding *c-myc*, *c-fos*, *c-jun*, and protein kinase C. These results substantiate our original observations which showed that the effects of EM fields are detected at the level of

transcription. More recently, an increase in *c-myc* transcript levels following short exposures to EM fields has been shown to be coordinate with an increase in intracellular calcium in thymocytes stimulated with Con A (Liburdy, 1992).

Whether the phenomenon of transcript increase can be related specifically to transforming characteristics or to augmentation of pre-existing neoplasia is unclear, but the observations are consistent with changes in the growth characteristics of the cells. The results are also consistent with data on the short-term effects of other promoters. This suggests a realistic strategy for pursuing the mechanism of interaction of cells with elf EM fields, since the effects observed are within the time frame for those observed for other types of induction (e.g., heat shock or TPA).

Our (and other) laboratories are currently using an experimental tactic which emphasizes regulation of transcription in two critical genes which are consistently increased in cells exposed to EM fields. These are the transcripts for *c-myc* and *c-fos*. The transcription of *c-myc* and *c-fos* is rapidly modified in many cells responding to various types of induction. It is known that induction of *c-fos* can be observed within 5 min after treatment with serum; the transcriptional activation peaks at about 15 min and decreases to basal levels within 2 h (Prywes et al., 1988). This is exactly the type of pattern that we have measured following exposure of cells to elf EM fields (reviewed in Goodman et al., 1992b). As an example, at the field strength used in our experiments (80  $\mu$ T), an increase in *c-myc* transcripts above control levels can be detected as early as 4 to 8 minutes, with a peak at 20 min. If exposures are continued, however, the transcript levels approach those of the controls at about 2 hours. The effect is the same when cells are exposed for 20 min and then removed from the field. Thus, the response is typical of induction—an initial response is observed, but then a return to normal levels occurs at a time characteristic of the type of induction, and the gene involved.

Interpreting results from experiments in which cells have been exposed to EM fields is complicated by the absence of a direct relationship between time of exposure and field strength. For example, RNA transcripts for several house-keeping genes, as well as *c-src*, *c-fos* and *c-myc*, are increased in HL60 cells exposed for short time periods to 60-Hz fields (Goodman et al., 1992b). Exposures started with a magnetic field

approximately twice that of laboratory background levels (0.8  $\mu$ T). The quantity of each of the transcripts at a B-field of 8  $\mu$ T (E-field = 11  $\mu$ V/m) and 20 min of exposure was consistently higher than at other times of exposure or lower or higher field strengths. A time-dependent effect for the transcription of genes encoding *c-myc*, *c-fos*, *c-jun*, and protein kinase C in cells exposed to 100- $\mu$ T fields at 60 Hz has also been reported (Phillips et al., 1991b).

Although the effect on certain RNA transcript levels is specific, the characteristics of the subset of genes involved is still unknown. Alpha globin transcripts, which are not expressed in HL-60 cells, are not detected in either exposed or unexposed cells. On the other hand,  $\beta_2$ -microglobulin mRNA is expressed in HL-60 cells, and normal levels are observed in exposed cells (Blank et al., 1992). These observations are consistent with other studies which show that the expression of  $\beta_2$ -microglobulin is not normally inducible in HL-60 cells (Solomon et al., 1991). No effect on transcription of genes encoding transferrin, insulin receptor, metallothionein, ornithine decarboxylase or actin was observed in human T-lymphoblastoid cells exposed to EM fields (Phillips et al., 1991a).

In spite of a vast quantity of research, the mechanism(s) by which cells detect EM fields is far from being solved. There is little relevant information on the significance of field strength, cellular geometry and exposure geometries on biologic response. It is still unclear whether it is the magnetic field, the electric field, the induced electric field or any combination that is the biologically effective agent. One possibility is that the cell is responding to EM field exposure in a manner analogous to that observed under conditions of cellular stress. This idea is supported to some extent by the observation that there is an increase in transcripts for some heat shock genes (e.g., *hsp70*) in dipteran salivary gland cells (Goodman et al., 1992a) following exposure to elf EM fields where no detectable increases in temperature were measured (or expected on the basis of the design of the exposure system).

#### HYPOTHESES: THE INTERFACE BETWEEN THE CELL AND EM FIELDS—THE CELL SURFACE

The resolution of whether exposure of cells to elf EM fields can be directly related to malignancy are wholly dependent on studies that will answer how fields couple to cells. The nemesis

lies in theoretical considerations; voltage fluctuation resulting from normal cellular and molecular interactions would presumably swamp any exogenously applied elf EM fields. Elf EM fields are too low to act through known physical mechanisms associated with higher electric fields, such as dielectric breakdown or particle displacement, and are nonthermal (see Tenforde and Kaune, 1987). In spite of proposed constraints imposed by the already high endogenous fields around cells, there are other factors that could be involved in extremely low fields [defined by Adey and Sheppard (1987) as  $10^{-2}$ – $10^{-7}$  V/m]. A primary consideration, as discussed by several investigators, is that the transmembrane potential is not stationary and at least local changes at membrane channels could regulate the voltage sensitivity of an effector molecule.

The most viable and consistent clue as to mechanism is the change in calcium flux (both influx and efflux) patterns in cells exposed to elf EM fields (reviewed in Adey and Sheppard, 1987; Adey et al., 1982; Blackman et al., 1989; Wallacek and Liburdy, 1990). While the existing data is consistent with signal transduction events, the means for triggering the unknown signal transduction events, presumably via calcium flux changes, is enigmatic, but perhaps not theoretically impossible.

A rationale for proposing  $\text{Ca}^{+2}$  ions as one of the messengers in this process has as a basis the extremely low concentration of free calcium in the cell ( $\sim 10^{-7}$  M). Neher (1992) discusses the fact that calcium-specific currents of only 2 pA can raise the level of intracellular  $\text{Ca}^{+2}$  at a rate of  $100 \text{ nMs}^{-1}$ . The usual  $\text{Ca}^{+2}$  concentration in the extracellular fluid is about  $10^{-3}$  M, resulting in an enormous concentration gradient on the plasma membrane. The gradient is maintained in several ways. The family of  $\text{Ca}^{+2}$  transport systems in non-excitable cells includes receptor-activated channels, or those activated by second messengers such as calcium, inositol 1,4,5-triphosphate, or G proteins (reviewed in Meldolesi et al., 1991). Although the concentration of calcium inside the cell remains constant, the flow across the cellular membrane can vary significantly. The intracellular concentration of free calcium is determined by the balance of the influx through calcium channels and leaks and efflux through pumps. A rise in submembrane calcium concentration stimulates the activity of the calcium pump by activating the calcium

binding protein calmodulin and protein kinase C (PKC), restoring the balance in efflux vs. influx.

The exchange between free  $\text{Ca}^{+2}$  and calcium in intracellular stores must also be taken into account. The exchange is of importance for calcium oscillations (Berridge, 1990; Marty, 1991; Peterson and Wakui, 1990; Jacob, 1990), since a model based on calcium as a mediator of EM fields could also explain the presence of frequency windows. Frequency and other windows could be related to the oscillatory properties of the  $\text{Ca}^{+2}$  reaction circle within the cell (Berridge, 1990). Other models have attributed frequency windows to auto-oscillatory properties of hypothetical transport enzymes (Markin and Tsong, 1992).

In most theoretical considerations, the membrane transport system is considered to be in a state near equilibrium, i.e., net flux in the second order is assumed (Tsong and Astumian, 1986; Astumian and Robertson, 1989) (and net flux in the first order is thus equal to zero). The living cell, however, is never in a state of equilibrium. Assuming a state of nonequilibrium, first order kinetics could be used (a mathematical treatment of this is in manuscript). This is of importance since the increase in effect would be on the order of  $10^7$ . Calcium channels would then serve as a unidirectional pathway for influx in an electric field. In the first half-period phase of the sinusoidal wave, some additional number of calcium ions will penetrate into a cell. In the second half-period, the  $\text{Ca}^{+2}$  efflux through the channels will be zero, since the  $\text{Ca}^{+2}$  gradient across the membrane is very high. The additional influx of calcium under the influence of a very small outer electric field will be modest compared with the normal efflux induced by the concentration gradient. The background influx, however, could be compensated by the pumps, and the activity of the pump is a sigmoid function of the intracellular concentration of calcium. Critical to this hypothesis is how effective this mechanism would be relative to accumulation of calcium in the cell. The normal electric influx can be estimated on the basis of existing information on the permeability of the cell membrane in the resting state ( $T_{\text{migr}} \approx 2$  particles per second, assuming an electric field strength of  $10^{-8}$  V). The actual permeable portion of the plasma membrane formed by open ionic channels is very small, however, and not measurable directly. Intuitively, the flow through specific channels would increase the influx.

In this model,  $\text{Ca}^{+2}$  plays a role as both a "first" and "second" messenger. The downhill electromigration of  $\text{Ca}^{+2}$  into the cell produces the first small signal which activates  $\text{Ca}^{+2}$  channels and leads to a fast increase in intracellular calcium through positive feedback. This reaction loop also includes an increase in concentration of some of the byproducts which are regulators of transcription, expression and other basic functions of the cell. An alternative possibility is that  $\text{Ca}^{+2}$  is only a second messenger, and the influx of calcium is induced by an initial messenger (as yet not identified), but is perhaps some charged ligand which attaches to the receptor and opens calcium channels. At least one receptor protein is affected by EM fields, that for parathyroid hormone (PTH) (Luben et al., 1982; Luben and Duong, 1989).

Irrespective of mechanism, the effects of  $\text{Ca}^{+2}$  flux could directly affect signal transduction processes. It is postulated that signal transduction events would subsequently activate specific genes associated with growth processes. Finally, membrane modulators that control signal transduction can also act as promoters of cancer. Based on published data, it is possible, but still unproven, that elf EM fields can act to enhance neoplastic progression, possibly during the latency period.

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