SECTION 7

Evidence for Stress Response (Stress Proteins)

Health Risk of Electromagnetic Fields: Research on the Stress Response

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A Scientific Perspective on Health Risk of Electromagnetic Fields: Research on the Stress Response

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I. Abstract

The stress response is a protective cellular mechanism that is characterized by stress protein synthesis. The stress response, by its very nature, shows that *cells react to EMFs as potentially harmful*. The stress response is an important protective mechanism that enables cells from animals, plants and bacteria to survive environmental stressors with the aid of heat shock proteins (hsp). It is stimulated by both non-thermal power (ELF), and non-thermal radiofrequency (RF) as well as thermal radio (RF) frequency EMFs, so the greatly differing energies are not critical in activating the DNA to synthesize proteins. Direct interaction of both ELF and RF EMFs with DNA is likely, since specific DNA sequences are sensitive to EMFs and retain their sensitivity when transferred to artificial molecular constructs. Basic science research is essential for determining the biological parameters needed to assess health risks of electromagnetic fields (EMFs) and the molecular mechanisms that explain them. However, the adversarial nature of the debate about risk has clouded the evaluation of the science. To clarify the results of research on EMF stimulation of the stress response, it is necessary to consider the scientific context as well as the research. There is ample evidence that ELF and RF fields activate DNA in cells and cause damage at exposure levels that are considered 'safe' (i.e., below current exposure limits that are based on tissue heating as measured in Specific Absorption Rate or SAR). Because non-thermal EMFs are biologically active and potentially harmful, new safety standards must be developed to protect against possible damage at non-thermal levels, and the standards must be defined in terms of a non-thermal biological dose. Fewer than one quarter of the relevant references listed in Table 1 appear in the IEEE list leading to the newly revised IEEE C95.1 recommendations (April, 2006).

II. Stress Proteins - Conclusions (Heat Shock Proteins)

<u>Conclusion</u>: Scientific research has shown that the public is not being protected from potential damage that can be caused by exposure to EMF, both power frequency (ELF) and radio frequency (RF).

<u>Conclusion:</u> DNA damage (e.g., strand breaks), a cause of cancer, occurs at levels

of ELF and RF that are below the safety limits. Also, there is no protection against cumulative effects stimulated by different parts of the EM spectrum.

Conclusion: The scientific basis for EMF safety limits is flawed when the same biological mechanisms are activated in ELF and RF ranges at vastly different levels of the Specific Absorption Rate (SAR). Activation of DNA to synthesize stress proteins (the stress response), is stimulated in the ELF at a non-thermal SAR level that is over a billion times lower than the same process activated in the RF at the thermal level.

Conclusion: There is a need for a biological standard to replace the thermal standard and to also protect against cumulative effects across the EM spectrum.

III. ELF and RF activation of the stress response

Much detailed information about the stress response will be presented in the following sections and in the tables, but the most important finding to keep in mind is that *both ELF and RF fields activate the synthesis of stress proteins*. All cells do not respond to EMF, but activation of the same cellular mechanism by both thermal and non-thermal stimuli in a variety of cells shows that both ELF and RF are biologically active and that a biological 'dose' of EMF cannot be described in terms of SAR (Blank and Goodman, 2004a). SAR is irrelevant for non-thermal ELF responses, where energy thresholds are many orders of magnitude lower than in RF. A new definition of EMF dose is necessary for describing a safety limit, and SAR must be replaced by a measure of exposure that can be defined in biological terms.

The stress response, by its very nature, shows that *cells react to EMFs as potentially harmful*. The stress response is an important protective mechanism that enables cells from animals, plants and bacteria to survive environmental stressors, such as sharp increases in temperature (originally called 'heat shock'), hypoxia, and dissolved toxic heavy metals like Cd^{+2} and oxidative species that can damage proteins and DNA ('oxidative stress'). The stress response is evolutionarily conserved in essentially all eukaryotic and prokaryotic organisms, but not all stressors are effective in all cells, and different stress proteins are activated under different conditions. Stress proteins are a family of about 20 different proteins, ranging in size from a few kilodaltons to over 100kD. The 27kD and 70kD protein families are the most common and most frequently studied.

Kültz (2005) has called the stress response a '... defense reaction of cells to damage that environmental forces inflict on macromolecules.', based on evidence from gene analysis showing that the stress response is a reaction to molecular damage. The genes activated as a group along with stress genes, which Kültz calls the 'universally conserved proteome', are those associated with sensing and repairing damage to DNA and proteins.

Stress proteins help damaged proteins refold to regain their conformations, and also act as "chaperones" for transporting cellular proteins to their destinations in cells. The molecular damage stimulated by non-thermal ELF fields occurs in the absence of an increase in temperature. ELF energy thresholds are estimated to be about 10^{-12} W/kg, over a billion times lower than the thermal stimuli that cause damage in the RF range (Blank and Goodman, 2004a).

The classic stress response to a sharp increase in temperature (i.e., 'heat shock') is associated with a biochemical pathway where transcription factors known as heat shock factors, HSFs, translocate from the cytoplasm to the nucleus, trimerize and bind to DNA at the heat shock elements (HSEs) in the promoters of the genes. The promoter is the DNA segment where protein synthesis is initiated and it is not part of the coding region. The HSEs contain specific nucleotide sequences, nGAAn, that are the consensus sequences for thermal stimuli. The binding of HSFs to HSEs, etc is similar for heat shock in plant, animal and bacterial cells. ELF range EMFs have been shown to follow the same sequence of events in inducing stress response proteins in human cells, including breast (MCF7, HTB124), leukemia (HL60), epithelial cells, as well as E. coli and yeast cells.

Studies done with chick embryos and cells from *Drosophila* and *Sciara* salivary gland chromosomes have produced graphic evidence of the effects of EMF. In *Drosophila* and *Sciara* salivary gland chromosomes, EMF causes the formation of 'puff's, enlarged regions along the chromosome, at loci associated with activation of heat shock genes. This is followed by elevated concentrations of transcripts at the sites and eventually stress protein synthesis (Goodman and Blank, 1998). The changes in chromosome morphology are characteristic of the stress response to both EMF and elevated temperature. Chick embryos develop hearts that stop beating when the oxygen concentration is lowered, but that can be protected and kept beating if stress proteins have been induced by ELF fields (DiCarlo et al, 1998) and in the RF range (Shallom et al, 2002).

The cellular response pathways to EMF have been characterized in the ELF range (Goodman and Blank, 2002), and have been found to share some of the characteristics of heat shock stress, such as the movement of heat shock factor monomers from the cytoplasm to the nucleus. The biochemical mechanism that is activated, the MAPK signaling pathway, differs from the thermal pathway (Goodman and Blank, 2002), but is the same as the non-thermal pathway in the RF range (Leszczynski et al, 2002).

The HSP70 gene is activated within minutes in cells exposed to ELF fields (Lin et al, 1997), and is accompanied by the binding of HSFs to the specific nucleotide sites in the promoter of the gene. However, different segments of the DNA promoter function as HSEs. Research in the ELF range has shown that the promoter of the major stress protein, hsp70, has two domains that respond to two different physical stimuli, EMF and an increase in temperature (Lin et al, 1999). The stimulus-specific domains have different DNA sequences that cannot be interchanged. The ***DNA consensus sequences that respond to EMF are nCTCTn*** (Lin et al, 1997; 1999). These differ from the nGAAn consensus sequences for thermal stimuli. The existence of two different consensus sequences that respond to EMF and temperature increase, respectively, are molecular

evidence of different pathways that respond to non-thermal and thermal stimuli.

In another series of experiments, a DNA sequence from the promoter of an EMF sensitive gene was included in a construct containing a reporter gene, either chloramphenicol amino transferase (CAT) or luciferase. In each case, the construct proved to be EMF sensitive and reacted when an ELF field was applied (Lin et al, 2001). The ability to transfer EMF sensitive DNA sequences that subsequently respond to an EMF is further evidence linking the cellular response to a DNA structure.

In heat shock, the stress response is activated when extracellular signals affect receptors in the plasma membrane. This probably does not happen with an EMF, which can easily penetrate throughout the cell and whose actions are therefore not limited to the membrane. One can transfer the EMF response by transferring the DNA consensus sequences (Lin et al, 2001), so it is likely that the activation mechanism involves direct EMF interaction with the DNA consensus sequences. The cell based signal transduction pathways of the heat shock response are involved in regulation of the EMF stimulated process, probably through the feedback control mechanisms that respond to the stress proteins synthesized or the mRNA concentrations that code for them (Lin et al, 1998).

Repeated induction of the stress response in a cell has been shown to induce cytoprotection, a reduced response associated with restimulation (Blank and Goodman, 1998). This is analogous to thermotolerance, the reduced response to an increase in temperature after an initial heat shock response. Experiments with developing chick embryos show similar habituation to repeated stimulation in the ELF range (DiCarlo et al, 2002). There are different effects of continuous and intermittent EMF exposures that show feedback control features in the EMF stimulated stress response (Lin et al, 1997). This autoregulatory reaction is an indication that the thermotolerance mechanism is inherent in the response to a single stimulus as well.

It has now been shown in many laboratories that RF also stimulates the cellular stress response and cells start to synthesize stress proteins in many different kinds of cells (e.g., Kwee et al, 2001; Shallom et al, 2002; Leszczynski et al, 2002; Weisbrot et al, 2004). Cotgreave (2005) included many cells that did not synthesize stress proteins in response to RF stimulation in his summary of data. The listings in Table 1 contain additional positive and negative results. It is quite clear that certain cell lines do not respond to EMF by synthesizing stress proteins. The reasons are not known, but the changes in cells in tissue culture and in cancer cells may render some of them unable to respond to EMF. In addition to mutations in cell lines, pre-exposure to ambient ELF and RF fields in the laboratory can also affect an ability to respond. What we can say in summary at this stage is that:

- the stress response has been demonstrated in many cells and linked to changes in the DNA and chromosomes.

• there are similarities in stress protein synthesis stimulated in the non-thermal ELF and thermal RF frequency ranges.

• the biochemical mechanism that is activated is the same non-thermal pathway in both ELF and RF, and is not associated with the thermal response.

IV. DNA activation mechanisms: EMFs and electrons

We think of DNA as a very stable polymer that stores and transmits genetic information from generation to generation. However, DNA must also come apart relatively easily to enable the continuous protein synthesis that is needed to sustain living cells. Usually, this process is started when specialized proteins called transcription factors bind to DNA. However, both ELF and RF fields also stimulate DNA to start protein synthesis. EMF stimulation of stress protein synthesis indicates activation of DNA, even by relatively weak non-thermal ELF. This raises the possibility that EMF can cause other changes in DNA that interfere with the copying and repair processes in DNA, and that can lead to mutations and cancer.

Protein synthesis starts when the two chains of DNA come apart to make an mRNA copy of the amino acid code for a particular protein. This occurs at the specific DNA segment where the transcription factor binds, and in forming a bond changes the electron distribution. Since recent research has shown electron conduction in DNA (Wan et al, 1999; 2000; Ratner, 1999; Porath et al, 2000; Giese and Spichty, 2000), it is possible that EMF affects electron distribution and movement in DNA, and helps it to come apart to initiate protein synthesis, not unlike the action of a transcription factor. Charge transport through DNA depends on the DNA sequence (Shao et al, 2005), and there are reasons to believe that EMFs would cause the DNA to come apart at the EMF consensus sequence, nCTCTn (Blank and Goodman, 2002).

The ability of relatively small perturbations to stimulate DNA to initiate biosynthesis is consistent with larger perturbations that lead to DNA strand breaks. Several experimental studies have reported both single and double strand breaks in DNA and other chromosome damage after exposure to ELF fields (Lai and Singh, 1997a; Ivancsits et al, 2005, Diem et al, 2005; Winker et al, 2005). Ivancsits et al (2005) found DNA damage in fibroblasts, melanocytes and rat granulosa cells, but not in lymphocytes, monocytes and skeletal muscle cells. Single and double strand breaks and other DNA damage after exposure to RF fields have also been reported (Phillips et al, 1998; Sarimov et al, 2004; Lai and Singh, 2005).

The Ivancsits, Diem and Winker studies cited above are part of the REFLEX Project, a collaboration of twelve laboratories in seven countries of the European Union (REFLEX, 2004). The group found that both ELF and RF exposures, below the current safety limits, modified the expression of many genes and proteins. They also reported DNA damage (e.g., strand breaks, micronuclei, chromosomal damage) due to ELF fields at exposures

of 35μT. Similar genotoxic effects were produced in fibroblasts, granulosa cells and HL60 cells by RF fields at SARs between 0.3 and 2W/kg. The expression and phosphorylation of the stress protein hsp27 was one of the many proteins affected.

The REFLEX Project Report (2004) is available on the internet and well worth consulting as a source of much information about the effects on cells *in vitro* due to the ELF and RF exposures we encounter in our environment. The Report has an introduction by Ross Adey, one of the last things he wrote, telling us about the importance of establishing "...essential exposure metrics ... based on mechanisms of field interactions in tissues". One needs a biological metric in order to characterize EMF exposure.

The possibility that EMFs could cause greater damage to DNA in the RF range and at longer exposures was demonstrated by Phillips et al (1998) who reported more DNA breaks when cells were exposed at higher SARs. They suggested that the rate at which DNA damage can be repaired (or eliminated by apoptosis) is limited, and when the rate of damage at the higher SARs exceeds the repair rate, there is the possibility of retaining mutations and initiating carcinogenesis. Chow and Tung (2000) reported that exposure to a 50Hz magnetic field enhances DNA repair through the induction of DnaK/J synthesis. The eternal struggle in cells and organisms between the forces tending to break things down (catabolism) and those tending to build up and repair (anabolism) probably accounts for much of the variability one finds in experiments with cells as well as with people.

The changes in DNA initiated by ELF fields cannot be explained by thermal effects. Electric and magnetic fields interact with charges and magnetic dipoles, and fundamental mechanisms must ultimately be based on these interactions. From the data in Table 2, it is clear that relatively little energy is needed for effects on electron transfer (Blank and Goodman, 2002; 2004b; Blank, 2005). The low energies needed to perturb DNA in the ELF range suggest that the mechanism involves electrons, e.g., probably in the H-bonds that hold the two chains of DNA together. Electrons have very high charge to mass ratio and are most likely to be affected even by weak electric and magnetic fields.

There are many indications that electrons are involved in EMF reactions with DNA. In experiments that stimulate the stress response, the estimated force of ~10^{-21} newtons that activates DNA can move a free electron about the length of a H-bond (~.3nm) in 1ns. The calculated electron velocity is comparable to electron velocities measured in DNA (Wan et al, 1999; 2000), and is also expected if electrons move at the ~nanometer/picosecond flickering rate of protons in H-bonded networks (Fecko et al, 2003) that would be present at normally hydrated DNA sites. Electrons can tunnel nanometer distances in proteins (Gray and Winkler, 2003), and experiments have shown comparable electron movement in DNA (Wan et al, 1999; 2000). Electrons might be expected to move more readily from the CTCT bases in the consensus sequence, because of their low electron affinities. Finally, ELF fields have been shown to accelerate electron transfer in oxidation-reduction reactions (Blank and Soo, 1998; 2003).

The fact that the same non-thermal mechanism is activated in ELF and RF ranges

emphasizes that it is not the total energy associated with the EMF that is critical, but rather the regular oscillations of the stimulating force. As already mentioned earlier, the energy associated with each wave (i.e., energy/cycle) is more or less independent of the frequency. If the same energy is needed to reach threshold in both ELF and RF, the many repetitions at the higher frequency cause the non-thermal threshold to be reached in a shorter time and the total energy absorbed over time to increase with frequency. Even in the ELF range, where SAR levels are very low, the stress response is activated by short exposures to fields of less than 1μT, while single and double strand breaks in DNA have been reported at longer exposures to higher field strengths ~0.1mT (Lai and Singh, 2005). The two mechanisms appear to be related in that breaks in DNA appear to result from free radical mechanisms that also involve electron transfer reactions (Lai and Singh, 1997b).

The reaction of EMFs with DNA differs from those listed in Table 2 in that they appear to occur with equal ease at the widely differing frequencies in ELF and RF ranges. The frequency dependence of a reaction provides information about how time constants of charge transfer processes are affected by fields, and the frequency responses of the few EMF sensitive biological systems that have been studied suggest that fields are most effective at frequencies that are close to the natural rhythms of the processes affected (Blank and Soo, 2001a; Blank and Goodman, 2004b; Blank, 2005). Frequency optima for the enzymes, Na,K-ATPase and cytochrome oxidase, differ by an order of magnitude with maximums at about 60Hz and 800Hz, respectively (Blank and Soo, 2001a), in both cases close to the observed frequency maximum of the enzyme reaction. The rate constant of the BZ reaction is about 250Hz, the frequency of the rate limiting step in a multi-step process with at least 10 sub-reactions (Blank and Soo, 2003).

The electrons in DNA that are affected by EMFs are probably not engaged in electron transfer reactions. They respond to frequencies that range from ELF to RF and are more likely to be tied to the wide frequency range of fluctuations than to the frequency of a particular reaction. The displacement of electrons in DNA would charge small groups of base pairs and lead to disaggregation forces overcoming H-bonds, separating the two chains and enabling transcription. Studies have shown that biopolymers can be made to disaggregate when the molecular charge is increased (Blank, 1994; Blank and Soo, 1987). This explanation would also apply to the effect of applied electric fields that also activate DNA. Electric fields exert a force on electrons, and have been shown to stimulate protein synthesis in HL60 cells (Blank et al, 1992), E coli (Laubitz et al, 2006) and muscle *in vivo* (Blank, 1995). The genes for the hsp70 stress protein are more likely to be activated since they have been shown to be ‘bookmarked’ on the DNA chain, that is, more exposed to externally applied forces (Xing et al, 2005).

The outline of a plausible mechanism to account for EMF activation of DNA through interaction with electrons has relied on evidence from many lines of research. This mechanism may or may not hold up under further testing, but the experimental facts it is based on have been verified. It has been clearly demonstrated that exposure of cells to non-thermal power and thermal radio frequency EMFs, at levels deemed to be safe for human exposure, activate DNA production of stress proteins and could increase the

number of DNA breaks. There is ample experimental evidence to support the possibility of DNA damage at non-thermal levels of exposure, and the need for greater protection.

V. The critical role of scientific research

The connection between the results of scientific research and assessing EMF risk does not appear to be working well. We all agree that EMFs are unsafe at the level where they cause electrocution, and that we must protect against that possibility. We also agree that if other risks are associated with EMFs, we must identify them and determine the exposure levels at which they occur. This task requires that we define a biological dose of EMF, and that we obtain information about cellular mechanisms activated at different doses. As we have seen, the currently accepted measure of EMF dose, the specific absorption rate (SAR), is definitely not a measure of the effective biological dose when stress protein synthesis can be stimulated by SAR levels that differ by many orders of magnitude in the ELF and RF ranges (Blank and Goodman, 2004a). Yet, there is strong opposition to accepting the consequences of these experimental facts.

Regarding EMF mechanisms, we still have much to learn, but we know that the energy and field strength thresholds of many biological reactions are very low (Table 2). These findings indicate that safe exposure levels for the public should be substantially lowered, if only as a precautionary measure. Even when stated in vague terms, so as to require little more than lip service, a precautionary policy has not yet been recommended by the WHO. Thus, the two main problems of research on EMF risk, defining a biological dose and the desired level of exposure protection, remain to be solved.

Scientific research can contribute to defining a biological dose, but the desired level of exposure protection is a more complicated issue. Guidance for EMF policy on exposure protection has come primarily from epidemiology studies of health risks associated with power lines in the case of ELF, and cell phones in the case of RF. Basic research studies do not provide insight into the effects of long term exposures that are so important in determining risk, and they appear to have been used almost entirely to probe biochemical mechanisms that might underlie health risks identified in epidemiology studies. However, the research does overcome a basic weakness of epidemiology studies, an inability to determine a causal relation and to rule out effects of possible confounders. Epidemiology studies can correlate EMF exposure and health effects in human populations, and show quantitative dose-response relations, but it is only when coupled with basic research on molecular mechanisms that one can test and establish the scientific plausibility of effects of exposure. This scientific capability has become more important with recent advances in research on DNA, where mutations associated with initiation and promotion of cancer can be identified. EMF laboratory research has also played an indirect role in the practical aspects of risk by showing that:

- many biological systems are affected by EMFs,
- EMFs compete with intrinsic forces in a system, so effects can be variable,

- many frequencies are active,
- field strength and exposure duration thresholds are very low,
- molecular mechanisms at very low energies are plausible links to disease (e.g., effect on electron transfer rates linked to oxidative damage, DNA activation linked to abnormal biosynthesis and mutation).

Research on the stress response, a protective mechanism that involves activation of DNA and protein synthesis, was not included in previous scientific reviews prior to evaluating safety standards, and thus provides additional insights into EMF interactions (Blank and Goodman, 2004a). Activation of this protective mechanism by non-thermal as well as thermal EMF frequencies has demonstrated:

- the reality and importance of non-thermal effects of EMFs,

- that cells react to an EMF as potentially harmful,

- the same biological reaction to an EMF can be activated in more than one division of the EM spectrum,

- direct interaction of ELF and RF with DNA has been documented and both activate the synthesis of stress proteins,

- the biochemical pathway that is activated is the same pathway in both ELF and RF and it is non-thermal,

- thresholds triggering stress on biological systems occur at environment levels on the order of 0.5 to 1.0 μT for ELF,

- many lines of research now point to changes in DNA electron transfer as a plausible mechanism of action as a result of non-thermal ELF and RF.

Given these findings, the *specific absorption rate (SAR) is not the appropriate measure of biological threshold or dose*, and should not be used as a basis for a safety standard since it regulates against thermal effects only.

Cellular processes are unusually sensitive to non-thermal ELF frequency fields. The thresholds for a number of biological systems are shown in Table 2, and many are in the range of 0.5 to 1.0 μT, not very much higher than the usual environmental backgrounds of ~0.1μT. The low biological thresholds in the non-thermal ELF range undermine claims that an EMF must increase the temperature in order to cause changes in cells. They also show that many biochemical reactions can be affected by relatively low field strengths, similar to those in the environment. -Non-thermal ELF fields can also cause DNA damage, and therefore add to health and safety concerns.

In addition to very low thresholds, exposure durations do not have to be very long to be effective. Litovitz et al (1991, 1993), working with the enzyme ornithine decarboxylase,

have shown a full response to an EMF when cells were exposed for only 10sec. This occurred with ELF sine waves or ELF modulated 915MHz sine waves. The exposure had to be continuous, since gaps in the sine wave resulted in a reduced response. Interference with the sine wave in the form of superimposed ELF noise also reduced the response (Mullins et al, 1998). The interfering effect of noise has been shown in the RF range by Lai and Singh (2005), who reported that noise interferes with the ability of an RF signal to cause breaks in DNA strands. The decreased effect when noise is added to a signal is yet another indication that EMF energy is not the critical factor in causing a response.

The finding that the stress response threshold can be stimulated in both ELF and RF frequency ranges appears to suggest that the threshold is independent of EMF energy. Energy increases with the frequency, so compared to an ELF energy of ~1a.u. (arbitrary unit of energy), the energy at RF is ~10^{11}a.u. Actually, it is the energy/cycle that is independent of frequency. A typical ELF cycle at 10^{2}Hz lasts 10^{-2}sec and a typical RF cycle at 10^{11}Hz lasts 10^{-11}sec. Because the energy is spread over a different number of cycles each second in the two ranges, the same value of ~10^{-2} a.u./cycle applies to both ELF and RF ranges.

An early review of the stress response in the ELF range (Goodman and Blank, 1998) summarized basic findings, and a more recent review by Cotgreave (2005) has provided much additional information, primarily on the RF range. Table 1 summarizes both ELF and RF studies (mainly frequencies 50Hz, 60Hz, 900MHz, 1.8GHz) relevant to stimulation of DNA and stress protein synthesis in many different cells. The list is not exhaustive, but the citations represent the different frequencies and biological systems, as well as the diversity of results in the literature. As already noted by Cotgreave (2005), the stress response does not occur in reaction to EMFs in all cells. A paper by Jin et al (2000), to be discussed later, shows that even the same cell line can give opposite results in the same laboratory. The stress response is an important topic in its own right, but its importance for EMF research is that it offers insights into EMF interaction mechanisms in the stimulation of DNA. On the practical level, the stress response has shown the need to replace the SAR standard to take into account non-thermal biological effects.

Differences in experimental results shown in Table 1 are not uncommon when studying phenomena that are not as yet well understood, and this frequently gives rise to controversy. In EMF research, however, other factors have contributed to a controversial scientific atmosphere. The following sections on the scientific context, as well as a critique of the review by Cotgreave, will show how discussion of the stress response and the absence of discussion on related topics have compromised the evaluation of the science. The discussion of stress response stimulation in ELF and RF ranges together with ideas on DNA mechanisms, has important implications regarding EMF risk and safety.

VI. The troubling context of today's science

The need to include basic research findings in assessment of health risks is clear, but it is

equally important to make sure that these findings are properly evaluated. No less an authority on science than Donald Kennedy (2006), the current Editor of *Science*, wrote "...how competitive the scientific enterprise has become, and the consequential incentive to push (or shred) the ethical envelope". He was referring primarily to the controversial religious/ political atmosphere over such issues as evolution, stem cell research, etc, but he could just as easily have included economic factors. In the following quote, editors of the *Journal of the American Medical Association* (JAMA 284:2203-2208, 2000) pointed out distortions in the proof of effectiveness of drugs in studies supported by the drug industry:

> "*There is a growing body of literature showing that faculty who have industry ties are more likely to report results that are favorable to a corporate sponsor, are more likely to conduct research that is of lower quality, and are less likely to disseminate their results to the scientific community*".

Even *The Wall Street Journal* (Jan 9, 2007), which generally presents favorable views of business, had a front page article on the controversy over whether mycotoxins produced by molds are harmful, that was critical of scientist-business community connections. They pointed out that some scientific experts in the professional societies, who had issued statements minimizing harmful effects, had not disclosed their links to companies defending lawsuits in this area.

The connection between scientific expertise, the research that is done, and the source of support, has always been an ethical gray area, but the above examples and recent instances of experimental fraud have reinforced the impression that the ethical standards of scientists have deteriorated considerably. In our area of interest, insufficient attention has been paid to the influence the power and communication industries may be having on the research of those assessing EMF safety. At the Third International Standard Setting Seminar (October 2003) in Guilin, China, Prof. Henry Lai of the University of Washington summarized 179 cell phone studies showing that independent researchers were twice as likely to report biological effects due to RF in comparison to those funded by industry. This was very much in line with the earlier JAMA comment on the drug industry. Published reports have started to appear (Hardell et al, 2006; Huss et al, 2007) documenting the correlation of EMF research outcome with the source of support. Recognition of the phenomenon is a first step toward minimizing abuses, and one hopes that this information will eventually be factored into evaluation of the experimental results. I am not overly optimistic, since those who wish their influence to remain hidden can channel support through unaffiliated committees with non-committal names.

Science is a cooperative enterprise in the long run, but in day-to-day practice, there has always been competition among scientists for recognition and support. In EMF research, the atmosphere has become especially adversarial in the selection of participants and subjects to be covered in recent evaluations. Two important examples are the International Committee on Electromagnetic Safety (ICES) and IEEE sponsored symposium on "Reviews of Effects of RF Energy on Human Health" (BEMS Supplement 6, 2003), and the more recent WHO sponsored symposium "Sensitivity of Children to

EMF Exposure" (BEMS Supplement 7, 2005). Both collections of papers appeared in *Bioelectromagnetics*, the journal of the primary research society in this scientific specialty, where publication carries a certain aura of authority in the field. Of course, one expects the highest of ethical standards, and the editor assured everyone that normal reviewing procedures, etc, had been followed. However, all that had come after the scope of the papers had been narrowly defined so that there was no coverage of recent research on the EMF stimulated stress response or stimulation of DNA to initiate protein synthesis. An older mind set pervaded the choice of the topics and the papers. That mind set appeared to be stuck in the belief that non-thermal EMF was biologically inert, that the nucleus was an impregnable structure that unlocked the genetic information in its DNA only at the time of cell division, etc. These two meetings took place only a few years ago, in a world of science where it had already been known for some time that biochemical signals are continuously changing DNA in cell nuclei and mitochondria, turning on protein synthesis, checking and repairing DNA itself, etc. Research on the stress response had even shown that DNA was unusually sensitive to EMF by finding responses in the non-thermal ELF range. One expects to find such papers in symposia organized by the Mobile Manufacturers Forum, but not in *Bioelectromagnetics*.

A science based evaluation process cannot limit its scope of interest so as to ignore a research area that is so central in biology today, and that is obviously affected by EMF. Information on the EMF stimulated stress response and stimulation of DNA to initiate protein synthesis must be an integral part of the evaluation process, and its omission in earlier evaluations compromised the scientific basis of those reviews and distorted their conclusions.

It is ironic that the review in *Bioelectromagnetics* Supplement 6 listed as its first guiding principle that "The RF safety standard should be based on science", essentially a reaffirmation of the IEEE guideline for the revision of C95.1-1991 safety standards. Scientific research is designed to answer questions, and answers do not come from deciding *a priori* that certain types of studies are not relevant or can be ignored because they have not been adequately proven in the eyes of the organizers. Scientific method is not democratic. The word 'proof' in 'scientific proof' is best understood in terms of its older meaning of 'test'. It does not rely on an adversarial 'weight of the evidence', where opposing results and arguments are presented and compared. Answers do not come from keeping a scoreboard of positive versus negative results and merely tallying the numbers to get a score. In scientific proof, number and weight do not count. It is hard to see how the review in *Bioelectromagnetics* Supplement 6 could reconcile its advocacy of science as a guiding principle with its subsequent endorsement of "the weight of evidence approach" to be used in their assessment.

We should be reminded that 'scientific proof' is not symmetric (Popper, 1959). One cannot prove that EMF is harmless no matter how many negative results one presents. One single reproducible (significant) harmful effect would outweigh all the negative results.

The above characteristics of science are generally acknowledged to be valid as abstract

principles, but in EMF research, it has been quite common to list positive and negative findings and thereby imply equal weights. Table 1 is an alphabetical listing by first author of positive and negative findings, with the negative studies indicated as **NO** in bold. There is no scoreboard, since the studies are on many different systems, etc, and not of the same quality. The listing is not meant to be complete or to be scored, but rather to present the variety of biological systems studied in the different EMF ranges.
Negative studies play an important role in science, and there is good reason to publish them when they are failures to replicate earlier positive results. This can often lead to important clarifications of the effect, the technique, etc. However, negative studies are being used in another way. Although they cannot prove there is no positive effect, they do have an influence in the unscientific 'weight of evidence approach'. In epidemiology, where it is difficult to compare studies done under different conditions, it is common to make a table of the positive and negative results. The simple listing has the effect of a tally, and the overall score substitutes for an evaluation. In any case, one can write that the evidence is 'not consistent', 'not convincing' or claims are 'unsubstantiated' and therefore 'unproven'. The same is true in experimental studies. Funds are generally not available for an independent study to track down the causes of the differences in results, so the contradictory results are juxtaposed and a draw is implied. This is a relatively cheap but effective way to neutralize or negate a positive study.

VII. Replication and failures to replicate experimental results

Independent replication of experiments is an essential criterion for acceptance of a result and one of the pillars of scientific proof. However, as we shall see below, it is very difficult to actually replicate a biological experiment. We need only remember the experience with the 'Henhouse' project run by the Office of Naval Research many years ago, when chicken eggs from different suppliers led to different effects of EMFs on chick embryo development.

While scientists generally shun replications, some failures to replicate have been analyzed and explained. The two discussed below had the earmarks of replications, but neither was. In one case, it was clearly shown by Jin et al (2000) that the investigators failed to use the precise cell type population of the original experiment. Jin et al obtained HL60 cells from the two different sources used in the papers with the contradictory results, and showed that the cells had very different growth characteristics, significantly different reactivities and reactions to EMFs. It appears that even different samples of the same cell line in the same laboratory can have different responses to EMFs. The changes that occur in tissue culture over time can result in very different responses to EMFs.

In another example, Utteridge et al (2002) published a paper in *Radiation Research* meant to test the positive results of an earlier study (Repacholi et al, 1997) that had shown a twofold increase in lymphoma in mice exposed to cell phones. They failed to replicate the findings, but even a cursory reading of the paper showed that the study was

poorly designed and executed, and was definitely not a replication. They had used a different exposure regimen and had manually handled the animals, an added stress on the mice. The cancer rate in the control group was three times the rate of the earlier study, possibly due to the handling, making it almost impossible to find any effect of cell phone exposure. There were also unusual inconsistencies in the published data, such as listing the weights of animals that had died months earlier. It is hard to see how the paper passed peer review. The Utteridge study self-destructed, and the results of the Repacholi study are still looked upon as showing a relation between RF and cancer in an animal model. However, there were scientific casualties, the peer review process of the journal and the credibility of its editors.

It may be appropriate to mention that *Radiation Research*, a journal devoted to research with ionizing radiation frequencies, has published studies that almost exclusively show no EMF effects. A quick glance at Table 1 will show that many of the '**NO** effect' listings are published in that journal. It has even gone beyond the frequency range defined in its title and published 'negative' studies in the non-ionizing frequency range. The internet edition of *Microwave News* has an explanation for why this journal repeatedly publishes negative research and appears to have become so politicized on the EMF issue.

It is not unusual for scientists to deviate from an original experimental protocol when repeating an experiment. They generally view the deviations as improvements in technique. Readers who have not worked on that particular system are unlikely to focus on a small difference that does not appear to be significant. Yet, even a small difference may lead to a failed replication. Blank and Soo (2003) showed that EMF accelerated the Belousov-Zhabotinsky (BZ) reaction, which is the catalyzed oxidation of malonic acid. A subsequent study reported no effect of EMF on the BZ reaction (Sontag, 2006), in essence a failed replication. In the second study, the authors did not apply the field at the time the reactants were mixed, as in the original, but only after the reaction was well under way for about seven minutes. This time difference was critical for a reaction that responds to EMF. Other reactions had responded to EMF (Blank and Soo, 2001b; Blank, 2005) only when the field was applied at time zero, when the intrinsic chemical forces were relatively weak. The effect of EMF was even shown to vary inversely with the opposing chemical forces of an enzyme (Blank, 2005). After seven minutes, the BZ reaction was running at full speed and the applied ELF fields were not strong enough to overcome the built up chemical forces.

The above paragraph points up a critical factor often overlooked in EMF experiments. EMF is only one of the factors that can affect the rate of a biochemical reaction, and a relatively weak one in the ELF range. It appears that when an EMF accelerates charge movements associated with a reaction, the applied field competes with intrinsic forces, and the ability to see an effect of the applied EMF depends on minimizing the other forces in the system. It is obvious that an important strategy to minimize unwanted biological effects due to EMF is to maintain intrinsic forces at optimal (healthy) levels.

In the above mentioned experiments with the Na,K-ATPase (Blank, 2005), it was found

that the effect of an applied electric or magnetic field varied inversely with the activity of the enzyme, which could be changed by changing ion concentrations, temperature, inhibitors, or by the normal aging of the preparation. The effect of intrinsic activity was also observed in other systems, electron transfer from cytochrome C to cytochrome oxidase (Blank and Soo, 1998), and in the effect of temperature on the oxidation of malonic acid (Blank and Soo, 2003). Since the effect of EMF in an experiment can vary depending on the other forces acting in the system, it is important to make sure that all relevant parameters are identified and controlled. Replication of biological experiments must ensure a comparable level of intrinsic biological activity before a perturbing EMF is applied. This is especially difficult with enzyme preparations as they age.

In studies of stress protein synthesis, many factors must be considered, but the choice of cells is particularly important. Not all cells respond to EMF, and the results of many experiments have suggested ideas about critical properties that are apt to determine the response and also affect the ability to replicate an experimental result.

A quick look at Table 1 shows that tissue culture cells are more likely to show '**NO** effect'. That is not really surprising. Cells in tissue culture have changed significantly to enable them to live indefinitely in the unnatural conditions of a flask in a laboratory, and the changes could have made them unresponsive to EMF. The same is true of the changes in cancer cells, although some (e.g., MCF7) have responded to EMF (e.g., Liburdy et al, 1993), and in one cell line, HL60, some samples respond to EMF and others do not (Jin et al, 2000). On the other hand, the study by Czyz et al (2004) found that p53-deficient embryonic stem cells showed an increased EMF response, but the wild type did not. It is obviously difficult to make generalizations about the necessary conditions for a response to EMF when there are so many variations, and cells can undergo changes in tissue culture.

Some insight into differences between cells has been obtained from a broad study of genotoxic effects in different kinds of cells (Ivancsits et al, 2005). They found no effects with lymphocytes, monocytes and skeletal muscle cells, but did find effects with fibroblasts, melanocytes and rat granulosa cells. Other studies (e.g., Lantow et al, 2006b; Simko et al, 2006) have also found that the blood elements, such as lymphocytes and monocytes are natural cells that have not responded. From an evolutionary point of view, it may be that mobile cells can easily move away from a stress and there is little selective advantage to develop the stress response. The lack of response by skeletal muscle cells is easier to explain (Blank, 1995). It is known that cells containing fast muscle fibers do not synthesize hsp70, while those with slow fibers do. This evolutionary development protects cells from over-reacting to the high temperatures reached in fast muscles during activity.

Other natural cells listed in Table 1, such as epithelial, endothelial and epidermal cells, fibroblasts, yeast, E coli, developing chick eggs, the cells of *Drosophila*, *Sciara* and C elegans, have all been shown to respond. While experiments with non-responding cells have provided little information, studies of the differences between responding and non-

responding cells may be the best experimental strategy for studying the stress response mechanism. Proteomics appears to be an excellent tool for answering many of the questions about the molecular mechanisms that are activated (Leszczynski et al, 2004).

In studies of stress protein synthesis, the time course of a response must be determined. There is generally a rapid induction and a slower falloff of response, but the kinetics can be affected by many other conditions of the experiment. It is, therefore, important to look for stress proteins when they are apt to be present, and not before they have been synthesized or after the response has decayed. This may be the explanation for the inability of Cleary et al, (1997) to observe stress proteins twenty-four hours after exposure. Some additional cautions to be aware of in contemplating or evaluating a study. For example, different stresses elicit different responses, so it is important to determine which of the ~20 different stress proteins are synthesized. The most frequently studied stress proteins are hsp70 and hsp27, but others may be involved and undetected. The exposure history of a cell population must be known, since there are differences in the responses to an initial stimulus and subsequent ones. The need to provide shielding for cells becomes far more complicated when they respond to RF as well as ELF fields and one must insure no pre-exposure.

Obviously, many experiments must be done to determine the optimal conditions for the study of a particular system. This does not shift the burden of proof to those unable to find an effect, but it adds weight to the cautions generally voiced in papers that state their failure to observe stress proteins ‘under our experimental conditions’. Those words mean just that, and not that stress proteins were absent.

An experiment on EMF stimulation of cell growth that has almost disappeared from the EMF literature is the work of Robert Liburdy (Liburdy et al, 1993). He reported that weak 60Hz fields can interfere with the ability to inhibit growth in MCF7 breast cancer cells. This finding has been replicated six times, but the original experiment and its replications have been ignored by many health oriented scientists (Liburdy, 2003), including the recent WHO review (BEMS Supplement 7, 2005). Even breast cancer researchers (e.g., Loberg et al, 1999), who have not been directly involved in the EMF debate, appear to be totally unaware of results showing the ability of weak 60Hz fields to affect cancer cell growth. It is shocking when an EMF research review by a presumably scientifically neutral WHO fails to even mention any of the papers that offers insight into the mechanism of a devastating disease that is so prevalent in the population (Blank and Goodman, 2006). Let us not forget the asymmetry in scientific proof (Popper, 1959), where a single reproducible harmful effect would outweigh all the negative results. The many replications of the Liburdy experiment have given us a crucial finding regarding the question of EMF risk, and they cannot be ignored.

VIII. A critical look at a recent review of the stress response

The earlier discussion of non-scientific influences in the design and presentation of the results of EMF research serves as an introduction to a critical look at the recent review on

RF and the stress response by Cotgreave (2005) 'with contributions of the Forschunggemeinschaft Funk'. I agree with the major conclusion-of the review, the need for more research on the stress response with better controls. However, Cotgreave was highly selective in his omission of papers on ELF and stress proteins. Given that there are many relevant ELF papers reporting effects on stress proteins at non-thermal levels, this omission results in significant under-reporting of what is scientifically established. These obvious and scientifically questionable omissions were used to cast doubt on the ability of RF to have a significant biological effect, at a time when much evidence pointed in the opposite direction.

Cotgreave stated correctly that RF is pleiotropic (produces more than one gene effect) for many regulatory events, in addition to the stress response. That observation comes as no surprise to biologists who know that cellular systems are interconnected and that the complexity of the signaling pathways resembles that of the old interlinked intermediary metabolism charts. It is also no surprise to those familiar with early papers on EMFs, which showed activation of genes such as c-*myc* (Goodman and Shirley-Henderson, 1991; Lin et al, 1994;1996) and c-*fos* (Rao and Henderson, 1996) at about the same time the EMF stress response was first described (Blank et al, 1994; Goodman et al, 1994). The EMF stimulated synthesis of many proteins (Goodman and Henderson, 1988) and the binding of specific transcription factors AP-1, AP-2 and SP-1 were also previously described (Lin et al, 1998).

By highlighting the previously known pleiotropic nature of the EMF response, Cotgreave played down the role of the stress response as a protective mechanism. Had he analyzed the biological implications of the many genes activated, he could have pointed to evidence from proteomics and gene analysis that there is a relevant pattern to the pleiotropism. Kültz (2005) recently summarized the evidence that specific groups of genes are activated along with stress genes across the biological spectrum. It is of particular interest to the EMF discussion that this 'universally conserved proteome' consists largely of genes involved in sensing and repairing damage to DNA and proteins, evidence that the stress response is a reaction to molecular damage across the biological spectrum. The stress response is one of many stimulated by RF, but other parts of the response also show evidence of damage control in reaction to an EMF.

By limiting the scope of his review to effects of RF, Cotgreave overlooked much that is relevant to understanding the effects of EMFs. That was a bit like writing a review on the physiological effects of alcohol and limiting the discussion to scotch whiskey. The EM spectrum is continuous and its divisions arbitrary, so there is no good reason to limit the discussion to RF when living cells are activated and synthesize stress proteins in both RF and ELF ranges (Blank and Goodman, 2004a). Furthermore, emissions from cell phones include both RF and ELF frequencies (Linde and Mild, 1997; Jokela, 2004; Sage et al, 2007). The bulk of the original research on EMFs and the stress response was done using ELF (see review by Goodman and Blank, 1998). ELF studies also led to information about the DNA consensus sequence sensitive to EMFs that differs from the 'heat shock' consensus sequence (Lin et al, 1999). This is a critical piece of molecular evidence showing the difference between thermal and non-thermal responses. Cotgreave described

the heat shock consensus sequence, but not the EMF consensus sequence or the experiments in which such sequences were transferred and retained sensitivity to an EMF (Lin et al, 2001). For any insight into EMF-DNA interaction, it was absolutely essential to describe the molecularly based biological sensitivity to EMFs, inherent in DNA structure, that differs from thermal sensitivity and that can be manipulated.

More importantly, by considering both ELF and RF responses, it becomes obvious that the practice of describing EMF 'dose' in terms of SAR is meaningless for the stress response (Blank and Goodman, 2004a). The research on ELF stimulated stress response has shown unequivocally that SAR at the threshold is many orders of magnitude lower than in the RF range. The separation of thermal and non-thermal mechanisms had already been shown by Mashevich et al (2002), where chromosomal damage observed under RF in lymphocytes was not seen when the cells were exposed to elevated temperatures. The importance of non-thermal mechanisms was also made clear in the experiments of Bohr and Bohr (2000) in a much simpler biochemical system, showing that both denaturation and renaturation of β-lactoglobulin are accelerated by microwave EMF, and by de Pomerai et al (2003), who showed that microwave radiation causes protein aggregation without bulk heating. These as well as the ELF enzyme kinetics studies listed in Table 2 should have indicated that EMFs can cause changes in molecular structure without requiring heating.

Cotgreave overlooked a similarity between electric and magnetic ELF stimulation of DNA and endogenous electric stimulation of protein synthesis. Blank (1995) had reviewed this effect in striated muscle, and recently Laubitz et al (2006) showed that myoelectrical activity in the gut can trigger heat shock response in E coli and Caco-2 cells. The mechanism in striated muscle is well known. Body builders stimulate muscle activity to increase muscle mass, and biologists have known that the electric fields associated with muscle action potentials stimulate the synthesis of muscle proteins. The particular proteins synthesized appear to be related to the frequency of the action potentials, and one can even change the protein composition of a muscle by changing the frequency of the action potentials (Pette and Vrbova, 1992). Under normal physiological conditions, the action potentials along the muscle membrane drive currents across the DNA in nuclei adjacent to the membrane. The estimated magnitude of electric field, ~10V/m, provides a large safety margin in muscle, since fields as low as 3mV/m stimulate biosynthesis in HL60 cells (Blank et al, 1992). The fact that a physiological mechanism links electric stimulation to protein synthesis suggests that EMF can cause stress protein synthesis by a similar mechanism.

As a matter of proper scholarly attribution "heat shock' was first described in Drosophila by Ritossa (1962), and the first description of stress response due to EMF was in back-to-back papers showing similar protein distributions stimulated by temperature and ELF (Blank et al, 1994), and that both stimuli resulted in proteins that reacted with the same specific antibody for the stress protein hsp70 (Goodman et al, 1994). The ability of power frequency fields to alter RNA transcription patterns had been reported even earlier by Goodman et al (1983).

The above discussion acknowledges that Cotgreave's review was a positive contribution that summarized much useful information, but one that failed to properly assess the state of knowledge in EMF stress protein research. He gave the impression that much of the information was tenuous and that the thermal mechanism was the only one to consider. This may be his point of view and that of co-contributor, Forschunggemeinschaft Funk. However, at the very least, he should have incorporated relevant research on stimulation of the stress response by non-thermal EMFs. The ELF data have convinced many to reject the paradigm of thermal effects only. A reader would have learned more about the stress response had the author devoted more space to the ELF papers than to papers on something called 'athermal heating'.

IX. Rethinking EMF safety in a biology context

Studies of the stress response in different cells under various conditions have enabled us to characterize the molecular mechanisms by which cells respond to EMF and their effects on health risk. That information can now correct assumptions about biological effects of EMF, and establish a scientific basis for new safety standards.

In setting standards, it is essential that basic findings in all relevant research areas are taken into account. Relevance is not subjective. It is determined by whether a study adds to our knowledge of how cells react to EMF, and this criterion determined inclusion of the references in Table 1. The criteria for the references in the IEEE list were not focused on the molecular biology of cellular responses that illuminate disease mechanisms, but were based on such assumptions as arbitrarily defined divisions of the spectrum, on thermal responses only, etc. It is therefore not surprising that many relevant studies were omitted in the IEEE literature review. Fewer than one quarter of the references listed in Table 1 appear in the IEEE list. The result of having omitted many EMF studies, including those on the stress response, is that many research results have not been utilized in setting EMF safety standards. A careful examination of basic assumptions will show that the omissions are crucial and that they indicate an urgent need to reconsider the entire basis for EMF safety standards. Here in bold are the assumptions, followed by the re-evaluations:

- **Safety standards are set by division of the EM spectrum.** It may come as a surprise to the engineers and physicists who set up the divisions of the EM spectrum, but biology does not recognize EM spectrum divisions. The same biological reaction can be stimulated in more than one subdivision of the EM spectrum. The arbitrarily defined divisions of the spectrum do not in any way confine the reactions of cells to EMF, and ELF studies do indeed contribute to an understanding of how cells respond to RF. This was discussed in the critique of Cotgreave's (2005) review. This area clearly demands immediate attention. People are getting ELF and RF simultaneously from the same device, and they are being protected from thermal effects only. This ignores the potentially harmful

effects from non-thermal ELF and RF discussed next.

• **EMF standards are based on the assumption that only ionizing radiation causes chemical change.** The stress response in both ELF and RF ranges has shown that non-ionizing radiation also causes chemical change. Several additional examples of EMF stimulated chemical change in the ELF range are listed in Table 2.

• **EMF standards are based on the assumption that non-ionizing EMF only causes damage by heating (i.e., damage by thermal effects only).** Research on the stress response in the ELF range has shown that a thermal response to a rise in temperature and the non-thermal response to EMF are associated with different DNA segments of the same gene. Both the thermal and the non-thermal mechanisms are natural responses to potential damage. Furthermore, the non-thermal stress response can occur in both the ELF and RF ranges. Other non-thermal effects of EMF have been demonstrated, e.g., acceleration of electron transfer reactions and DNA strand breaks.

• **Safety limits in the non-ionizing range are in terms of rate of heating (SAR).** The above described effects occur below the thermal safety limits in the non-ionizing range, so the safety limits provide no protection against non-thermal damage. Safety limits must include non-thermal effects.

X. Summary

It is generally agreed that EMF safety standards should be based on science, yet recent EMF research has shown that a basic assumption used to determine EMF safety is not valid. The safety standard assumes that EMF causes biological damage only by heating, but cell damage occurs in the absence of heating and well below the safety limits. This has been shown in the many studies, including the cellular stress response where cells synthesize stress proteins in reaction to potentially harmful stimuli in the environment, including EMF. The stress response to both the power (ELF) and radio (RF) frequency ranges shows the inadequacy of the thermal (SAR) standard.

The same mechanism is stimulated in both ranges, but in the ELF range, where no heating occurs, the energy input rate is over a billion times lower than in the RF range.

The stress response is a natural defense mechanism activated by molecular damage caused by environmental forces. The response involves activation of DNA, i.e., stimulating stress genes as well as genes that sense and repair damage to DNA and proteins. Scientific research has identified specific segments of DNA that respond to EMF and it has been possible to move these specific segments of DNA and transfer the sensitivity to EMF. At high EMF intensities, the interaction with DNA can lead to DNA strand breaks that could result in mutation, an initiating step in the development of cancer.

Scientific research has shown that ELF/RF interact with DNA to stimulate protein synthesis, and at higher intensities to cause DNA damage. The biological thresholds (field strength, duration) are well below current safety limits. To be in line with EMF research, a biological standard must replace the thermal (SAR) standard, which is fundamentally flawed. EMF research also indicates a need for protection against the cumulative biological effects stimulated by EMF across the EM spectrum.

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Table 1. Studies of EMF Stimulation of DNA and Protein Synthesis
(page 1)

Table 1 summarizes both ELF and RF studies (mainly frequencies 50Hz, 60Hz, 900MHz, 1.8GHz) relevant to stimulation of DNA and stress protein synthesis in many different cells.

Study/Journal	Frequency	Cells/effect on hsps
Balcer-Kubicek et al, 1996 Radiation Res	60Hz	HL60 **NO** synthesis of myc
Blank et al, 1994 Bioelectrochem Bioenerg	60Hz	*Sciara* salivary glands [temperature, EMF, cause same new proteins]
Capri et al, 2004 Int J Radiat Biol	1800MHz	monocytes **NO** effect on apoptosis, hsp70
Caraglia et al, 2005 J Cell Physiol	1.95GHz	epidermoid cancer cells Induces apoptosis, hsp70
Chauhan et al, 2006 Radiation Res	1.9GHz	human lymphoblastoma (TK6) **NO** hsp response
Chauhan et al, 2006 Int J Radiat Biol	1.9GHz	two human immune cell-lines HL60,MM6 **NO** hsp response
Cleary et al, 1997 Bioelectromagnetics	27MHz	HeLa, CHO (also at 2450MHz mammalian cells **NO** hsp after 2 hr exposure, 24 hr to measurement
Chow and Tung, 2000 FEBS Letters	50Hz	E. coli strain XL-1 BLUE + plasmid pUCB DNA repair improved
Czyz et al, 2004 Bioelectromagnetics	modulated 1.71GHz	p53-deficient embryonic stem cells hsp70 expression, but not in wild type

Table 1. Studies of EMF Stimulation of DNA and Protein Synthesis
(page 2)

Daniells et al, 1998 Mutat Res	750MHz	C elegans induced hsp16
Dawe et al, 2005 Bioelectromagnetics	750MHz	C elegans (same lab as above paper) hsp 16 may be due to temperature rise
Di Carlo et al, 2002 J Cell Biochem	60Hz	chick embryo repeated EMF causes lower hsp response
Diem et al, 2005. Mutation Res	1800MHz	fibroblasts, GFSH-R-17 granulosa cells non-thermal DNA breakage
Fritze et al, 1997 Neuroscience	900MHz	rat brain blood brain barrier leakage at high SAR
Goodman et al, 1983 Science	pulsed 60Hz	*Sciara* larvae induce cellular transcription
Goodman et al, 1994 Bioelectrochem Bioenerg	60Hz	*Sciara* larvae increased hsp70 transcripts
Harvey et al, 2000 Cell Biol Int	864.3MHz	human mast cell line, HMC-1 effects on protein kinase C , stress genes
Hirose et al, 2006a Bioelectromagnetics	2.1425GHz	Human IMR-90 fibroblasts **NO** effect on gene expression of p53
Hirose et al, 2006b Bioelectromagnetics	2.1425GHz	human glioblastoma A172, IMR-90 fibroblasts **NO** effect on apoptosis, phosphorylation of hsp27
Ivancsits et al, 2005 Mutation Res	intermittent 50Hz	**NO** effect lymphocyte, monocyte, muscle: DNA damage: fibroblast, melanocyte, rat granulose
Jin et al, 1997 Bioelectrochem Bioenerg	60Hz	HL60 cells from two sources *myc* expression in one population, not in other
Kwee et al, 2001 Electro- and Magnetobiology	960MHz	human epithelial amnion (AMA) cells hsp70 increased

Table 1. Studies of EMF Stimulation of DNA and Protein Synthesis
(page 3)

Lacy-Hulbert et al, 1995 Radiation Res	50Hz	HL60 **NO** synthesis of myc or β-actin
Lai & Singh, 1997a Bioelectromagnetics	60Hz	rat brain cells melatonin blocks DNA strand breaks
Lai & Singh, 2005 Electromag Biol Med	1800MHz	rat brain cells noise blocks DNA strand breaks
Lantow et al, 2006a Radiation Res	1800MHz	human Mono Mac 6 and K562 cells **NO** hsp response
Lantow et al, 2006b Radiat Environ Biophys	1800MHz	primary human monocytes, lymphocytes **NO** hsp response
Lantow et al, 2006c Radiation Res	1800MHz	human Mono Mac 6 and K562 cells **NO** effect on apoptosis or necrosis
Laszlo et al, 2005 Radiation Res	835MHz	cultured mammalian cells **NO** 'effect within sensitivity of assay'
Laubitz et al, 2006 Experimental Physiol	muscle generated ELF	E coli, Caco-2 cells induce hsp70, protect vs apoptosis
Lee JS et al, 2005 Int J Radiat Biol	849, 1763 MHz	hsp70.1-deficient mice **NO** hsp induction
Lee S et al, 2005 FEBS Lett	2.45GHz	cultured human cells gene regulation: apoptosis 88, cell cycle99
Leszczynski et al, 2002 Differentiation	900MHz	human endothelial cells activate hsp27/p38MAPK stress pathway
Liburdy et al, 1993 J Pineal Res	60Hz	ER^+ MCF7 breast cancer cells block melatonin's oncostatic action
Lim et al, 2005 Radiation Res	900MHz	human leukocytes. **NO** effect on hsp
Lin et al, 1994 J Cell Biochem	60Hz	human HL60 cells EMF region of the c-*myc* promoter

Table 1. Studies of EMF Stimulation of DNA and Protein Synthesis
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Lin et al, 1996 Bioelectrochem Bioenerg	60Hz	human HL60 cells changes in c-myc transcript levels
Lin et al, 1999 J Cell Biochem	60Hz	human HL60 cells EMF consensus sequence in HSP70 promoter
Lin et al, 2001 J Cell Biochem	60Hz	human HL60 cells EMF consensus sequence response elements
Lixia et al, 2006 Mutat Res	1.8GHz	human lens epithelial cells increased hsp70 protein
Maes et al, 2006 [Epub] Mutagenesis	900MHz	peripheral blood lymphocytes **NO** effect on DNA damage
Malagoli et al, 2004 Comp Biochem Physiol	50Hz	mussel immunocyte activate p38 MAP kinase, induce hsp70, hsp90
Mashevich et al, 2003 Bioelectromagnetics	830MHz	human peripheral blood lymphocytes chromosomal instability
McNamee et al, 2002 Radiat Res	1.9Ghz	human leukocytes **NO** effect on DNA damage, micronuclei
Miyakawa et al, 2001 Bioelectromagnetics	60Hz	C elegans induction of hsp16
Nylund & Leszczynski,2004 Proteomics	900MHZ	human endothelial cell line EA.hy926 effects on cytoskeletal proteins
Nylund & Leszczynski,2006 Proteomics	900MHZ	human endothelial cell line EA.hy926 response genome- and proteome-dependent
Oktem et al, 2005. Arch Med Res	900MHz	rats (oxidative kidney damage) oxidative damage protected by melatonin
Ozguner et al, 2005 Toxicol Ind Health	900MHz	rats (oxidative myocardial damage) protection by caffeic acid phenethyl ester

Table 1. Studies of EMF Stimulation of DNA and Protein Synthesis
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Penafiel et al, 1997 Bioelectromagnetics	840MHz (AM, FM)	mouse L929 cells (ornithine decarboxylase activity) frequency dependent AM effect, no FM effect
Phillips et al, 1998 Bioelectrochem Bioenerg	813, 836MHz	Molt-4 T-lymphoblastoid cells DNA damage (and ability to repair) varied with SAR
Saffer & Thurston, 1995 Radiation Res	60Hz	HL60, Daudi cells **NO** synthesis of myc
Sanchez et al, 2006 FEBS J	900MHz	human skin cells slight but significant increase in hsp70
Sarimov et al, 2004 IEEE Trans Plasma Sci	895, 915MHz	transformed human lymphocytes affect chromatin conformation
Shallom et al, 2002 J Cell Biochem	915MHz	chick embryos induces hsp70, protects against hypoxia
Shi et al, 2003. Environ health Perspect	60Hz	human keratinocytes **NO** phosphorylation, expression of hsp27
Simko et al, 2006 Toxicol Lett	900MHz	human Mono Mac 6 cells **NO** hsp reponse
Vanderwaal et al, 2006 \Int J Hyperthermia	900MHz	cultured HeLa, S3 and EA Hy296 cells **NO** hsp27 phosphorylation increases
Velizarov et al, 1999 Bioelectrochem Bioenerg	960MHz	human epithelial cells cell proliferation
Wang et al, 2006 Bioelectromagnetics	2450MHz	human glioma A172 cells **NO** hsp70, hsp27
Weisbrot et al, 2003 J Cell Biochem	900MHz	*Drosophila* hsp708, affects development, reproduction
Winker et al, 2005 Mutation Res	intermittent 50Hz	human diploid fibroblasts micronuclei, chromosomal damage

Table 2 Biological Thresholds in the ELF Range

Biological System	Threshold*	Reference
Enzyme reaction rates		
Na,K-ATPase	**.2-.3μT**	**Blank & Soo, 1996**
cytochrome oxidase	**.5-.6μT**	**Blank & Soo, 1998**
ornithine decarboxylase	**~2μT**	**Mullins et al, 1999**
Oxidation-reduction rate		
Belousov-Zhabotinsky	**<.5μT**	**Blank & Soo, 2001b**
Biosynthesis of stress proteins		
HL60, Sciara, yeast,	**<.8μT**	**Goodman et al, 1994**
breast (HTB124, MCF7)	**<.8μT**	**Lin et al, 1998**
chick embryo (anoxia)	**~2μT**	**DiCarlo et al, 2000**
Disease related **block melatonin inhibition**		
of breast carcinoma	**.2<1.2μT**	**Liburdy et al, 1993**
leukemia epidemiology	**.3-.4μT**	**Ahlbom et al, 2000**
		Greenland et al, 2000

*The estimated values are for departures from the baseline, although Mullins et al (1999) and DiCarlo et al (2000) generally give inflection points in the dose-response curves. The leukemia epidemiology values are not experimental and are listed for comparison.