Evidence for Disruption by the Modulating Signal

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I. Introduction

Modulation signals are one important component in the delivery of EMF signals to which cells, tissues, organs and individuals can respond biologically. At the most basic level, modulation can be considered a pattern of pulses or repeating signals which have specific meaning in defining that signal apart from all others. Modulated signals have a specific 'beat' defined by how the signal varies periodically over time. Pulsed signals occur in an on-off pattern, which can either be smooth and rhythmic, or sharply pulsed in quick bursts. Amplitude and frequency modulation involves two very different processes where the high-frequency signal, called the carrier wave, has a low-frequency signal that is superimposed on or 'rides' on the carrier frequency. In amplitude modulation, the lower-frequency signal is embedded on the carrier wave as changes in its amplitude as a function of time, whereas in frequency modulation, the lower-frequency signal is embedded as slight changes in the frequency of the carrier wave. Each type of low-frequency modulation conveys specific 'information', and some modulation patterns are more effective (more bioactive) than others depending on the biological reactivity of the exposed material. This enhanced interaction can be a good thing for therapeutic purposes in medicine, but can be deleterious to health where such signals could stimulate disease-related processes, such as increased cell proliferation in precancerous lesions. Modulation signals may interfere with normal, non-linear biological functions. More recent studies of modulated RF signals report changes in human cognition, reaction time, brainwave activity, sleep disruption and immune function. These studies have tested the RF and ELF-modulated RF signals from emerging wireless technologies (cell phones) that rely on pulse modulated RF to transmit signals. Thus modulation can be considered as information content embedded in the higher frequency carrier wave that may have health consequences beyond any effect from the carrier wave directly.

In mobile telephony, for example, modulation is one of the underlying ways to categorize the radiofrequency signal of one telecom carrier from another (TDMA from CDMA from GSM). Modulation is likely a key factor in determining whether and when biological reactivity might be occurring, for example in the new technologies which make use of modulated signals, some modulation (the packaging for delivery for an EMF ‘message’) may be bioactive, for example, frequencies are similar to those found in brain wave patterns. If a new technology happens to use brain wave frequencies, the chances are higher that it will have effects, in comparison, for
example, to choosing some lower or higher modulation frequency to carry the same EMF information to its target. This chapter will show that other EMF factors may also be involved in determining if a given low-frequency signal directly or as a modulation of a radiofrequency wave can be bioactive. Such is the evolving nature of information about modulation. It argues for great care in defining standards that are intended to be protective of public health and well-being. This section describes some features of exposure and physiological conditions that are required in general for non-thermal effects to be produced, and specifically to illustrate how modulation is a fundamental factor which should be taken into account in public safety standards.

II. The Old Standards (Based on Heating and Electric Current Flow in Tissues)

It is universally accepted that radiofrequency radiation (RFR) can cause tissue heating and that extremely low frequency (ELF) fields, e.g., 50 and 60 Hz, can cause electrical current flows that shock and even damage or destroy tissues. These factors alone are the underlying bases for present exposure standards. EMF exposures that cause biological effects at intensities that do not cause obvious thermal changes, that is, effects via non-thermal mechanisms, have been widely reported in the scientific literature over the last several decades. The current public safety limits do not take modulation into account and thus are no longer sufficiently protective of public health where chronic exposure to pulsed or pulse-modulated signal is involved, and where sub-populations of more susceptible individuals may be at risk from such exposures.

III. Laboratory Studies

Published laboratory studies have provided evidence for more than 40 years on bioeffects at much lower intensities than cited in the various widely publicized guidelines for limits to prevent harmful effects. Many of these reports show EMF-caused changes in processes associated with cell growth control, differentiation and proliferation which are biological processes of considerable interest to scientists who study the molecular and cellular basis of cancer. EMF effects have been reported in gene induction, transmembrane signaling cascades, gap junction communication, immune system action, rates of cell transformation, and breast cancer cell
growth. These reports have cell growth control as a common theme. Other more recent studies on brainwave activity, cognition and human reaction time lend credence to modulation (pulsed RF and ELF-modulated RF) as a concern for wireless technologies, most prominently from cell phone use.

Experimental results are described below to illustrate the influence of each EMF parameter, while also demonstrating that it is highly unlikely the effects are due to EMF-caused current flow or heating.

Several papers in the 1960s and early 1970s reported that ELF fields could alter circadian rhythms in laboratory animals and humans. In the latter 1960s, a paper reported that the EMF environment in planned space capsules could cause human response time changes, i.e., the interval between a signal and the human response (Hamer, 1968). Subsequent experiments by that research group were conducted with monkeys, and showed similar response time changes and also EEG pattern changes (Gavalas, 1970; Gavalas-Medici, 1976). The investigators shifted the research subject to cats and observed EEG pattern changes, ability to sense and behaviorally respond to the ELF component of RFR, and the ability of minor electric current to stimulate the release of an inhibitory neurotransmitter, GABA, and simultaneous release of a surrogate measure, calcium ions, from the cortex (Kaczmarek, 1973, 1974). At this time the investigators adopted newly hatch chickens as sources of brain tissue and observed changes in the release of calcium ions from in vitro specimens as a function of ELF frequency directly or as amplitude modulation ('am') of RFR (RFRam) (Bawin, 1975, 1976, 1978a, 1978b; Sheppard, 1979). Tests of both EMF frequency and intensity dependences demonstrated a single sensitive region (termed 'window') over the range of frequency and intensity examined. This series of papers showed that EMF-induced changes could occur in several species (human, monkey, cat and chicken), that calcium ions could be used as surrogate measures for a neurotransmitter, that ELF fields could produce effects similar to RFRam (note: without the 'am', there was no effect although the RFR intensity was the same), and that the dose and frequency response consisted of a single sensitivity window.

An independent research group published a series of papers replicating and extending this earlier
work (Blackman et al., 1979, 1980a, 1980b, 1981, 1982, 1985, 1988a, 1988b, 1989, 1990; Joines and Blackman et al., 1981a, 1981b, 1986). These papers reported multiple windows in intensity and in frequency within which calcium changes were observed in the chick brain experimental systems under EMF exposure. Three other independent groups reported intensity and frequency windows for calcium, neurotransmitter or enolase release under EMF exposure of human and animal nervous system-derived cells in vitro (Dutta et al., 1984, 1989, 1992, 1994), of rat pancreatic tissue slices (Albert et al., 1980), and of frog heart (Schwartz et al., 1990) but not atrial strips in vitro (Schwartz et al., 1993). This series of papers showed that multiple frequency and intensity windows were a common phenomenon that required the development of new theoretical concepts to provide a mechanism of action paradigm.

Additional aspects of the EMF experiments with the chick brain described by Blackman and colleagues, above, also revealed critical co-factors that influenced the action of EMF to cause changes in calcium, including the influence of the local static magnetic field, and the influence of physico-chemical parameters, pH, temperature and ionic strength of the bathing solution surrounding the brain tissue during exposure. This information provides clues for and constraints on any theoretical mechanism that is to be developed to explain the phenomenon. These factors demonstrate that the current risk assessment paradigms, which ignore them, are incomplete and thus may not provide the level of protection currently assumed.

The detailed set of frequency and intensity combinations under which effects were observed, were all obtained from chickens incubated for 21 days in an electrically heated chamber containing 60-Hz fields. Tests were performed to determine if the 60-Hz frequency of ELF fields (10 volts per meter in air) during incubation, i.e., during embryogenesis and organogenesis, would alter the subsequent calcium change responses of the brain tissue to EMF exposure. The published papers (Blackman et al., 1988b; Joines et al., 1986) showed that the brain tissue response was changed when the field during the incubation period was 50 Hz rather than 60 Hz. This result is consistent with an anecdotal report of adult humans, who were institutionalized because of chemical sensitivities, were also responsive to EMF fields that were present in the countries where they were born and raised (Blackman, 2006). This information indicates there may be animal and human exposure situations where EMF imprinting could be an
important factor in laboratory and epidemiological situations. EMF imprinting, which may only become manifest when a human is subjected to chemical or biological stresses, could reduce ability to fight disease and toxic insult from environmental pollution, resulting in a population in need of more medical services, with resulting lost days at work.

Fundamental exposure parameters that must be considered when establishing a mode (or mechanism) of action for non-thermal EMF-induced biological effects.

A. Intensity

There are numerous reports of biological effects that show intensity “windows”, that is, regions of intensity that cause changes surrounded by higher and lower intensities that show no effects from exposure. One very clear effect is 16-Hz, sine wave-induced changes in calcium efflux from brain tissue in a test tube because it shows two very distinct and clearly separated intensity windows of effects surrounded by regions of intensities that caused no effects (Blackman et al., 1982). There are other reports for similar multiple windows of intensity in the radiofrequency range (Blackman et al., 1989; Dutta et al., 1989, 1992; Schwartz et al., 1990). Note that calcium ions are a secondary signal transduction agent active in many cellular pathways. These results show that intensity windows exist, they display an unusual and unanticipated “non linear” (non-linear and non-monotonic) phenomenon that has been mostly ignored in all risk assessment and standard setting exercises, save the National Council for Radiation Protection and Measurements. (NCRP) 1986 publication. Protection from multiple intensity windows has never been incorporated into any risk assessment; to do so would call for a major change in thinking. These results mean that lower intensity is not necessarily less bioactive, or less harmful.

Multiple intensity windows appeared as an unexpected phenomenon in the late 1970s and 1980s. There has been one limited attempt to model the phenomenon (Thompson et al., 2000). However, there are publications from two independent research groups showing multiple intensity windows for 50 MHz, 147 MHz, and 450 MHz fields when amplitude-modulated at 16 Hz using the calcium ion release endpoint in chicken brains, in vitro. The incident intensities (measured in air) for the windows at the different carrier frequencies do not align at the same values. However, Joines et al., (1981a, 1981b) and Blackman et al. (1981) noted the windows of
intensity align across different carrier frequencies if one converts the incident intensity to the intensity expected within the sample at the brain surface, but correcting for the different dielectric constants in the samples at the different carrier frequencies. The uniqueness of this response provides a substantial clue to theoreticians but it is interesting that no publications have appeared attempting to address this relationship. It is obvious that this phenomenon is one that needs further study.

B. Frequency

Frequency-dependent phenomena are common occurrences in nature. For example, the human ear only hears a portion of the sound that is in the environment, typically from 20 to 20000 Hz, which is a frequency “window.” Another biological frequency window can be observed for plants grown indoors. Given normal indoor lighting the plants may grow to produce lush vegetation but not produce flowers unless illuminated with a lamp that emits a different spectrum of light. Similarly, there are examples of EMF-caused biological effects that occur as a result of EMF of concern to us in a frequency-dependent manner that cannot be explained by current flow or heating. The examples include reports of calcium ion efflux from brain tissue in vitro at low frequency (Blackman et al., 1988a, 1988b) and at high frequency (Blackman et al., 1981; Joines and Blackman, 1981). The bioactive frequency regions observed in these studies have never been explicitly considered for use in any EMF risk assessments, thus demonstrating the incomplete nature of current exposure limits.

There are also EMF frequency-dependent alterations in the action of nerve growth factor (NGF) to stimulate neurite outgrowth (growth of primitive axons or dendrites) from a peripheral-nerve-derived cell (PC-12) in culture (Blackman et al., 1995, 1999; Trillo et al., 1996). The combined effect of frequency and intensity is also a common occurrence in both the sound and the light examples given above. Too much or too little of either frequency or intensity show either no or undesirable effects. Similarly, in low intensity EMF work, “islands” of effective combinations of intensity and frequency are surrounded by a “sea” of null effects (Blackman et al., 1988a). Although the mechanisms responsible for these effects have not been establish, the effects represent a heretofore unknown phenomenon that may have ramifications for risk assessment and standard setting. Nerve growth and neurotransmitter release that can be altered by different
combinations of EMF frequencies and intensities, especially in developing organisms like children, could conceivably produce over time a subsequent altered ability to successfully or fully respond behaviorally to natural stressors in the adult environment; research is urgently need to test this possibility in animal systems.

Nevertheless, this phenomenon is ignored in the development of present exposure standards that rely primarily on biological responses to intensities within a relatively narrow band of frequencies, based on an energy deposition endpoint.

C. Static Magnetic Field
The magnetic field of the earth at any given location has a relatively constant intensity as a function of time. However, the intensity value, and the inclination of the field with respect to the gravity vector, varies considerable over the face of the earth. More locally, these features of the earth’s magnetic field can also vary by more than 20% inside man-made structures, particularly those with steel support structures. There are many reports of EMF-caused effects being dependent on the static magnetic field intensity (cf. Blackman et al., 1985) and of its orientation, with respect to an oscillating magnetic field (Blackman et al., 1990; Blackman et al., 1996). One aspect common to many of these reports is that the location in the active frequency band is determined by the intensity of the static magnetic field. There have been many attempts to explain this phenomenon but none has been universally accepted. However, it is clear that if a biological response depends on the static magnetic field intensity, and even its orientation with respect to an oscillating field, then the conditions necessary to reproduce the phenomenon are very specific and might easily escape detection (cf. Blackman and Most, 1993). The consequences of these results are that there may be exposure situations that are truly detrimental (or beneficial) to organisms but that are insufficiently common on a large scale that they would not be observed in epidemiological studies; they need to be studied under controlled laboratory conditions to determine impact on health and wellbeing.

D. Electric & Magnetic Components
Both the electric and the magnetic components have been shown to directly and independently cause biological changes. There is one report that clearly distinguishes the distinct biological
responses caused by the electric field and by the magnetic field. Marron et al. (1988) show that
electric field exposure can increase the negative surface charge density of an amoeba,
Physarum polycephalum, and that magnetic field exposure of the same organism causes
changes in the surface of the organism to reduce its hydrophobic character. Other scientists
have used concentric growth surfaces of different radii and vertical magnetic fields to determine
if the magnetic or the induced electric component is the agent causing biological change.
Liburdy (1992), examining calcium influx in lymphocytes, and Greene et al. (1991), monitoring
ornithine decarboxylase (ODC) activity in cell culture, showed that the induced electric
component was responsible for their results. In contrast, Blackman et al. (1993a, 1993b)
monitoring neurite outgrowth from two different clones of PC-12 cells and using the same
exposure technique used by Liburdy and by Greene showed the magnetic component was the
critical agent in their experiments. EMF-induced changes on the cell surface, where it interacts
with its environment, can dramatically alter the homeostatic mechanisms in tissues, whereas
changes in ODC activity are associated with the induction of cell proliferation, a desirable
outcome if one is concerned about wound healing, but undesirable if the concern is tumor cell
growth. This information demonstrates the multiple, different ways that EMF can affect
biological systems. Current analyses for risk assessment and standard setting have ignored
this information, thus making their conclusions of limited value.

E. Sine and Pulsed Waves
Important characteristics of pulsed waves that influenced the number and characteristics of the sine
wave representations include the following: 1) frequency, 2) pulse width, 3) intensity, 4) rise and fall
time, and 5) the frequency, if any, within the pulse ON time. Chiabrera et al. (1979) showed that
pulsed fields caused de-differentiation of amphibian red blood cells. Scarfi et al. (1997) showed
enhanced micronuclei formation in lymphocytes of patients with Turner’s syndrome (only one X
chromosome) but no change in micronuclei formation when the lymphocytes were exposed to sine
waves (Scarfi et al., 1996). Takahashi et al. (1986) monitored thymidine incorporation in Chinese
hamster cells and explored the influence of pulse frequency (two windows of enhancement seen),
pulse width (one window of enhancement seen) and intensity (two windows of enhancement seen
followed by a reduction in incorporation). Ubeda et al. (1983) showed the influence of difference rise
and fall times of pulsed waves on chick
embryo development.

It is important to note that the frequency spectrum of pulsed waves can be represented by a sum of sine waves which, to borrow a chemical analogy, would represent a mixture or a soup of chemicals, anyone of which could be biologically active. Risk assessment and exposure limits have been established for specific chemicals or chemical classes of compounds that have been shown to cause undesirable biological effects. Risk assessors and the general public are sophisticated enough to recognize that it is impossible to declare all chemicals safe or hazardous; consider the difference between food and poisons, both of which are chemicals. A similar situation occurs for EMF; it is critical to determine which combinations of EMF conditions have the potential to cause biological harm and which do not.

Obviously, pulse wave exposures represent an entire genre of exposure conditions, with additional difficulty for exact independent replication of exposures, and thus of results, but with increased opportunities for the production of biological effects. Current standards were not developed with explicit knowledge of these additional consequences for biological responses.

**F. Mechanisms**

Two recent papers have the possibility of advancing understanding in this research area. Chiabrera et al. (2000) created a theoretical model for EMF effects on an ion's interaction with protein that includes the influence of thermal energy and of metabolism. Before this publication, theoreticians assumed that biological effects in living systems could not occur if the electric signal is below the signal caused by thermal noise, in spite of experimental evidence to the contrary. In this paper, the authors show that this limitation is not absolute, and that different amounts of metabolic energy can influence the amount and parametric response of biological systems to EMF. The second paper, by Marino et al. (2000), presents a new analytical approach to examine endpoints in systems exposed to EMF. The authors, focusing on exposure-induced lymphoid phenotypes, report that EMF may not cause changes in mean values of endpoints, but rather in variances in those same endpoints. They provide further evidence using immunological endpoints from exposed and sham treated mice (Marino et al., 2001a, 2001b, 2001c). Additional research has emerged from this laboratory on EMF-induced animal and human brain activity.
changes that provides more evidence for the value of their research approach (Marino et al., 2002, 2003, 2004; Carrubba et al., 2006, 2007a, 2007b). It is apparent that much remains to be examined and explained in EMF biological effects research through more creative methods of analysis than have been used before. The models described above need to be incorporated into risk assessment determinations.

IV. Problems with Segregation of Effects by Artificial Frequency Bands that Ignore Modulation

One fundamental limitation of most reviews of EMF biological effects is that exposures are segregated by the physical (engineering/technical) concept of frequency bands favored by the engineering community. This is a default approach that follows the historical context established in the past by the incremental addition of newer technologies that generate increasingly higher frequencies. However, this approach fails to consider unique responses from biological systems that are widely reported at various combinations of frequencies, modulations and intensities.

When common biological responses are observed without regard for the particular, engineering-defined EMF frequency band in which the effects occur, this reorganization of the results can highlight the commonalities in biological responses caused by exposures to EMF across the different frequently bands. An attempt to introduce this concept to escape the limitations of the engineering-defined structure occurred with the development of the 1986 NCRP radiofrequency exposure guidelines because published papers from the early 1970s to the mid 1980s (to be discussed below) demonstrated the need to include amplitude modulation as a factor in setting of maximum exposure limits. The 1986 NCRP guideline was the one and only risk evaluation that included an exception for modulated fields.

The current situation argues strongly for a change in the way risk assessment is conducted,
especially for the last 15 to 20 years. Unfortunately, subsequent risk evaluations did not follow the NCRP example, but returned to the former engineering-defined analysis conditions, in part because scientists who reported non-thermal effects were not placed on the review committees, and in the terms of Slovic (1999) "Risk assessment is inherently subjective and represent a blend of science and judgment with important psychological, social, cultural, and political factors. … Whoever controls the definition of risk controls the rational solution to the problem at hand. … Defining risk is thus an exercise in power." It appears that by excluding scientists experienced with producing non-thermal biological effects, the usually sound judgment by the selected committees was severely limited in its breadth-of-experience, thereby causing the members to retreat to their own limited areas of expertise when forced to make judgments, as described by Slovic (1999), "Public views are also influenced by worldviews, ideologies, and values; so are scientists' views, particularly when they are working at limits of their expertise." The current practice of segregating scientific investigations (and resulting public health limits) by artificial divisions of frequency dramatically dilutes the impact of the basic science results, thereby reducing and distorting the weight of evidence in any evaluation process (see evaluations of bias by Havas 2000, referring to NRC 1997 compared to NIEHS 1998 and NIEHS 1999).

A. Suggested Research

Are there substitute approaches that would improve on the health-effects evaluation situation? As mentioned above, it may be useful in certain cases to develop a biologically based clustering of the data to focus on and enrich understanding of certain aspects of biological responses. Some examples to consider for biological clustering include: 1) EMF features, such as frequency and intensity inter-dependencies, 2) common cofactors, such as the earth’s magnetic field or co-incident application of chemical agents to perturb and perhaps sensitize the biological system to EMF, or 3) physiological state of the biological specimen, such as age or, sensitive sub-populations, including genetic predisposition (Fedrowitz et al., 2004, 2005).

To determine if this approach has merit, one could combine reports of biological effects found in the ELF (including sub-ELF) band with effects found in the RF band when the RF exposures are amplitude modulated (AM) using frequencies in the ELF band. The following data should be used: 1) human response time changes under ELF exposure (Hamer, 1968), 2) monkey response
time and EEG changes under ELF exposure (Gavalas et al., 1970; Gavales-Medici & Day-Magdaleno, 1976), 3) cat brain EEG, GABA and calcium ion changes induced by ELF and AM-RF (Kaczmarek and Adey, 1973, 1974; Bawin et al. 1973), 4) calcium ion changes in chick brain tissue under ELF and AM-RF (Bawin et al., 1975, 1976, 1978a, 1978b; Sheppard et al., 1979; Joines and Blackman et al., 1981a, 1981b, 1986; Blackman et al., 1979, 1980a, 1980b, 1981, 1982, 1985, 1988a, 1988b, 1989, 1990), and 5) calcium changes under AM-RF in brain cells in culture (Dutta et al., 1984, 1989, 1992) and in frog heart under AM-RF (Schwartz et al., 1990). The potential usefulness of applying biological clustering in the example given above even though AM is used, is that the results may have relevance to assist in the examination of some of the effects reportedly caused by cellular phone exposures which include more complex types of modulation of RF. This suggestion is reasonable because three groups have recently reported human responses to cell phone emissions that include changes in reaction times (Preece et al., 1998, 1999; Koivisto et al. 2000a, 2000b; Krause et al., 2000a, 2000b) or to brain wave potentials that may be associated with reaction time changes (Freude et al., 1998, 2000).

The papers described above, published in the 1960s through 1991, foreshadowed the more recent publications in 1999 and 2000 showing response time changes, or associated measures, in human subjects during exposure to cell phone-generated radiation (although none of the earlier studies was acknowledged in these recent reports on cognition and reaction time). Without guidance from this extensive earlier work, the development of the mechanistic bases for non-thermal effects from EMF exposures will be substantially delayed.
V. Conclusions

• There is substantial scientific evidence that some modulated fields (pulsed or repeated signals) are bioactive, which increases the likelihood that they could have health impacts with chronic exposure even at very low exposure levels. Modulation signals may interfere with normal, non-linear biological processes.

• Modulation is a fundamental factor that should be taken into account in new public safety standards; at present it is not even a contributing factor.

• To properly evaluate the biological and health impacts of exposure to modulated RFR (carrier waves), it is also essential to study the impact of the modulating signal (lower frequency fields or ELF-modulated RF).

• Current standards have ignored modulation as a factor in human health impacts, and thus are inadequate in the protection of the public in terms of chronic exposure to some forms of ELF-modulated RF signals.

• The current IEEE and ICNIRP standards are not sufficiently protective of public health with respect to chronic exposure to modulated fields (particularly new technologies that are pulse-modulated and heavily used in cellular telephony).

• The collective papers on modulation appear to be omitted from consideration in the recent WHO and IEEE science reviews. This body of research has been ignored by current standard setting bodies that rely only on traditional energy-based (thermal) concepts.

• More research is needed to determine which modulation factors, and combinations are bioactive and deleterious at low intensities, and are likely to result in disease-related processes and/or health risks; however this should not delay preventative actions supporting public health and wellness.

• If signals need to be modulated in the development of new wireless technologies, for example, it makes sense to use what existing scientific information is available to avoid the most obviously deleterious exposure parameters and select others that may be less likely to interfere with normal biological processes in life.

• The current membership on Risk Assessment committees needs to be made more inclusive, by adding scientists experienced with producing non-thermal biological effects.

• The current practice of segregating scientific investigations (and resulting public health limits) by artificial divisions of frequency needs to be changed because this approach dramatically dilutes the impact of the basic science results and eliminates consideration of modulation signals, thereby reducing and distorting the weight of evidence in any evaluation process.

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