

Proceedings of a Joint NIOSH/DOE Workshop

**EMF Exposure Assessment and Epidemiology:
Hypotheses, Metrics, and Measurements**

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FOREWORD

Both NIOSH and the Department of Energy have for many years been sponsoring research on biological mechanisms and exposure assessment for electric and magnetic fields (EMF) from electric power. Epidemiology studies have brought to our attention an association between EMF exposure and disease, but past studies using exposure surrogates and measurements of the time-weighted average magnetic field have left us searching for more definitive answers. In 1994, both federal agencies were thinking about a meeting of researchers to discuss how these findings could be brought together to guide future epidemiological and laboratory studies on cancer and other diseases. When we discovered our common interests, we teamed up to sponsor this workshop on Exposure Assessment and Epidemiology: Hypotheses, Metrics and Mechanisms.

While there have been many meetings on the biological effects of ELF magnetic fields and many reviews of the scientific literature, this workshop attempted a different approach. NIOSH and DOE invited to the workshop knowledgeable EMF researchers from a broad range of disciplines: epidemiology, laboratory research, theoretical studies, exposure measurements, and instrument design. We asked them to focus on how existing hypotheses for biological action of ELF electric and magnetic fields can guide the design of future studies. In particular, what EMF features are most likely to alter biological systems, and how these insights can be used to design better studies involving exposure assessments, epidemiology, and laboratory research? We wanted to merge the theoretical and practical aspects of both EMF laboratory and field studies.

The intent of the workshop organizers was not to debate the data that supports the hypotheses. We recognized that they are not confirmed. We wanted instead to ask "How can these hypotheses be tested in future studies?" Our intent was to produce a report that will have practical value for a wide range of research applications by stating hypotheses and defining exposure metrics to be tested in future studies.

Purpose

The workshop participants considered the importance of exposure metrics in EMF epidemiological studies. The primary aim was to develop exposure assessment methods and epidemiological studies to test hypotheses that these metrics may be associated with disease. The product of the workshop is this report describing approaches for characterizing EMF exposure in terms of these metrics and designs for epidemiological studies.

Goals

1. To determine the 2-3 most plausible biological hypotheses for how occupational and residential EMF may be causing the reported associations with diseases (leukemia and breast cancer particularly) which could be tested in future NIOSH epidemiological studies.
2. To develop quantitative exposure metrics from these hypotheses and strategies for assessing exposures to these metrics in occupational and residential studies.
3. To propose exposure assessment strategies which will collect data needed to assess future hypotheses with various study populations.

Proceedings

These proceedings are a compilation in chronological order of selected slides provided by the speakers, reports from the chairs of the four working groups, the recorders' notes from plenary sessions and working groups, and reflections by the workshop organizers. Selected slides were used in this document as provided by the speakers.

ACKNOWLEDGMENTS

A special thanks goes out to Energetics for conference support, especially Mary Lee Blackwell and Doreen Hill. Appreciation also is given to all of the speakers, session chairs, and the reporters.

Denise Overton of Oak Ridge National Laboratory (without whom these proceedings would still be but be a twinkle in the organizer's eyes) formatted and typed the draft.

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ABSTRACT

This joint NIOSH / DOE workshop considered the importance of exposure metrics in EMF epidemiological studies. The primary aim was to develop exposure assessment methods and epidemiologic designs to test hypotheses that these metrics may be associated with disease. The specific goals of the discussions were: 1) To determine the 2-3 most plausible biological hypotheses for how occupational and residential EMF may be causing the reported associations with diseases (leukemia and breast cancer particularly) which could be tested in future NIOSH epidemiologic studies; 2) To develop qualitative exposure metrics from these hypotheses and strategies for assessing exposures to these metrics in occupational and residential studies; 3) To propose exposure assessment strategies which will collect data needed to assess future hypotheses with various study populations. This report on the workshop describes approaches for characterizing EMF exposure in terms of these metrics and designs for epidemiological studies. These proceedings consists of selected slides provided by the speakers, reports from the chairs of the four working groups, the recorders' notes from plenary sessions and working groups, and reflections by the workshop organizers.

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PLENARY SESSIONS

Plenary Speakers:

William Kaune
Carl Blackman
Theodore Litovitz
Reba Goodman
Joseph Bowman
Duncan Thomas
T. Dan Bracken
Michael Yost
William Feero
Robert Spear
Jan Deadman
Richard Stevens

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Catholic University
Columbia University
NIOSH
University of Southern California
T. Dan Bracken, Inc.
University of Washington
Electric Research and Management, Inc.
University of California
McGill University
Battelle Pacific Northwest Laboratory

Summary of Plenary Sessions

by reporter Bob Patterson, Temple University

Epidemiology and Magnetic-Field Exposure Metrics

William T. Kaune, EM Factors

The Workshop began with two keynote addresses from the viewpoints of epidemiologic and laboratory research. First, Dr. William Kaune presented an overview of exposure assessment methods that have been used in past childhood cancer studies. He noted that all significant associations have been with some form of wire codes rather than measured fields. He then listed four possible interpretations that have been ascribed to this result: (1) wire codes are a better predictor of historical exposure than are present measurements, (2) wire codes are associated with an unmeasured (but biologically important) property of the magnetic field, (3) wire codes are associated with some other (biologically important) factor that is not related to magnetic fields, and (4) the results reflect study bias.

Dr. Kaune's viewgraphs are as follows:

<p style="text-align: center;">Wertheimer-Leeper Studies (1979, 1982)</p> <ul style="list-style-type: none">• Case-control study in Colorado• Wire codes used to assess exposure• Elevated relative risk for various childhood and adult cancers
<p style="text-align: center;">New York Power-Lines Projects</p> <ul style="list-style-type: none">• Wire codes indirect measure of exposure – presumably high level of exposure misclassification• Magnetic-field measurements more direct• Expect higher odds ratios using measured magnetic fields

Savitz Study

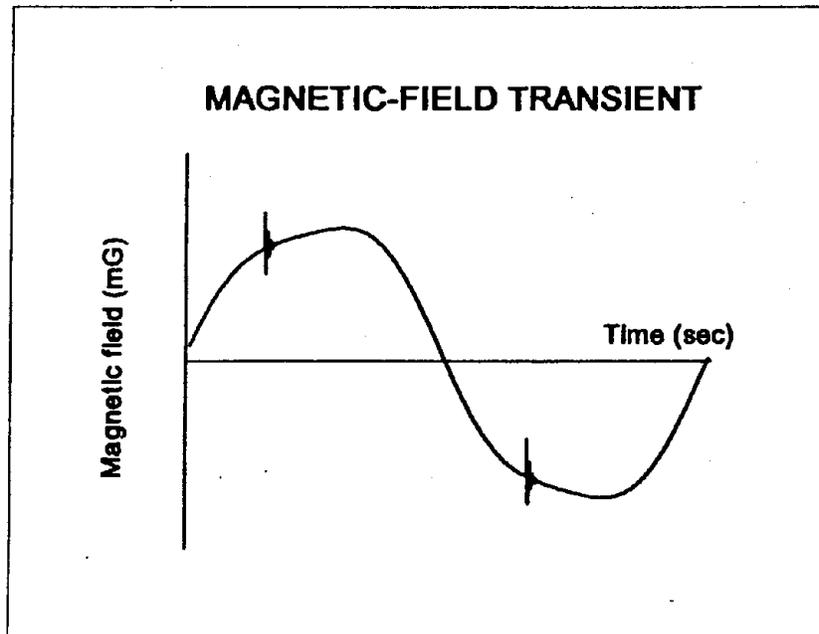
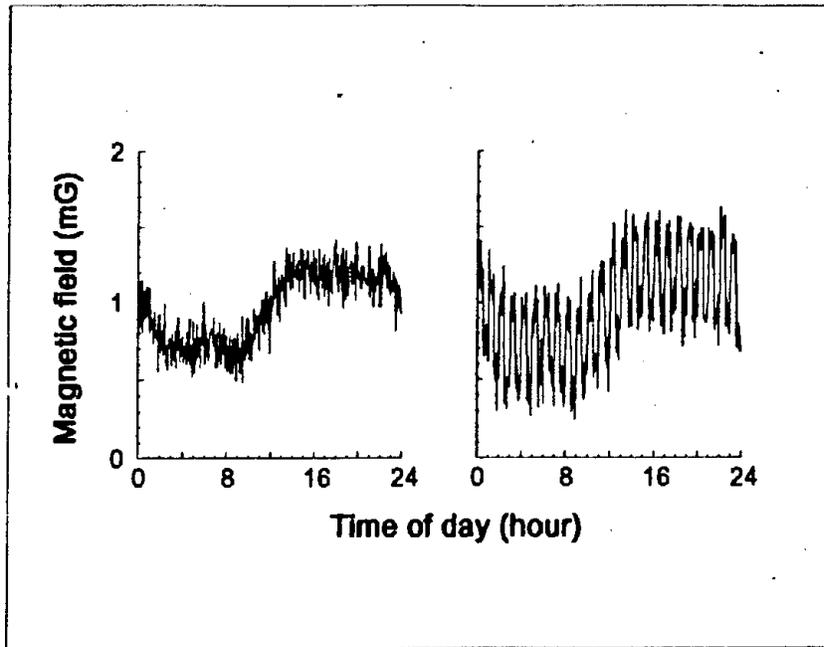
- Significant association between wire codes and childhood cancer
- Association between cancer and measured fields smaller (not significant)
 - measured fields only in subset of homes

London-Peters Study

- Los Angeles study of childhood leukemia and magnetic fields
- Significant association between wire codes and disease
- Weaker association between measured fields and disease

Why Are Wire Codes More Associated With Disease Than Measured Fields?

- Wire codes better predictor of historical exposure?
- Wire codes associated with unmeasured magnetic-field property?
- Wire codes associated with some factor unrelated to magnetic-fields?
- Result of study bias?



Laboratory Evidence: Is it useful to Epidemiologists?

Carl Blackman, US-EPA

The second keynote was given by Dr. Blackman, who spoke about the laboratory work relevant to the four hypothesized mechanisms.

Dr. Blackman's viewgraphs are as follows:

The Problem

(Savitz, 1993): If a problem exists, then as methodologies improve in epi studies, expect clarification of risk ratio:

← Risk Ratio →

1.0 10 100

BUT, we are not seeing this in EMF epi studies

Workshop Approach

Consider

- Resonances
- Induced currents / transients
- Magnetic moments
- Coherence & intermittency

as candidate biological results / theories from which to devise exposure metrics for epi studies

Laboratory Research

Value:

- control of exposure variables -> cause & effect relationships
- repeatable effects under defined exposure metric

Limits:

- extrapolation to humans
- actual exposure conditions - complex

Resonances

are based on a relation between specific system characteristics and distinct exposure parameters

- “Window” type effects possible
- Relative orientation of ac & dc may be critical
- Modulated fields vs. simple sine wave (ac)
Amplitude - high frequency carrier
Pulsed - complex characteristics

Transients

- Frequency spectrum
Multiple frequency exposure
- Induced currents (local)
- Numerous sources

**Magnetic Moments
DC / quasi-DC**

DC alterations can influence

- particles
- free radical based reactions

DC shifts around ambient can alter

- enzyme reaction rates
- newt embryo abnormalities

**Coherence & Intermittency
(biological status)**

- Integration of changes - subcellular
Molecular change
(coherence time)
Biochemical kinetics / dynamics
(feedback, phase locking, etc.)
- Physiological sensitivity
Natural variations
(enzyme & cell cycles to chronobiology)

Possible Physiological Sensitivities

- Prior exposure to EMF
- Toxic stress / health
- Genetic predisposition

Review - Exposure Details

TWA intensity is important but consider:

- Resonance - AC and DC fields
(frequency and intensity)
- Transients - induced current, frequency
(TWA, peak, time above given level, ?)
- Magnetic Moments - DC / quasi-DC
(ambient setting to measure)

Review - Biological Features

Time Dependent Sensitivity

- detection / amplification characteristics
- physiological status / sensitivity

Summary

There are many possible additions to the TWA intensity metric

Major challenges to this workshop:

Define
new metrics for epi studies

Recommend
lab results that need refinement

Disclaimer: Opinions are my own, not those of EPA

Hypothesis

Theodore Litovitz, Ph.D., Catholic University

Next, a series of presentations was made to provide a “case study” of a test of the “Litovitz Kinetic Hypothesis.” Dr. Litovitz explained the hypothesis, which is that biological response is not necessarily proportional to the product of field strength and time; the field can carry not only energy but important temporal information. He stated that cells require about 0.1 second to sense an external field, about 10 seconds to determine the constancy of the field and for transduction to occur, and about 1000 seconds for a biochemical response to take place. The mechanism is that the energy in the field changes the rate constants of a biochemical reaction, and this in turn implies that there are both an optimum field strength and time of exposure that will induce the maximum bioeffects. Litovitz then said that the model suggest the following: (1) epidemiological data will not correlate well with measures of the average field; (2) the number and duration of exposures per time period, such as a day, are important; and (3) the constancy of the field, for example as measured by the time autocorrelation function of the amplitude, is a major factor in the production of bioeffects – longer is worse than shorter.

Biological Evidence For and Against

Reba Goodman, Columbia University

The fourth keynote was given by Dr. Goodman, who spoke about the biological evidence for and against the hypothesis. Here her introductory remarks:

Savitz and Loomis have written that “In spite of our best efforts and some real advancements, classification of EMF exposure remains the biggest challenge in epidemiological studies [today].” While there is persistent evidence linking electromagnetic fields to cancer, epidemiological studies thus far have not been conclusive. We suggest that this is due to inherent inadequacies in the design of those studies. To develop a realistic basis for the design of epidemiological studies of the relationship of EM field exposure, it is essential to account for the fact that human exposure to EMFs in everyday life is *intermittent*. This is not reflected in the time-weighted average exposure currently in the measure of dose used by epidemiologists. This introduces a significant confounder into the study of EMFs as a link to cancer. There is a body of data, in addition to our experimental results, that indicate that intermittent EM field exposures increase the magnitude of the bioresponse. Taken together, these data suggest the need for a new dose-response metric. The effect of intermittent EMF exposure should form a basis for the definition of “effective dose” which could then be used in epidemiological studies; the design of dose-response exposure metrics would replace the current assumption that dose is simply the product of field strength and time. The kinetic model of Litovitz/Montrose corroborates our preliminary data that suggest that brief intermittent exposures to EM fields induce a greater gene over expression than does continuous exposure.

This introduction was followed by supporting experimental data, which has since been published in the paper “Electromagnetic field stimulation of biosynthesis: changes in *c-myc* transcript levels during continuous and intermittent exposures” by Lin, Blank, Jin and Goodman (next pages).

Electromagnetic field stimulation of biosynthesis: changes in *c-myc* transcript levels during continuous and intermittent exposures

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Abstract

We studied the effects of continuous and single limited exposures of HL60 cells to 60 Hz electromagnetic (EM) fields. Results showed an increase in transcript levels for *c-myc* peaks after 20 min of exposure, but the rate of return of this transcript to control levels is dependent upon whether the field is left on or turned off after 20 min. Turning off the field prolongs, by a factor of 3, the interval during which *c-myc* transcript levels remain elevated in response to EM field exposure. The effect of a second EM field stimulation on HL60 cells at some interval after an initial 20 min exposure was also examined. We found that the cells became refractory to a second stimulation at the same field amplitude, but that stimulation with a field of different amplitude (either higher or lower than the initial field) produced a restimulatory response.

Keywords: Intermittent exposure; Continuous exposure; Messenger RNA; Transcription

1. Introduction

Human populations live and work in an environment permeated with electric and magnetic fields. A number of epidemiological studies have related exposure to adverse health effects and reported an elevated risk of a variety of cancers, including leukemia and brain tumors, among residentially exposed children and occupationally exposed adults [1–3].

Analyses of data from laboratory studies show that electromagnetic (EM) fields elicit biological responses at extremely low field strengths, but the dose–response characteristics are unusual. There are specific frequencies, field strengths and durations of exposure ranges, “windows”, to which the biological system shows heightened sensitivity. Further, the use of intermittent exposure protocols in cell and animal studies showed that epidemiological data may well not correlate with the average field measured in the home or workplace, because such studies do not take account of time duration [4,5]. Based on a review of published data, a mathematical multistep kinetic model was developed that predicts that the effects of short,

repetitively applied exposures rather than long-term exposures are more relevant to everyday life [6]. If there are adverse health effects of EM fields, then the number of times a day that one enters and the duration of each stay in a region of electromagnetic exposure become important.

Previously we reported that increased *c-myc* transcript levels occur with 4–8 min in cells exposed to a 60 Hz 8 μ T electromagnetic field and peak at 20 min [7]. We now report the results from experiments that repeat and extend these observations.

Experiments in the present study were designed to answer the following questions.

- (1) For cells exposed continuously:
 - (a) How soon after EM field stimulation do steady state *myc* transcript levels change?
 - (b) How soon after EM field stimulation do steady state transcript levels return to control levels?
- (2) For a single limited 20 min exposure:
 - (a) How soon after EM field stimulation do steady state transcript levels return to control levels?
 - (b) Can *myc* transcript levels be restimulated using the same field strength or using a different field strength?
 - (c) Can transcript levels be restimulated once transcript levels have returned to control levels?

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- (d) Is there a refractory period during which it is not possible to elicit a second response with the same stimulus?
- (e) Can "acquired tolerance" be developed using EM field as a stress, similar to that described for thermotolerance?

2. Materials and methods

2.1. Cells

Experiments utilized HL60 cells (originally supplied by Dr. I.B. Weinstein, Department of Environmental Medicine, Columbia University Health Sciences) maintained in RPMI1640 (GIBCO) with 10% fetal calf serum. Cells were exposed to electromagnetic fields at cell densities of about 1×10^6 in T25 flasks (15 ml per flask) at 37.5°C. Cells were prepared for each experiment the previous day by aliquoting cells from a single T75 flask into individual T25 flasks. This insured that control and experimental samples derived from the same original batch of cells. The medium was not changed again before exposure of cells to the EM field. Samples were coded.

2.2. Exposure conditions

Electromagnetic fields were generated by a pair of Helmholtz coils (164 turns of 19 gauge copper wire around a 13×14 cm² Plexiglass form with an 8 cm space (Electro-Biology, Inc.)). The magnetic field (*B* field) used was 0.8, 8 or 80 μ T. The induced electric field (*E* field) at 8 μ T was calculated as approximately 11×10^{-6} V m⁻¹, with corresponding changes at 0.8 and 80 μ T. The flasks containing the cells were placed horizontally on a Plexiglass stand in an area of the coil with a uniform magnetic field. The Helmholtz coils were shielded in a Mumetal container (Ammuneal Manufacturing Corp., Philadelphia, PA) within the incubator. The sinusoidal field was generated by a Wavetek function generator (Wavetek model 21, 11 MHz) connected to a power regulator (Electro-Biology, Inc.). The function generator and power regulator were maintained outside the incubator. Signal parameters were monitored using a calibrated inductive search coil with an oscilloscope (Hitachi V-1065, 100 MHz). Control cells were sham exposed at the same time in the same incubator shielded in an identical Mumetal container. Exposure for HL60 cell was at 37.5°C.

2.3. Isolation of RNA

Total cellular RNA was isolated from HL60 cells by the following procedure. At the conclusion of each exposure the cells were transferred to 50 ml centrifuge tubes and spun down in a clinical centrifuge for 5 min at 3000 rev/min. The medium was decanted and 0.65 ml of lysing

buffer (100 mM Tris, pH 8.5, 100 mM NaCl, 20 mM EDTA, 1% SDS) added to each tube. The cells were lysed using a 5 ml syringe (21G needle) by pushing the lysate through the needle at least 10 times; 0.65 ml of phenol-Sevag's (1:1) mixture was added to the solution and the entire mixture passed through the needle at least five times. The solution was placed in a 1.5 ml Eppendorf (E) tube and spun down in an Eppendorf centrifuge for 8 min at full speed. The top (aqueous) layer was placed in a fresh E tube with phenol-Sevag's (1:1) solution, mixed and spun for 3 min (full speed). The aqueous layer was recovered by centrifugation. This step was repeated twice, with a final extraction in Sevag's alone; 2.5 vol. of LiCl₂ (0.8 M) in 95% ethanol (cold) was added to the final aqueous layer in the E tube. The E tube was placed at -70°C for 2 h, then centrifuged for 30 min at 4°C in an E centrifuge. The ethanol was decanted and the pellet dried by inversion of the tube at room temperature for 5-10 min. The pellet was resuspended in 600 μ l Tris, pH 8 (50 mM) (adding 200 μ l at a time); 6 μ l of 1 M MgCl₂ was added; 8 μ l of DNase solution (BMB; RNase free) was added and the solution then incubated at 4°C for 45 min. The mixture was vortexed quickly and 12 μ l of EDTA (0.5 M) added to stop the reaction; 60 μ l of NaOAc (3 M) solution was added and the mixture vortexed; 600 μ l of phenol-Sevag's was added and mixed well, then spun for 3 min in an E centrifuge. The top layer was placed in a fresh tube with Sevag's and mixed well, then spun in an E centrifuge at full speed (3 min). The top layer was precipitated with 2.5 vol. of EtOH. Each sample was checked by agarose gel electrophoresis before use to make sure that the 18 and 28S fractions were intact and that no DNA remained in the sample.

2.4. Measurement of transcript levels

RNA was analyzed with both dot blot and Northern blot hybridizations using Hybond membrane. Probes were *c-myc* (3rd exon; P2110, Oncor) and β -2-microglobulin (gift of Dr. I.B. Weinstein, Department of Environmental Medicine, Columbia University Health Sciences). DNA probes were labeled in vitro using Random Primer (BMB) with α -³²P-dCTP (DuPont/New England Nuclear, Boston, MA; 6000 Ci mM⁻¹) to a specific activity of a minimum of $(5-8) \times 10^8$ dpm μ g⁻¹. Quantitation was by both Northern and dot blot hybridization. Hybridization conditions were as follows.

2.4.1. Northern blots

10 μ g of RNA from the total sample was denatured by formamide and formaldehyde at 65°C (15 min). The sample was electrophoresed in formaldehyde containing 1% agarose. RNA was blotted on to Hybond N membrane (Amersham), baked to 15 min at 80°C and UV cross-linked for 5 min. This was prehybridized for 2 h. Approximately 40 ng of the ³²P-labeled probe was added (this was

dependent on the specific activity of the probe); hybridization was overnight at 45°C with Hybrison TM1 (Oncor). The membrane was washed twice at 65°C with 2X SSC (1% SDS) for 30 min, followed by washes with 0.1X SSC and 0.1% SDS for 30 min at 65°C. The membrane was exposed overnight at –70°C to Kodak X-OMAT AR film.

2.4.2. Dot blots

The sensitivity of the dot blot process was measured by dotting equal amounts of control RNA on to a filter and quantitating the radioactive counts. Standard error is in the range of 5%. In using the RNA dot blot method for quantitative analysis, avoiding the presence of protein or DNA contamination is critical to prevent non-specific binding from occurring. Total RNA was spotted on to Hybond in dilutions of 4, 2, 1, 0.5 and 0.25 µg. Stringent conditions for hybridization were maintained, as described. *At least three analyses were done on an RNA sample from each exposure.* Transcript levels for *c-myc* were measured in new samples, as well as in stored samples (–70°C) from previous experiments. Radioactivity was measured by counting directly from the membrane with a betascope or by liquid scintillation counting of cut pieces of filter identified from the autoradiograph.

2.5. Internal standard

Measurements of *c-myc* transcript levels were expressed as the ratio of *c-myc* to β-2-microglobulin (internal standard) in exposed vs. unexposed cells. As in our previous studies [7], transcript levels for β-2-microglobulin in HL60 cells were unchanged after exposure to 60 Hz, 8 µT EM fields.

2.6. Statistical analysis

Our data are presented as experimental (E) values/control (C) values. The ratio E/C compares an experimental measurement with a control measurement and serves as a basis for determining whether the experimental procedure has caused a difference. (This accords with standard data-reporting practices in the experimental sciences.) If one uses instead $E - C/C$ or $C - E/C$, the outcome remains unchanged, it is simply another method of calculating the difference of the ratio E/C from 1.00. The ratio E/C, where E is then EM field exposed and C is the control, does not lead to any conclusion until experiments have been repeated sufficiently to yield a measure of dispersion of the data about the mean (usually standard error, but also average or standard deviation). Only then can the significance of the difference of the mean from 1.00 be gauged. Still there is no absolute conclusion—only a probability within confidence limits calculated from probability theory. Our results are examined with a two-tailed *t* test to test the hypothesis that the ratio of the unexposed samples over the control samples is equal to unity.

Details of differences in levels of EM response between those reported here and previous papers are discussed elsewhere [8].

2.7. Data management

Each exposure was repeated a minimum of three times, i.e. each data point on the figures represents at least three separate exposures—experiments. In addition, each sample (from each exposure—experiment) was tested for *myc* transcript levels three times. Thus each data point represents nine separate determinations. In most experiments Northern and dot blot hybridization were used for transcript measurement. When dot blots were employed, the amount of radioactivity in *each* dot was used in analyses.

3. Results

The time course for transcript levels during *continuous* exposure is shown in Fig. 1(a). The earliest time points

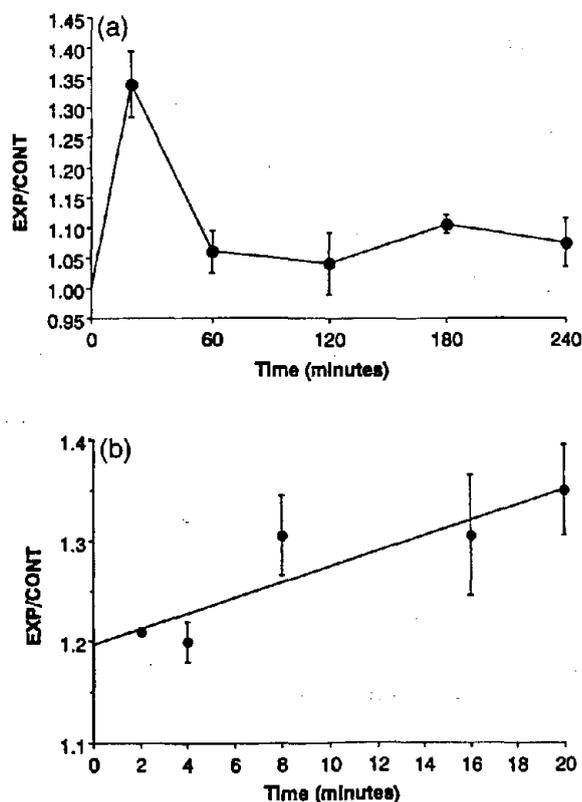


Fig. 1. Transcript levels for *c-myc* in HL60 cells exposed *continuously* (at 37.5°C) to a 60 Hz electromagnetic field, 8 µT peak for time periods up to 240 min. (a) Transcript levels return to control levels by 60 min. Data are plotted as experimental/control (E/C). Error bars represent standard errors. (b) The earliest time points for (a) are shown in detail. The points are linear with time and extrapolate by least squares to $E/C = 1.19$ at time zero, indicating that transcript levels for *c-myc* respond instantly in cells exposed to the EM signal. Since standard errors of individual points are in the range 0.1–0.15, the extrapolated value is close to 1.0.

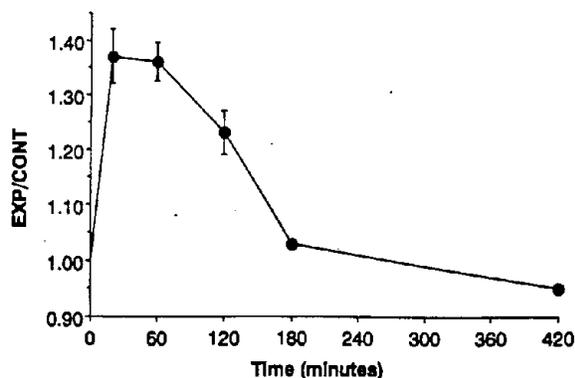


Fig. 2. Transcript levels for *c-myc* in cells exposed for a single limited 20 min period (8 μ T at 60 Hz) and then removed from the field. The rate of return of *c-myc* transcript levels to control levels is extended to 180 min. Data are plotted as experimentals/controls (E/C). Error bars represent standard errors.

show a quick increase to a peak at 20 min, followed by a decline to control levels by approximately 60 min. Measurements of transcript levels were carried out to 240 min. The earliest time points, shown in detail in Fig. 1(b), are linear with time and extrapolate by least squares to E/C = 1.19 at time zero. The data in Fig. 1(b) come from experiments for the first 20 min shown in Fig. 1(a). Since standard errors of individual points are in the range 0.1–0.15, the extrapolated value of 1.19 is very close to 1.0 and implies that exposure of cells to an EM field has an almost instantaneous effect on the steady state transcript level for *c-myc*.

Fig. 2 shows the time course for *c-myc* transcript levels in experiments using a *single* limited 20 min exposure and then removing cells from the field. The return to control levels in cells removed from the field was extended to 180 min as compared with approximately 60 min for cells exposed continuously to the magnetic field (Fig. 1). Turning off the field prolonged by a factor of 3 the interval

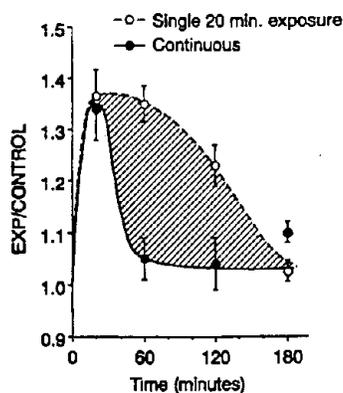


Fig. 3. Composite of the time curve for continuous exposure (Fig. 1(a)) and the time curve for a single limited 20 min exposure (Fig. 2). The hatched area between the two curves represents the difference in time for the return of *c-myc* transcript levels to control levels. Data are plotted as experimentals/controls (E/C). Error bars represent standard errors.

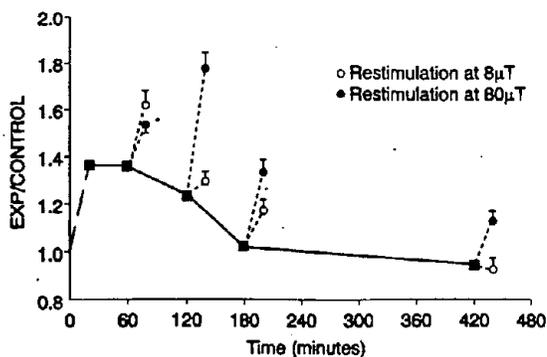


Fig. 4. Initial 20 min stimulation of HL60 cells by an 8 μ T, 60 Hz EM field followed by a 20 min restimulation using 8 or 80 μ T, 60 Hz electromagnetic field. The base line represents transcript levels for *c-myc* in HL60 cells after an initial 20 min exposure (8 μ T, 60 Hz). The broken lines show the change in transcript levels following restimulation (20 min) at 60, 120, 180 and 420 min using an 8 or 80 μ T, 60 Hz EM field. Data are plotted as experimentals/controls (E/C). Error bars represent standard errors.

during which *c-myc* transcript levels remained elevated in response to EM field exposure.

There is a range of response when cells are exposed initially for 20 min. This range can be seen in Figs. 1 and 2, where the peak responses vary from 30% to 45% for *c-myc*. The kinetics of the response, however, are qualitatively the same. Data for different populations of cells in terms of the maximal response were not normalized.

Fig. 3 presents a composite of the time curves for continuous exposure and a single 20 min exposure. The hatched area between the two time curves is the difference in time for the return of *c-myc* transcript levels to control levels (experimentals/controls, E/C).

The kinetics of the return to the base state and the refraction of the response system to restimulation were

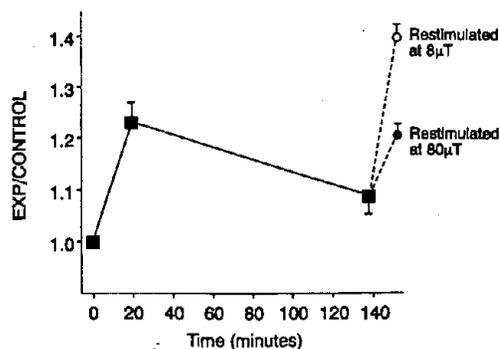


Fig. 5. Initial 20 min stimulation of HL60 cells by an 80 μ T, 60 Hz EM field followed by a 20 min restimulation using 8 or 80 μ T, 60 Hz electromagnetic field. The base line represents transcript levels for *c-myc* in HL60 cells after an initial 20 min exposure (80 μ T, 60 Hz). The broken lines show the change in transcript levels following restimulation (20 min) at 120 min using an 8 or 80 μ T, 60 Hz EM field. The magnitude of the field used for restimulation does not appear to be critical. Data are plotted as experimentals/controls (E/C). Error bars represent standard errors.

examined in cells exposed for a single 20 min period and then removed from the EM field (Fig. 4). In these experiments, four different sets of cells were *restimulated* for 20 min at 60, 180 and 420 min following the initial 20 min short exposure using either 8 or 80 μT as the field strength for restimulation (Fig. 4). Restimulation of *myc* transcript levels occurred using either field strength, although restimulation of transcript levels with 80 μT was greater than that with 8 μT after 1 h. However, at 7 h, restimulation with 8 μT did not occur, only with 80 μT . The cells were refractory to the initial field strength. While the magnitude of the field used for restimulation is not critical, it must be different (Fig. 5).

4. Discussion

With continuous exposure the return of *c-myc* transcript levels to control levels occurs in 60 min, in contrast with cells exposed to a single 20 min pulse where the return to control levels was extended three-fold. With two 20 min exposures, using various time intervals from 1 h (before transcript levels return to control levels) up to 7 h between exposures, the kinetics of the return to the control state and the refraction of the response system to restimulation *by the same field strength* became evident at 7 h. Under the conditions used in these experiments, restimulation with a *different field strength* was still possible, however.

Previously we showed that one effect of EM field exposure is the stimulation of the stress response; there are increased steady state transcript levels for the stress gene *hsp70* and synthesis of stress proteins in cells exposed to EM fields [9–12]. We believe that the production of these stress proteins has an inhibitory effect on transcription in cells continuously “stressed” by an EM field and also in intermittent exposures, but at a greatly reduced level.

The stress response is known to be initiated by many stimuli, including oxidative injury, heavy metals, free radicals, ischaemia and antineoplastic chemicals [13]. The genes encoding stress proteins are highly conserved and exquisitely regulated and range in molecular weights from approximately 20 to 104 kD. (Most studies concentrated on the *hsp70* family of genes [13,14].)

Activation of the stress response results in elevated and preferential synthesis of stress-induced proteins as well as inhibition of the synthesis of other proteins. The activation of stress gene expression and the resulting synthesis of stress proteins ensure survival of the organism under sub-optimal physiological conditions [13,14].

Protein products synthesized in response to EM fields may alter return times, which may be different for continuously exposed and intermittently (dual) exposed samples. In continuously exposed cells the stress proteins are synthesized in response to a single stress over a long period of time. In intermittent stimulation the cell is subjected to more than one stress; while several populations of different stress proteins may be synthesized, the concentrations may

be insufficient to induce inhibition within the short time intervals between stimulation and restimulation.

These results, together with earlier data showing increased transcript levels for some stress genes and increased translation of stress proteins in EM fields [9–12] suggest that a second increase in transcripts is inhibited by an increased concentration of stress proteins when cells are re-exposed to the same field strength. This mechanism is similar to that described for the development of *thermotolerance*, in which intermittently applied heat shock at various temperatures allows the organism to develop tolerance to a temperature that would be lethal if applied as the initial temperature [1–4]. Restimulation with a different field strength, however, may stimulate a different set of stress proteins, but not to a concentration sufficient to inhibit an increase in transcript levels.

These results corroborate the prediction embodied in the kinetic multistep model, namely that certain optimum relatively short-duration exposures can cause significantly larger biosynthetic effects than much longer exposures at a given field strength [6]. It is increasingly essential to determine the cellular mechanism(s) that detect and quantify physiological stress. Identifying the receptor for physiological stress would provide an important clue in determining the initiation of EM field interaction.

4.1. Implications for environmental exposures

The results have important implications for the design of both animal and cellular EM field studies and particularly the analysis of epidemiological data. The latter is extremely critical, since epidemiologists are seeking a more realistic “dose metric” for their protocols, which today use a time-weighted average exposure. However, this is not the norm of exposures in day-to-day life. To develop a protocol that is realistic, the time duration of each separate environmental exposure and the time variations in the field strengths must be considered. Determining the health risk from exposure to an EM field must take into account the number of entries into a particular field and the duration of each entry.

Acknowledgements

We thank the Electric Power Research Institute and the Heineman Foundation for their support. We are grateful to Dr. T.A. Litovitz, Department of Vitreous Physics, Catholic University of America for discussions and suggestions during the preparation of this manuscript and to A.J. Kremer for invaluable editorial advice and assistance.

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Exposure Metric and Measurements

Joseph Bowman, NIOSH

Dr. Bowman spoke about the exposure metrics and measurements which were used to test the Litovitz hypothesis with an epidemiologic study.

The Kinetic Hypothesis of Litovitz *et al.* Tested in an Epidemiologic Study: Exposure Metric and Measurements

by Joseph D. Bowman, NIOSH

Presentation to Opening Session of the NIOSH / DOE Workshop:
"EMF Exposure Assessment and Epidemiology: Hypotheses, Metrics and Measurements"

ABSTRACT

Data from a case-control study of childhood leukemia and electromagnetic fields in Los Angeles County were reanalyzed to test hypotheses relating the cancer to various exposure metrics for the temporal variability of the magnetic field. Magnetic field exposures had been monitored for 24 hours in the bedroom where the child had slept the longest prior to cancer diagnosis and by the Wertheimer-Leeper (WL) code for wire configurations. The original risk analysis had shown that the WL wire code was associated with leukemia risk, but time-weighted average (TWA) of the magnetic field measurements was not. In the reanalysis, the kinetic model for RNA transcription suggested by Litovitz *et al.* was the basis for one exposure metric. Nineteen empirical indices of temporal variability such as proportions of time above certain thresholds, frequencies of changes greater than certain amounts, and various autocorrelations were also computed. In this data set, the exposure index from the kinetic model is negatively correlated with the TWA and the WL wire code. The results of the leukemia risk analysis will be given in the following presentation by Duncan Thomas.

OUTLINE

- I. Introduction
 - A. the study of childhood leukemia in LA county [London *et al.*, 1991] was another example of the wire code paradox:
Associations with WL code but not EMF measurements
 - B. subsequently, further analyses were done to test more refined hypotheses about the temporal variability of residential EMF and childhood cancer
- II. The original study
 - A. Primary hypothesis: **Childhood leukemia is associated with long-term average ELF magnetic fields**
 - B. Exposure assessment to test this hypothesis:
 - 1. 24 hr monitoring at the site of the child's bed with:

2. Monitors:	<u>EMDEX-100</u>	<u>IREQ</u>
3. Sampling rate:	10 s	50 s
4. Filter:	broadband	narrowband
5. Data collection:	digital	logarithmic bins
6. Minimum response:	10 nT	< 3.1 nT

C. Definition of exposure metric

1. need for metrics with EMF
2. components of metrics:
 - a. frequency
 - b. spatial
 - c. temporal -- long and short time scales

D. Implicitly, the exposure metrics in the original analysis were:

1. quantity -- magnetic field, *i.e.* magnetic flux density
2. frequency metric -- ELF frequencies
3. spatial metric -- the vector magnitude *i.e.* the resultant
4. temporal metrics
 - a. short time scales -- root-mean-square over ~100 msec
 - b. long time scales
 - (1) time-weighted average (*i.e.* arithmetic mean over time)
 - (2) a variety of other temporal metrics (geometric mean, standard deviation, time above a threshold, etc.).
 - (3) All these statistics assumed that the temporal variations were *independent*.

III. Hypotheses for *posthoc* analyses: **Childhood leukemia is associated with:**

- A. a temporal metric derived from the Litovitz kinetic hypothesis, and/or
- B. temporal metrics which utilize the field's time series properties.

IV. Metric from the Litovitz hypothesis

- A. The pharmacokinetic differential equation from Litovitz *et al.* [1990] were solved over the 24 hr time period. Assumptions were needed to deal with:
 1. Discrete sampling of magnetic fields. Assumptions:
 - a. the magnetic field is constant for each sampling interval, and takes a discrete jump to the next sample
 - b. the mRNA concentration varies continuously from interval to interval
 2. Initial conditions:
The initial mRNA concentration at the beginning of the monitoring period is given by the steady-state solution (*i.e.* assume the concentrations are constant) with a constant magnetic field equal to the measured 24 hr TWA for that bed site.
- B. Results: [mRNA](t) often goes in the reverse direction from B(t)
- C. Exposure metric:
 1. integrate [mRNA](t) over 24 hr period
 2. normalize with k_1 and [A] to get a "kinetic index"

V. Other temporal metrics (19 in all)

- A. Time series statistics
 1. Autocorrelations - with lag times from the sampling rate up to 5 hours

- 2. Average of the log change in the magnetic field between samples
 - 3. Rate of changes above thresholds
 - B. TWA and standard deviation for day and night
 - C. Time above thresholds
- VI. Exposure assessment and results
- A. Average every 5 EMDEX samples to get 50 s averages, comparable to one IREQ sample
 - B. Results
 - C. Kinetic index correlation with other temporal metrics
 - D. Correlation with WL code
- VII. Conclusion -- an example of a biological mechanism turned into an exposure metric which could be measured in an epi population

Dr. Bowman's viewgraphs are as follows:

<p>ORIGINAL STUDY</p> <p>London S. J. , Thomas D. C. , Bowman J. D., Sobel E., Cheng T. C., Peters J. M., (1991): Exposure to residential electric and magnetic fields and risk of childhood leukemia. <i>Am J Epidemiol</i> 134: 923-937.</p> <p>Primary Hypothesis</p> <p>Childhood leukemia is associated with the time-averaged exposure to extremely low frequency (ELF) magnetic fields.</p>
<p>Exposure Assessment</p> <ul style="list-style-type: none"> • Questionnaire (residence history, appliances) • Spot measurements <ul style="list-style-type: none"> – AC electric and magnetic fields – Static magnetic field – Child's and parents' bedrooms, living room, outdoors • 24 hour magnetic fields (EMDEX / IREQ) • Wiring configurations

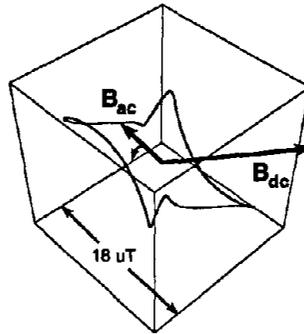
Exposure Metric

DEFINITION: A method (involving the measurement and the data processing) for reducing a complex exposure to a single number in order to assess health risks.

EXAMPLES:

Time-weighted average
Doses for ionizing radiation (rad and rem)
Respirable dust

One-cycle Trace of a Residential Magnetic Field

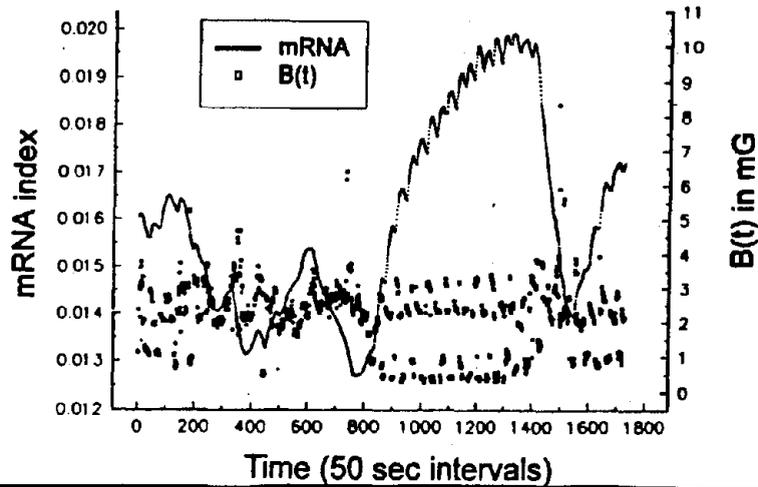


Question: How to reduce this complex pattern to an exposure metric?

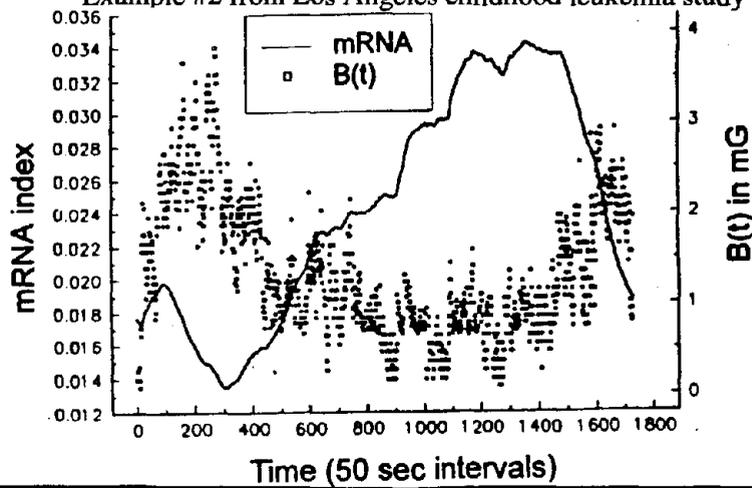
EMF Exposure Metrics used in London *et al.*

Units	Magnetic flux density (mG)
Frequency metric	Bandpass filter within the ELF range (3 - 3000 Hz)
Spatial metric	Vector magnitude (<i>i.e.</i> resultant)
<u>Time metrics:</u>	
by analog processing:	Root-mean-square over 100 ms
by data processing:	Time-weighted average over 24 hr
	Geometric mean
	Time above 2.5 mG

Modeled mRNA Concentrations from Bedroom Magnetic Fields
Example #1 from Los Angeles childhood leukemia study



Modeled mRNA Concentrations from Bedroom Magnetic Fields
Example #2 from Los Angeles childhood leukemia study



Empirical Time Metrics

- I. Statistics for independent data
 - A. Averages
 - 1. Time-weighted average (arithmetic mean)
 - 2. Geometric mean
 - B. Variability
 - 1. Standard deviation
 - 2. Coefficient of variation
 - C. Percent time above thresholds
Thresholds: 0.5, 1.0, 1.5, and 2.5 mG

Empirical Time Metrics (continued)

II. Day-only and night-only exposures

- A. Time-weighted average
- B. Standard deviation

II. Time series statistics

- A. **Autocorrelation**
Lag times: 50 s, 5 & 25 m, 2.5 & 5 hr
- B. Mean of the absolute changes between samples
- C. Percent time when changes are greater than two thresholds

20 empirical metrics in all

Exposure Measurements for Temporal Metrics
24 hr monitoring for 276 subjects

Metric	Median	90th Percentile
Kinetic index (unitless)	0.035	0.057
Time-weighted average	0.65 mG	2.91 mG
Autocorrelation for 50 sec lag time	0.77	0.89

Correlation with Kinetic Index

Metric	Correlation
Time-weighted average	-0.97
% time above 1 mG	-0.87
Coefficient of variation	-0.06
50 sec Autocorrelation	-0.51

Comparison with Wire Codes

Metric	Mean exposure by wire code	
	Very High	Lower codes
Time-weighted average	1.07 mG	0.63 mG
Kinetic index	0.029	0.038
50 sec Autocorrelation	0.82	0.69

All means tests are significant with $p < 0.001$

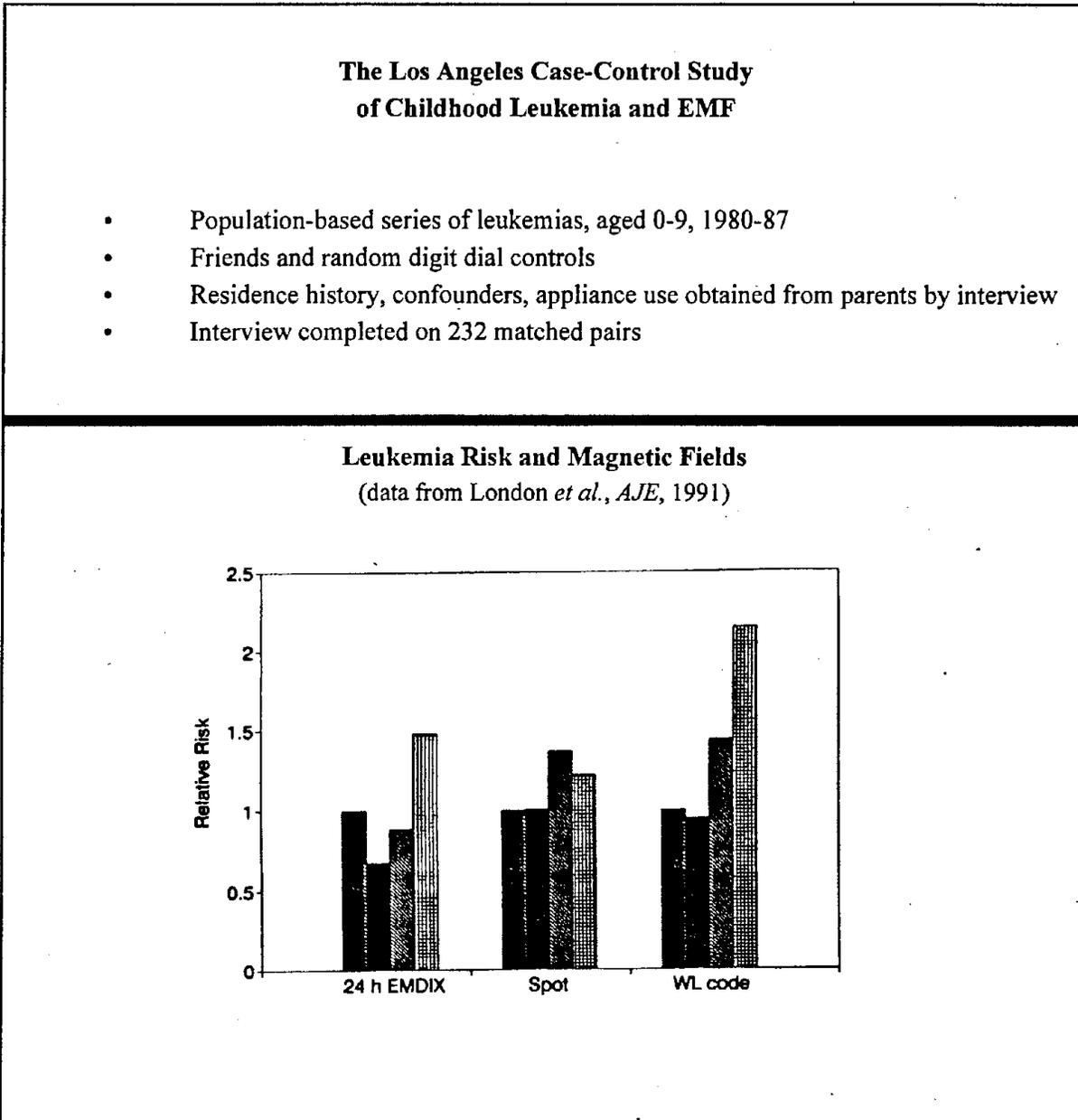
Conclusions

- * A new exposure metric was derived the kinetic hypothesis of Litovitz *et al.*
- * Exposures to this metric can be calculated from EMDEX and IREQ (Positron) monitoring.
- * The monitor's sampling rate must be faster than the reaction rate.
- * The kinetic index and 15 s autocorrelation are previously unrecognized metrics associated with high current configurations

Epidemiological Design and Results: Temporal Variability in Residential EMF and Risk of Childhood Leukemia, Duncan Thomas (Liangzhong Jiang, Stephanie London, John Peters) University of Southern California and Joseph D. Bowman, NIOSH

Dr. Thomas presented the design and results of the epidemiologic analysis which tested Dr. Litovitz's hypothesis.

Dr. Thomas's viewgraphs are as follows:



Hypotheses in Residential Studies

- Wiring is a surrogate for a causal effect of mean magnetic field
– Associations with measured fields due to variability
- Wiring is a surrogate for a causal effect of other aspect of magnetic field
- Wiring is a surrogate for a non-EMF confounder
- The wiring association is an artifact of selection bias

Univariate Associations of Temporal Variability with Childhood Leukemia

Variable	Percentiles:	Odds Ratios			<u>p-trend</u>
		50-74	75-89	90-100	
Kinetic index		0.85	1.20	1.81	0.23
– ($\delta k_3 = 0$)		0.96	1.50	2.25	0.07
Arithmetic mean		0.90	0.73	1.79	0.60
Coefficient of variation		1.10	1.30	1.48	0.28
Percent time > 1 mG		1.20	0.83	1.50	0.61
Mean absolute log change		0.83	0.76	1.65	0.74
Rate of changes > 2.72 fold		1.32	1.33	1.47	0.28
50s autocorrelation		1.08	1.36	1.75	0.16

Bivariate Analyses Involving the Kinetic Index

Variable	Odds Ratios			p-value		
	Percentiles:	50-74	75-89	90-100	Trend	Model
	Wire codes:	OLCC	OHCC	VHCC		
Kinetic index		1.12	1.72	2.77 ^b	0.03	
50s autocorrelation		1.42	1.90	2.50 ^a	0.02	0.03
Kinetic index		0.91	1.40	2.25 ^a	0.08	
WL code		0.95	1.48	2.29 ^a	0.01	0.02
50s autocorrelation		1.05	1.15	1.40	0.38	
WL code		0.74	1.25	1.79	0.07	0.07
Kinetic index		1.95	2.90	4.35	0.03	
Arithmetic mean		2.20	1.88	4.59	0.06	0.08

^ap < 0.10

^bp < 0.05

Conclusions

- * Findings:
 - Kinetic index does not significantly predict leukemia risk alone
 - Together with autocorrelation, WL code, or mean field is significant
 - Subset of data with 10s measurements did not fit as well
 - Kinetic index negatively correlated with mean & autocorrelation
- * Possible Explanations:
 - Statistical fluke
 - Failure to allow for coherence time
- * Future Studies:
 - More frequent measurements needed to test hypothesis

The EMF Environment: Complex or Simple?, The Role of Mechanisms
T. Dan Bracken, T. Dan Bracken, Inc.

Dr. Bracken's viewgraphs are as follows:

Perspective

The EMF environment is exceedingly complex.

To date we have relied on simple measures of field, such as daily mean, time above thresholds, and maximum to characterize exposures.

Some mechanisms that are under consideration suggest metrics that embody complexity and could require sophisticated measurement technologies.

Various field attributes or combinations of attributes are essential for the interaction mechanisms to occur.

What do we know about the variability of these attributes?

Are conditions stable enough outside the laboratory for meaningful exposures to occur?

Identification of a mechanism of interaction would allow the effort of exposure assessment to be directed efficiently and effectively to answer such questions.

Objective

To describe the complex nature of static and ELF magnetic fields with examples from the occupational, residential, and transportation environments.

Magnetic Field Attributes

Magnitude:	maximum, resultant, components
Temporal characteristic:	steady state, cyclic, sporadic, intermittent
Frequency:	static, broadband, harmonics, transients
Polarization:	axial ratio
Alignment of ac and dc fields:	angle between ac and dc; \parallel and \perp

Temporal and spatial variability is evidenced in all these attributes.

Magnitude

Field magnitude can vary over a wide range in occupational, residential, and other environments.

Range of Occupational Fields

<u>Location</u>	<u>Condition</u>	<u>Range. mG</u>
Offices	(5 - 95%)	0.2 - 6
Urban outdoor environment	(10 - 90%)	0.4 - 5.1
Utility substations	(5 - 95%)	0.4 - 60
Induction furnaces	(TWA) (Max.)	30 1.25 - 12.5 G
Electric train engines	(16.7 Hz)	0.1 - 11 G

Nature of Occupational Exposures

Occupational exposures characterized by magnitude are:

Highly variable:

Within a day:

Between days for an individual;

Between individuals with same job title; and

Between job titles.

Dependent on technology and work practices:

Between plants or sites (hydro vs. thermal)

Introduction of robotics; and

Use of new work methods.

Many of the same observations can be made for residential exposures.

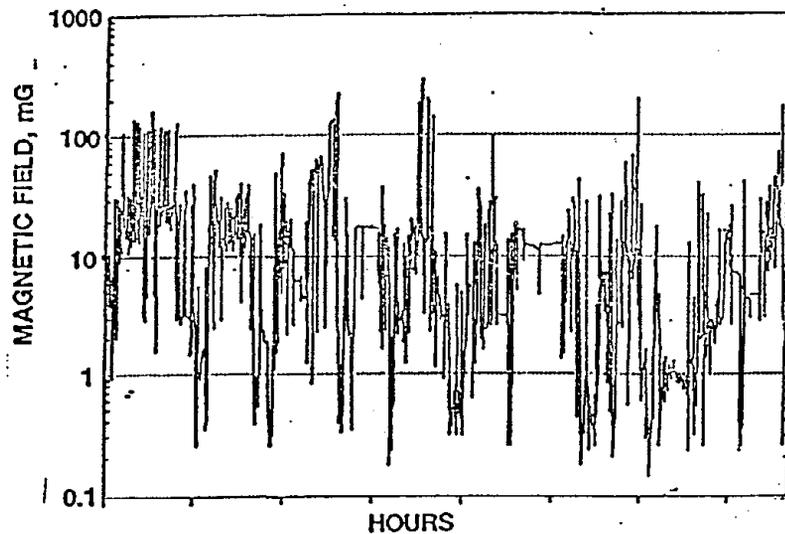
Temporal variability in exposures is introduced by source variation and by movement within spatially varying fields.

Example 1: Production Welder

Example 2: Live-line Worker

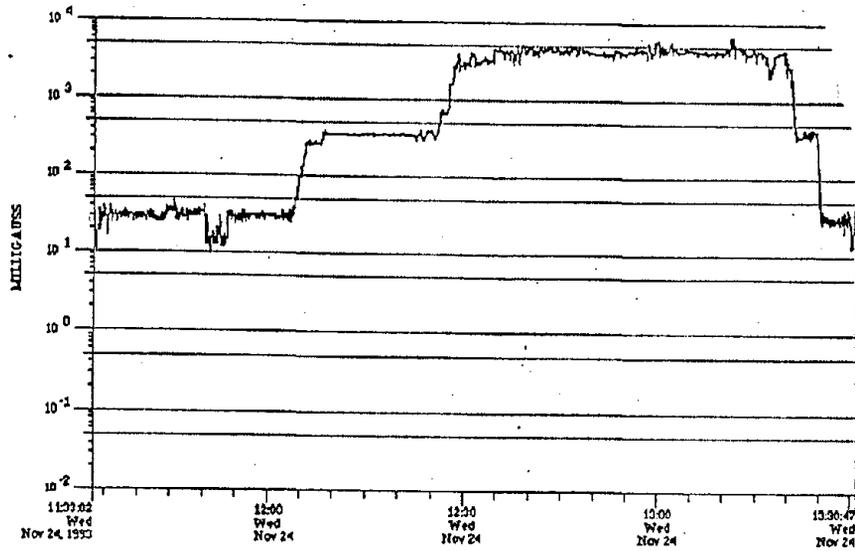
Example of Occupational Exposure

Exposure for Welder During Workday



n=5515 Median=7 mG Mean=15 mG 95th %ile=54 mG

Lineworker Exposure During Live-line Task



Measures of Variability

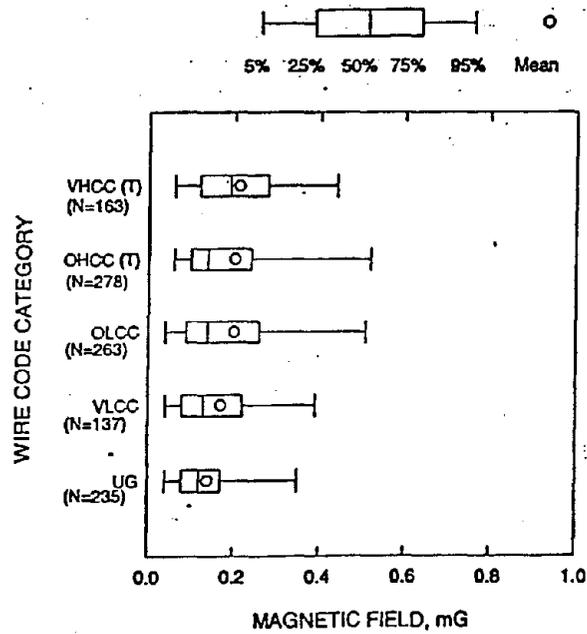
Short term variability of magnitude characterized by difference between succeeding measurements.

Example: First difference vs. wire code

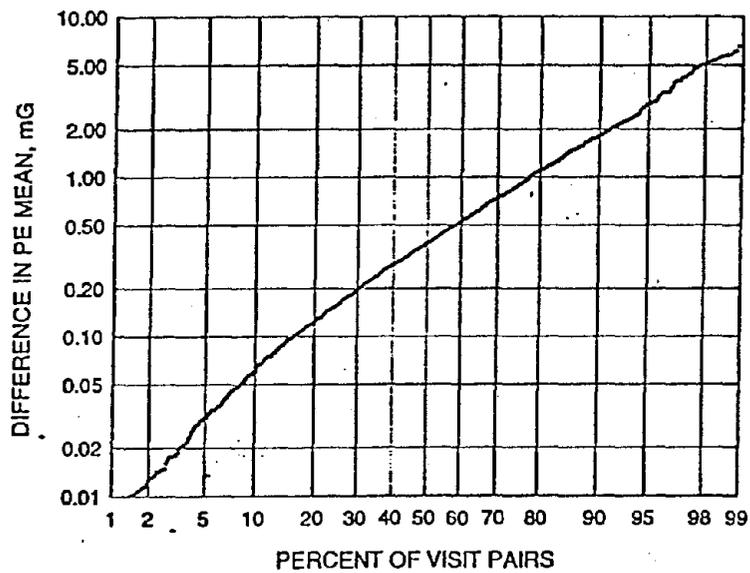
Long term variability characterized by differences over months or years.

Example: Differences between visits to a house

Personal Exposure First Difference Vs. Residential Wire Code



Differences Between Personal Exposure Means for Visits to a House, N = 1680 Visit Pairs



Temporal and Frequency Characteristics

Steady state source, single frequency:

Example: De-magnetizer

Steady state source, harmonics:

Example: Battery charger

Cyclic, broad frequency spectrum:

Example: MRI system

Sporadic:

Example 1: Electric vehicle

Example 2: Maglev train

Transient:

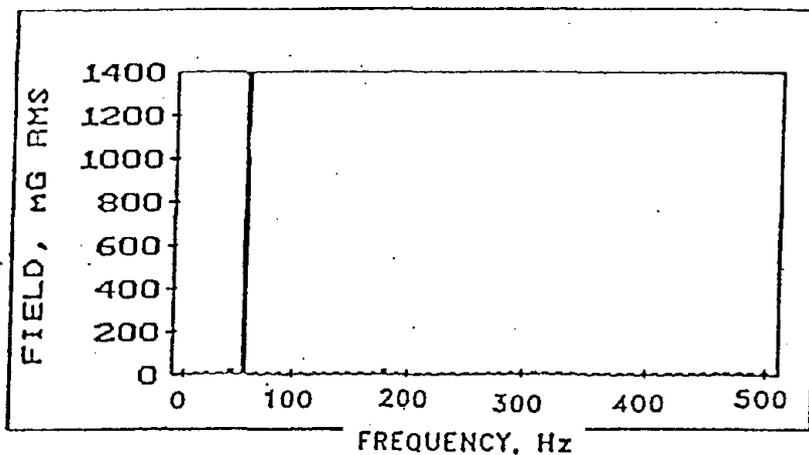
Example: Distribution capacitor bank closing

Static fields:

Example: Residential survey and fixed location measurements

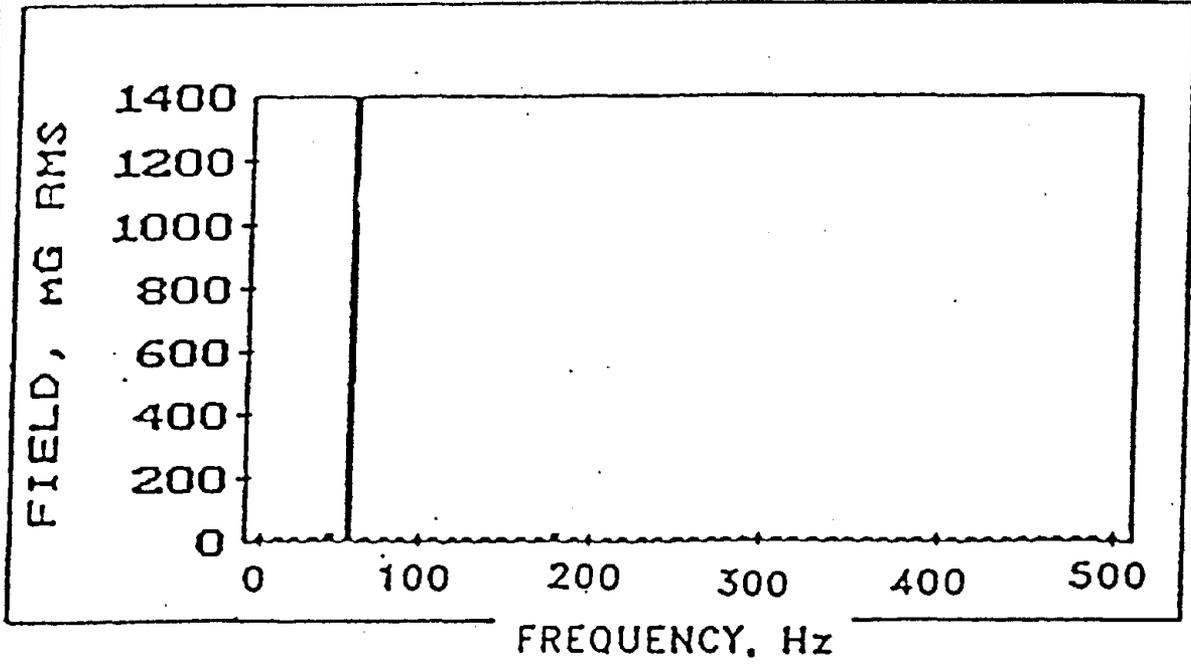
Steady State Source, Single Frequency:

Resultant Magnetic Field Near Demagnetizer



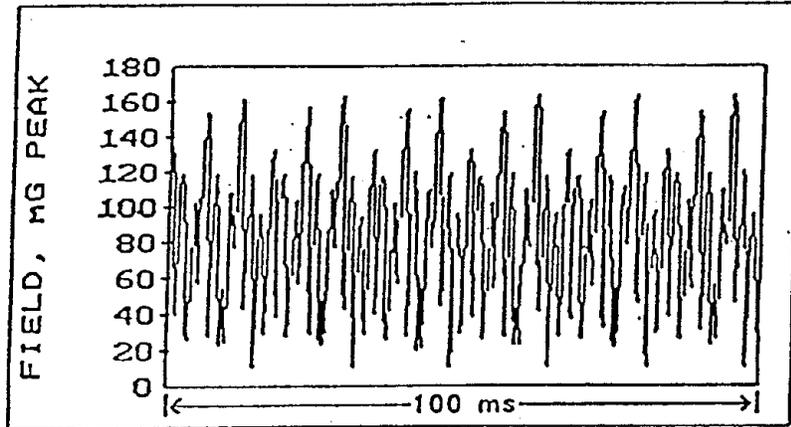
Steady State Source, Single Frequency:

Frequency Spectrum of Resultant Field Near Demagnetizer



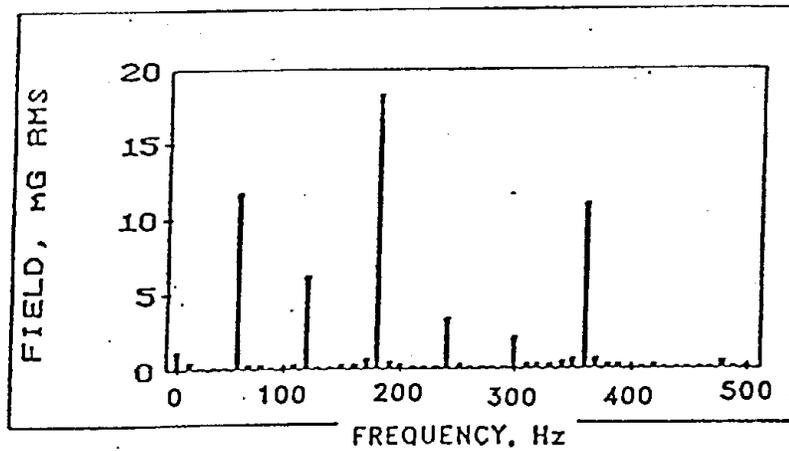
Steady State Source, Multiple Frequencies:

Resultant Magnetic Field Near Battery Charger Facility



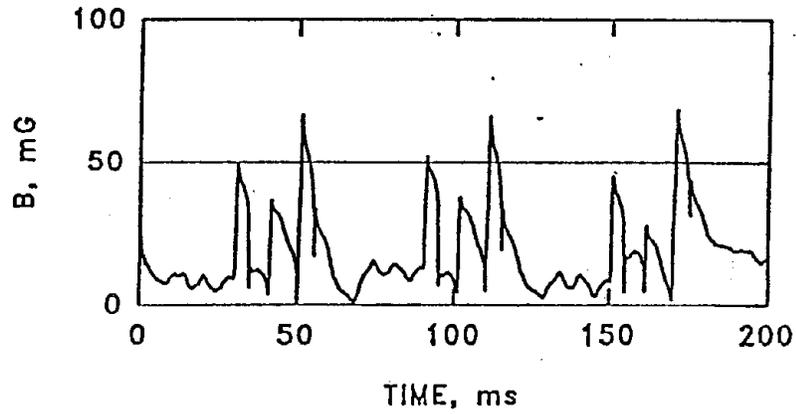
Steady State Source, Multiple Frequencies:

Frequency Spectrum of Resultant Field Near Battery Charger Facility



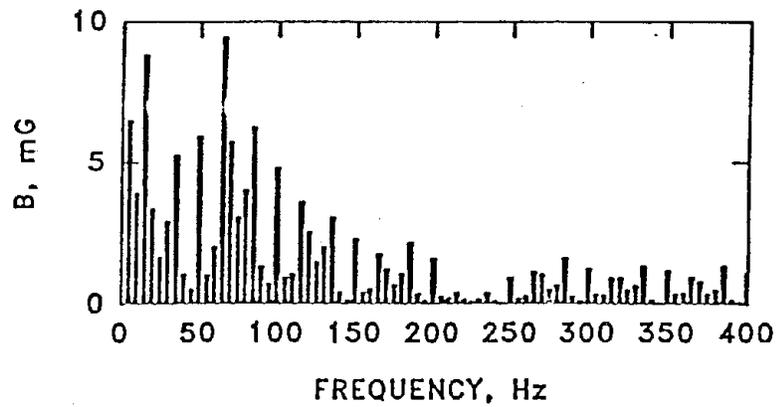
Cyclic Source, Broad Frequency Spectrum:

Resultant Magnetic Field Waveform Near MRI Facility

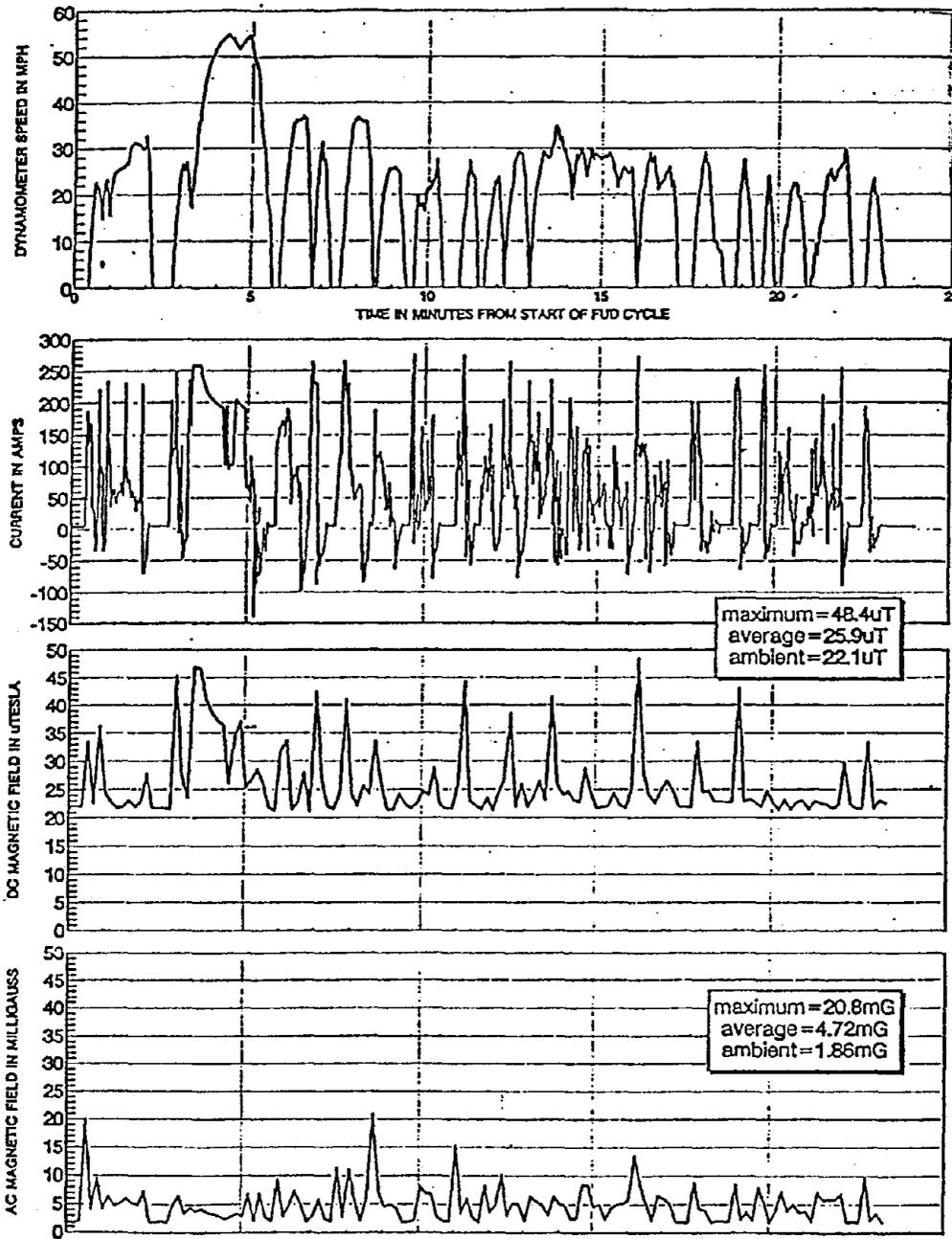


Cyclic Source, Broad Frequency Spectrum:

Frequency Spectrum of Resultant Magnetic Field Near MRI Facility



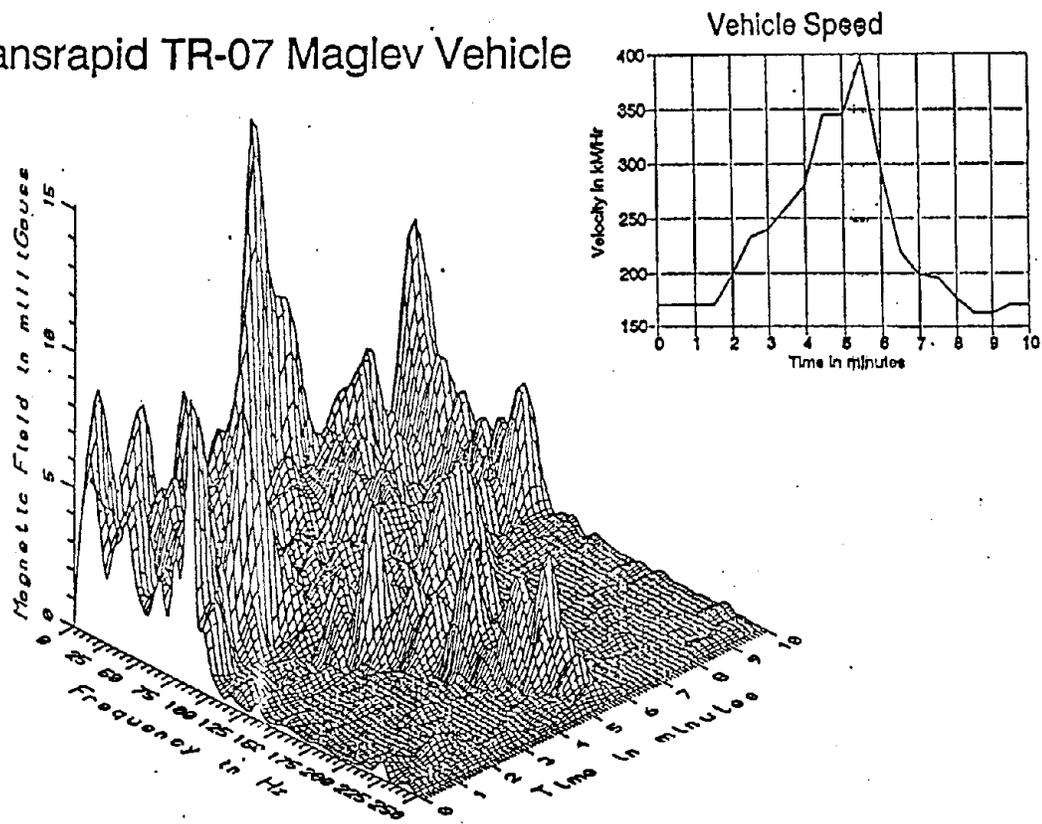
Sporadic, Electric Vehicle:



G-Van FUD Cycle Measurements

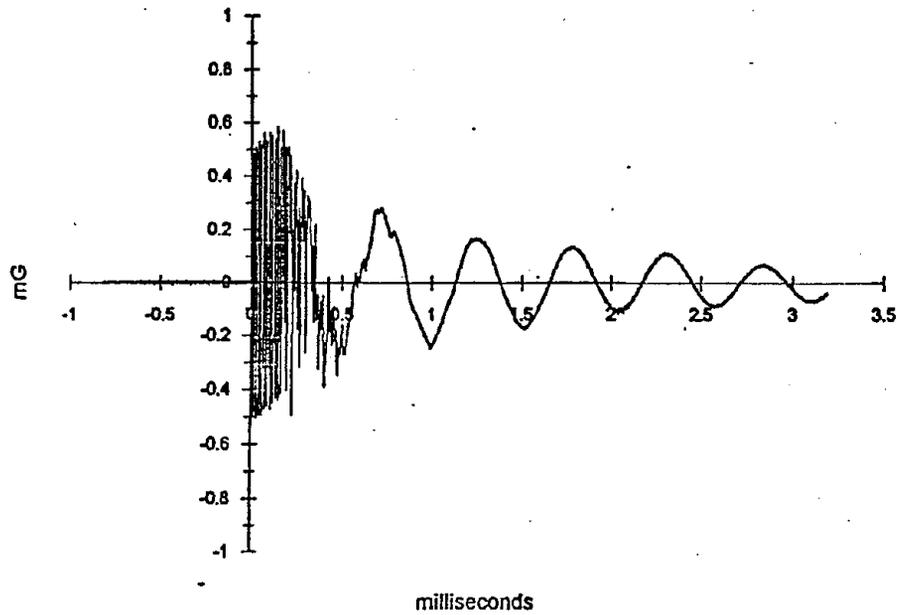
Sporadic, Dynamic Broad Frequency Spectrum:

Transrapid TR-07 Maglev Vehicle

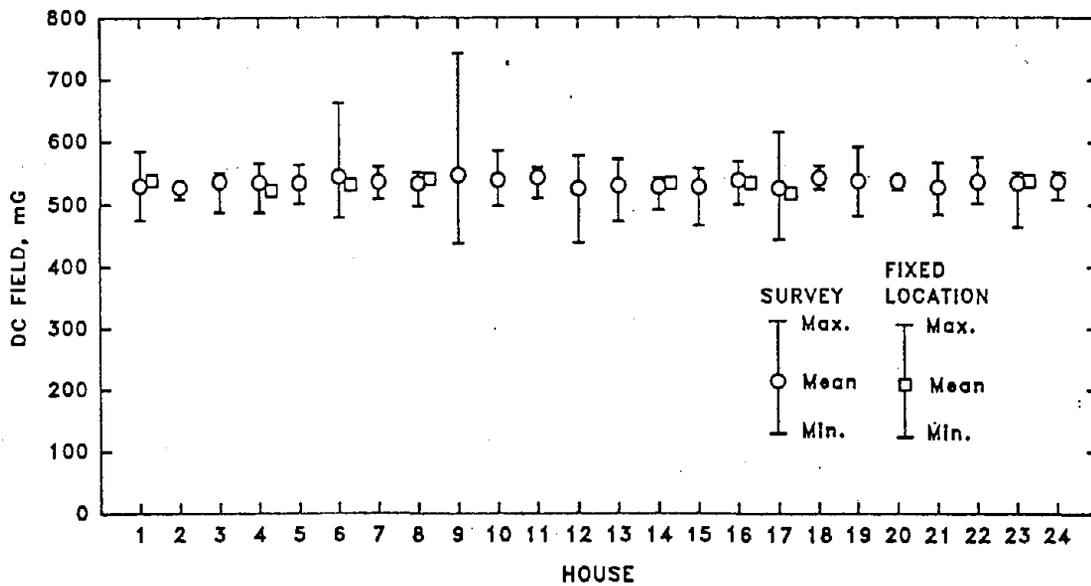


AC Probe Mounted at Standing Head Level

Transient: Distribution Capacitor Switch Closed



DC Field Measurements at 24 Houses



Polarization

Axial ratio

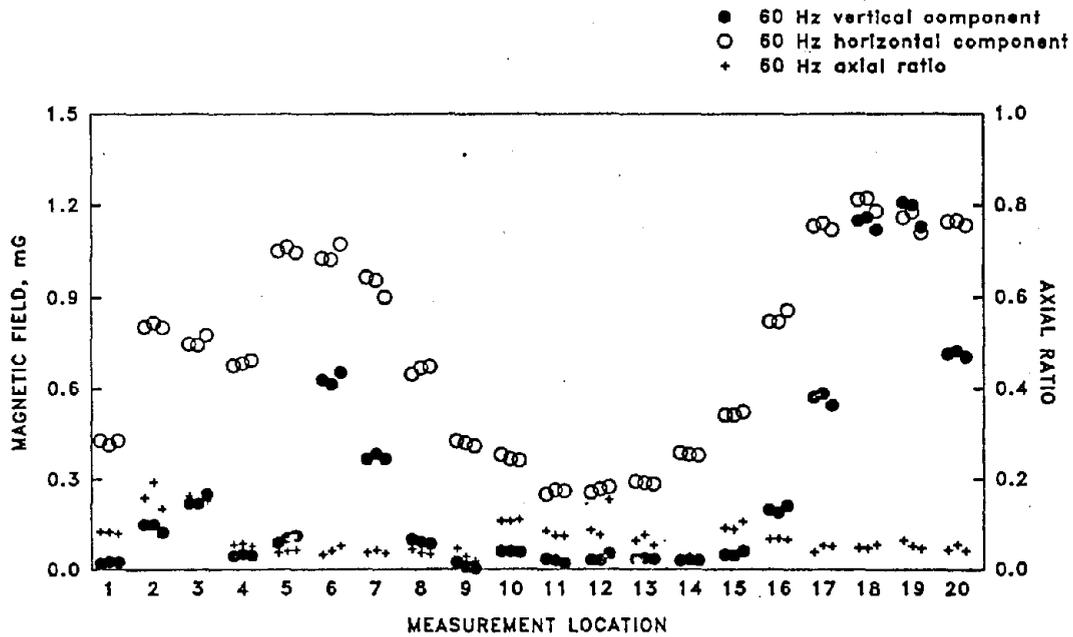
Example: Residential survey and fixed location measurements

Alignment of ac and dc Fields

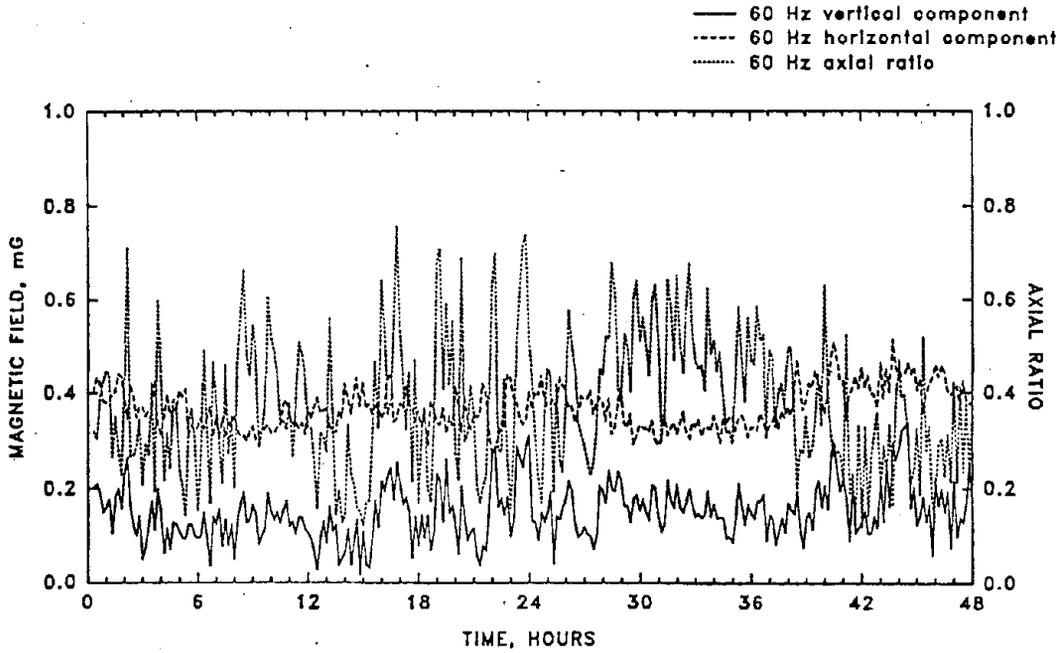
Angle between 60 Hz vector and static field vector Parallel and perpendicular 60 Hz components

Example: Residential survey and fixed location measurements

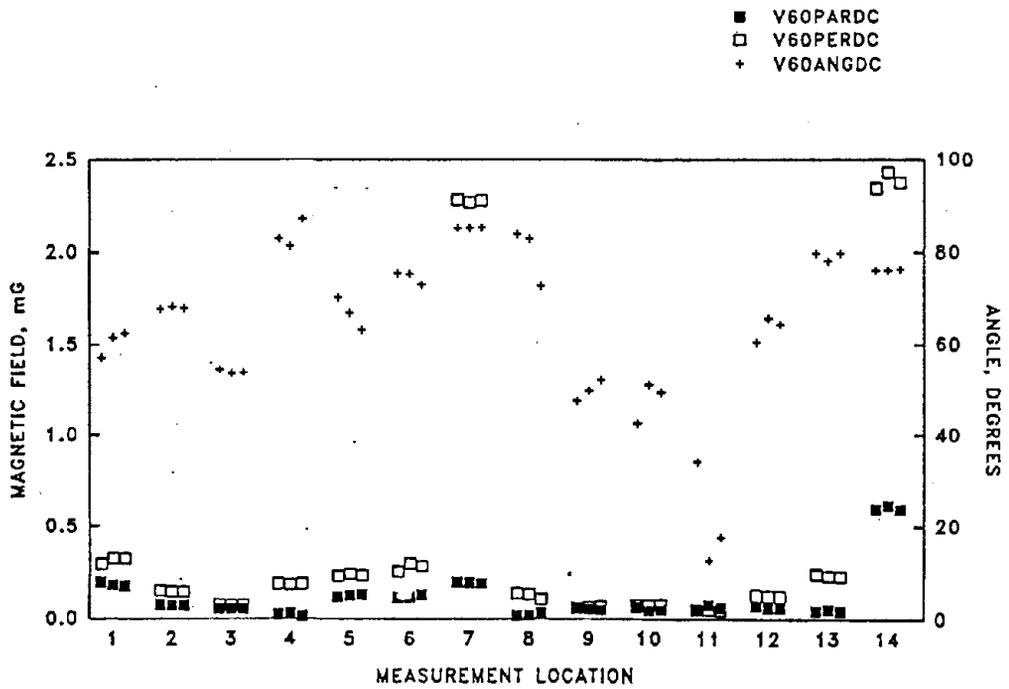
House A: Survey Measurements



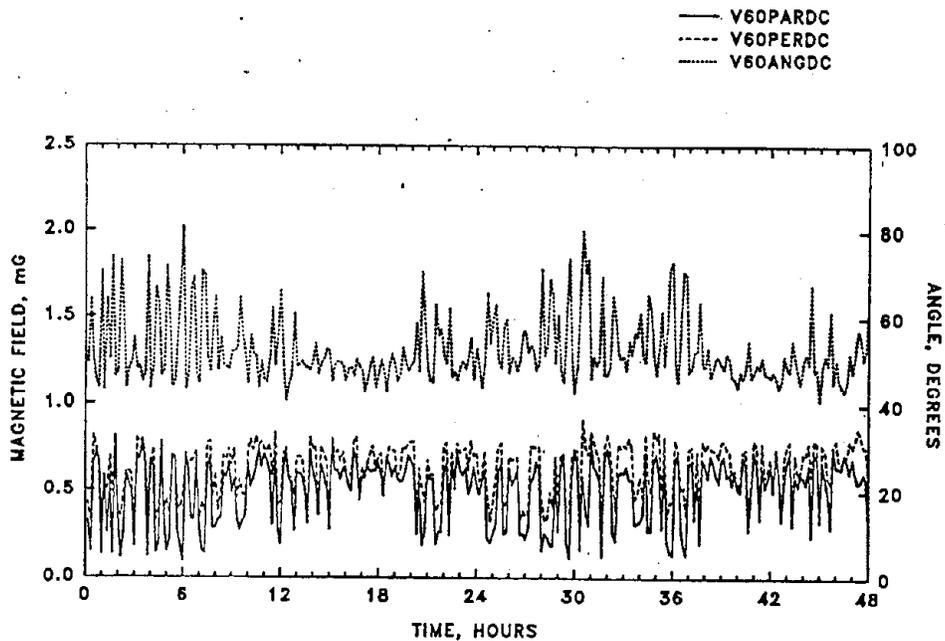
House D: Fixed Location Measurements



House E: Survey Measurements



House E: Fixed Location Measurements



Summary

The EMF environment is complex with many field attributes to consider as possible exposure metrics.

Just as we see variability in the magnitude of magnetic fields, we can expect considerable variability in other field attributes that might be considered as exposure metrics.

With many opportunities for exposure, it is probably possible to achieve any combination of field parameters for short periods of time or in very specific locations.

One value of establishing a mechanism for effects will be the ensuing reduction in the complexity of measurements needed for exposure assessment.

To accomplish such a reduction, a mechanism must provide guidance on:

whether dose is related to specific encounters with a field parameter configuration or to cumulative exposure to the configuration; and

which specific attributes of the field are of importance.

Personal Exposure Monitors

Michael Yost, Department of Environmental Health, University of Washington

Dr. Yost's viewgraphs are as follows:

Alternating Fields Can be a Mixture of Many Factors

- Electric or magnetic field intensity (scalar magnitude)
- Fundamental frequency
- Higher or lower frequency harmonics
- Transients or pulsed fields
- Orientation of AC field vector in the earth's DC field
- Polarization (rotating vector)

Key Factors for Personal Dosimetry

- Objective: capture 'dose' over time to an individual
 - Assuming 'dose' can be defined . . .
- Sampling strategy considerations:
 - Duration of measurements (8 hr, 24 hr., etc.)
 - Number of measurements
 - Location of measurements on the body
 - Relevant time period of interest
 - Summary metrics

Some Summary Measures of Exposure

- Central tendency (mean, GM, median)
- Variance
- Percentile distributions (time above some level)
- Orientation
- Harmonic fraction

Important Instrument Factors

- Operating principle
 - inductive coil, fluxgate, hall effect
- Waveform response
 - Peak, average, RMS, FFT
- Frequency response
- Transient response
- Data storage and output capabilities
- Sampling interval
- Meter sensitivity, accuracy and precision

What Can We Measure?

- 1 axis cumulative magnitude (AMEX)
- 3 axis cumulative magnitude (AMEX 3D)
- 3 axis avg. AC + datalog (EMDEX C)
- 3 axis RMS AC + datalog + harmonics (EMDEX II)
- 3 axis RMS AC = datalog = HF transients (Positron)
- 3 axis RMS AC + datalog + freq. (40-1kHz) (SpecLite)
- 3 axis AC freq. + phase (Waveform Capture*)
- 3 axis DC + AC freq. + phase (FG Waveform Capture*)

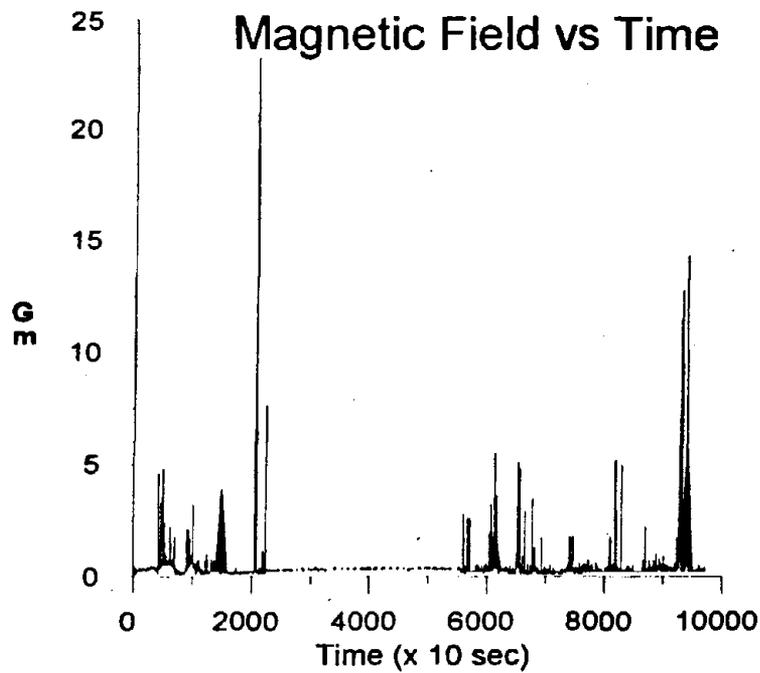
* portable

Issues to Resolve - What Simplifications can we Justify?

- Spatial vector or phase information
- Frequency range of interest
- Time resolution requirements
- Time, intensity, & frequency reciprocity

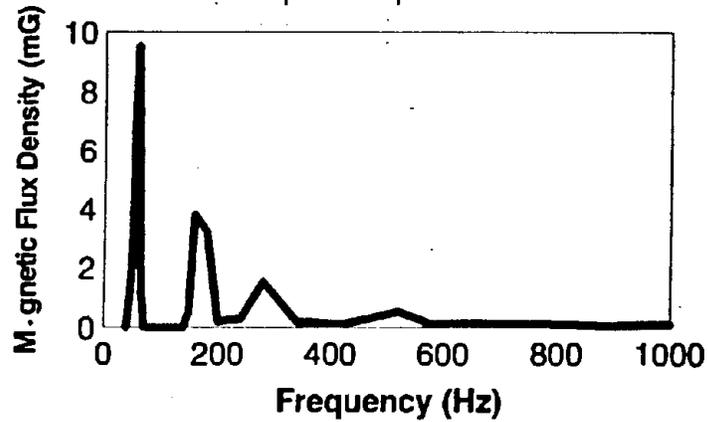
Limitations

- All meters have assumptions - try to know them!
- Recognize the uncertainty in what we measure
- Avoid extrapolating beyond the data
- Use caution when applying a device developed for a different purpose



Magnetic field frequency spectrum

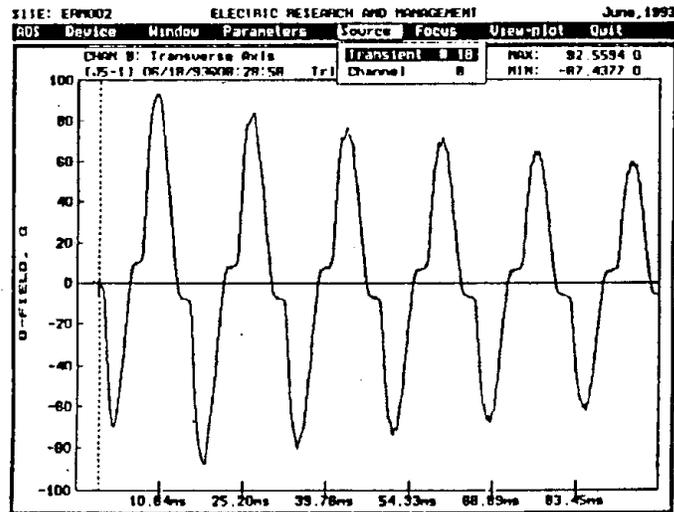
Computer Tape Drive



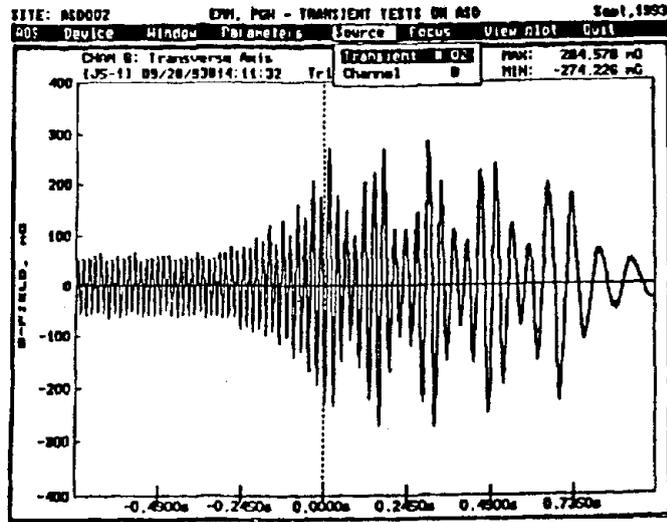
Waveform and Transient Capture Devices

William Feero, Electric Research and Management, Inc.

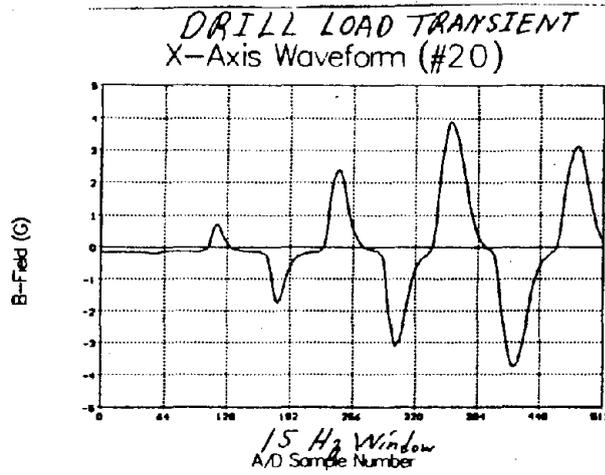
Dr. Feero's viewgraphs are as follows:



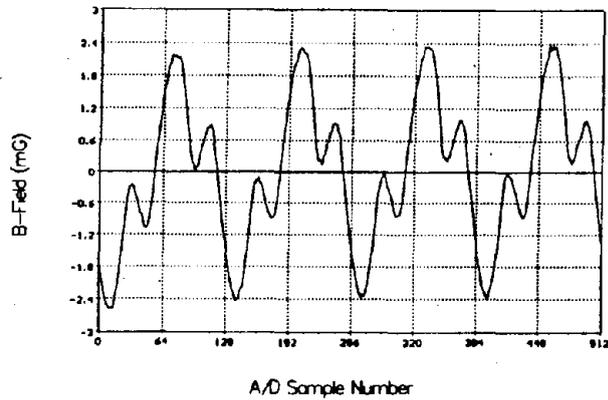
Cube sensor against surface of drill - T axis.



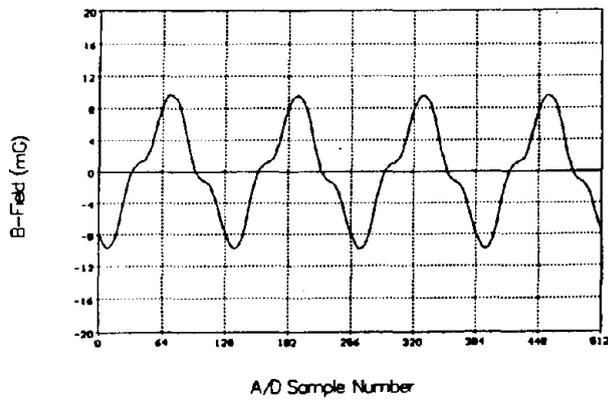
Motor stop with deceleration of 1 second, frequency was 60 Hz - T axis.



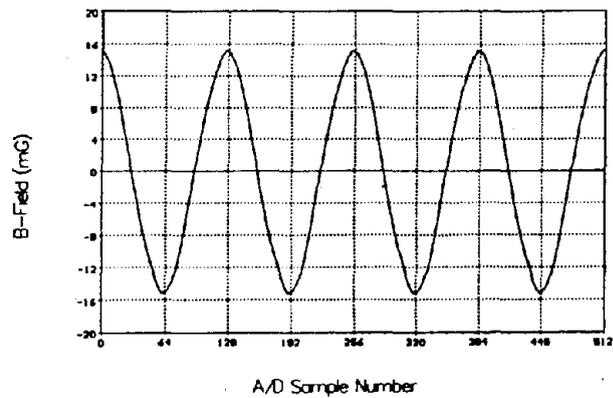
Distribution Line Leaving Substation
X-Axis Waveform (#29)



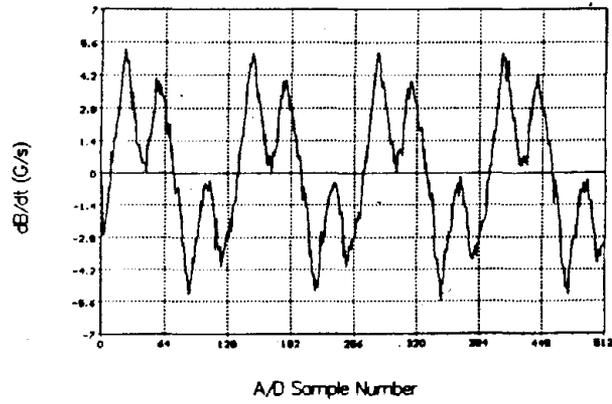
Y-Axis Waveform (#29)



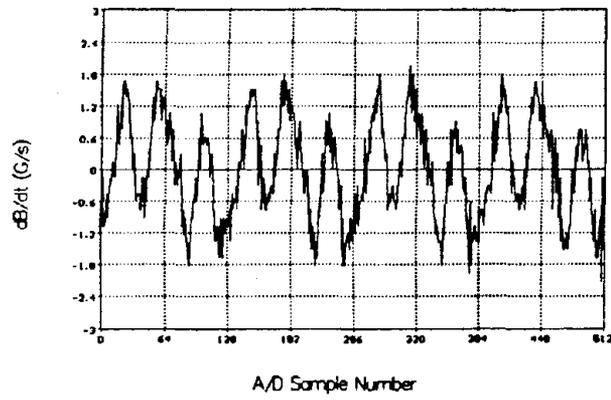
Z-Axis Waveform (#29)



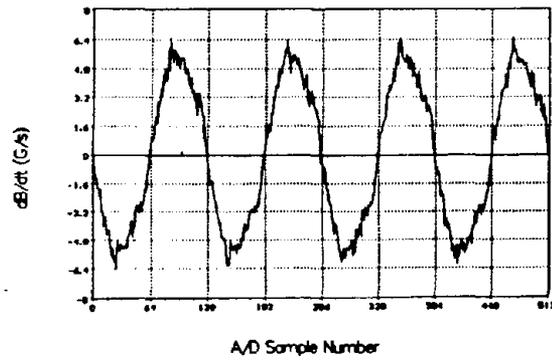
Y-Axis Waveform (#29)



X-Axis Waveform (#29)



Z-Axis Waveform (#29)

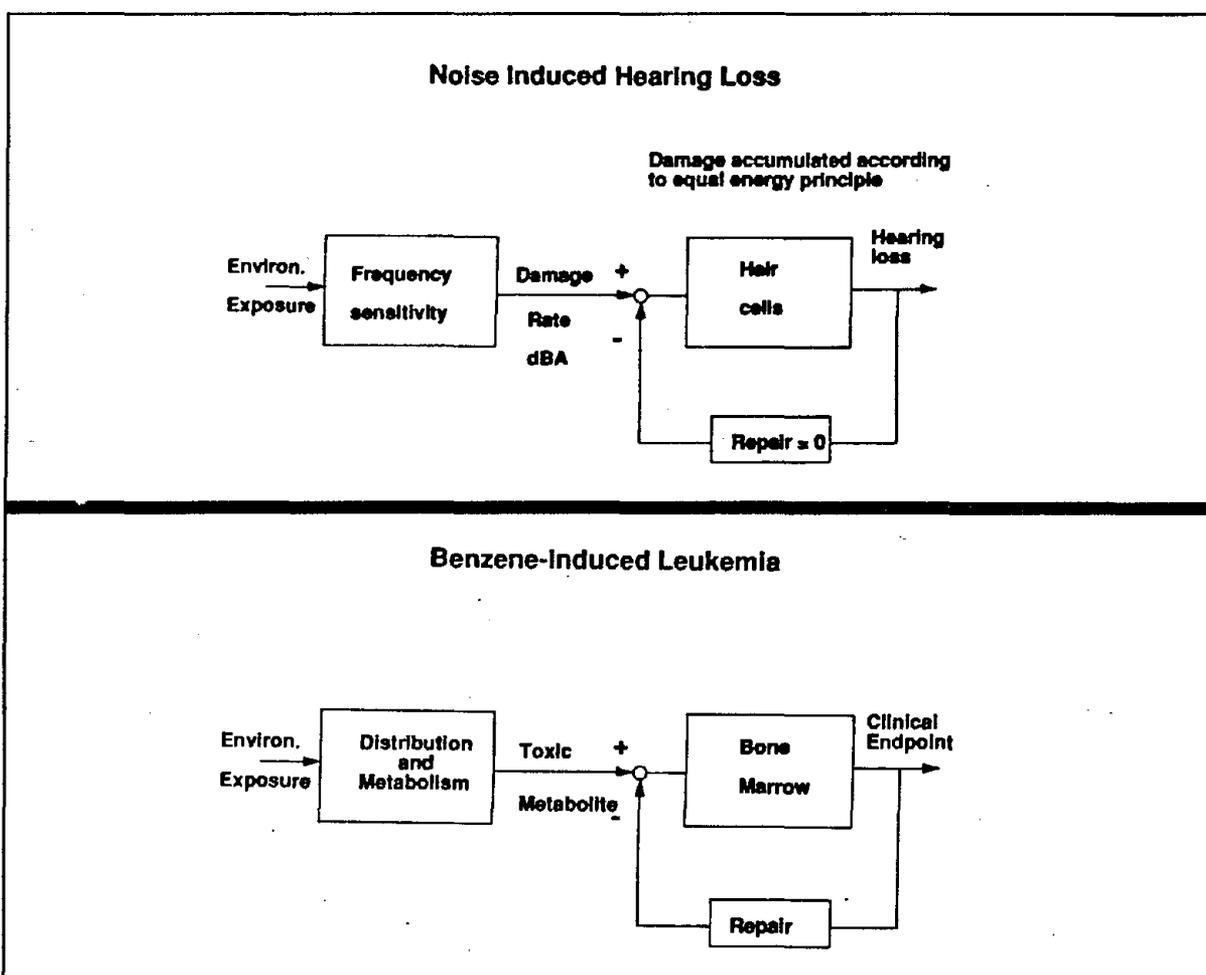


Exposure Metrics

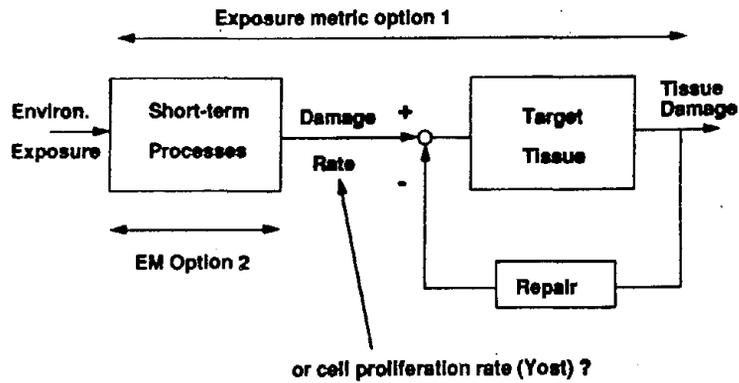
Robert C. Spear, Center for Occupational and Environmental Health
University of California, Berkeley

Dr. Spear discussed exposure metrics for noise induced hearing loss and benzene induced leukemia. He suggested that an exposure metric links environmental exposure and the rate at which damage (for noise) or cell proliferation (for benzene) occurs at the receptor site. A metric can be called complete if it contains the information necessary to predict damage or the cell proliferation rate. As examples, the noise spectrum is complete for a temporary threshold shift and for a permanent threshold shift, if it covers a lifetime. The metric dBA as a function of time is also complete for TTS but not PTS. A shift-long Leq is complete for PTS but not TTS, and long-term Leq is complete for PTS. For benzene, the concentration as a function of time in the breathing zone is not complete without some assumption or measurement of ventilation rate. A shift-long TWA of concentration, coupled with assumptions about ventilation rate, may produce a reasonable estimate of inhaled dose. He noted that for EMF the first challenge is to define a complete metric. The complete metric may be multivariate.

Dr. Spear's viewgraphs are as follows:



How to define an exposure metric?



Exposure Metric: A Proposed Definition

An exposure metric is a mathematical representation of the relation between an environmental exposure and the rate at which damage or cell proliferation is produced at the receptor site.

Completeness

An exposure measurement is *complete* if it contains the information necessary to predict the rate at which damage or cell proliferation is produced at the receptor (i.e. if there exists an exposure metric).

Completeness: Noise and Hearing Loss

Noise spectrum, as $f(t)$, is complete for TTS and PTS if t is a lifetime. dBA, as $f(t)$, is also complete for TTS and PTS. Shift-long Leq values complete for PTS, but not TTS. Long-term Leq values complete for PTS

Benzene and Leukemia

$c(t)$ in the breathing zone is not complete without assumption, or measurement, of ventilation rate.

The shift-long TWA value of $c(t)$ and appropriate assumptions about average ventilation rate probably produce reasonable estimates of the single-shift inhaled dose. However, total production of toxic metabolites over the shift may not be well-predicted by total inhaled dose.

EMF

The first challenge is to define a complete measurement.

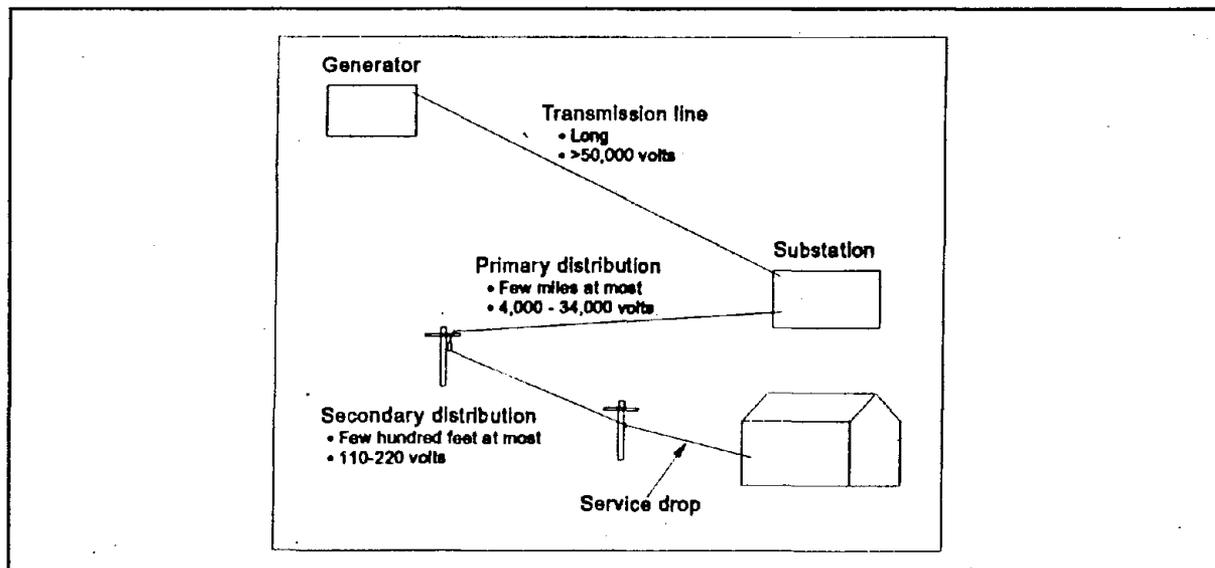
In the case of EMF, a complete measurement may be multi-variate.

Is there an analog of temporary threshold shift or toxic metabolite production to aid in the search for a plausible exposure metric?

Magnetic-Field Exposure Assessment in Past Residential Epidemiological Studies

William T. Kaune, EM Factors

Dr. Kaune reviewed exposure assessments from past residential studies. Dr. Kaune's viewgraphs are as follows:



Methods of Exposure Assessment

- • Wire Codes
- Calculated Magnetic Fields
- Spot Magnetic-Field Measurements
- Longer-Duration Magnetic-Field Recordings
- Personal Exposure Measurements
- Measurement of Geomagnetic Fields
- High-Frequency Electric Fields

Wertheimer-Leeper Wire Code

	VHCC	OHCC	OLCC	VLCC
Transmission line Thick 3-phase primary	≤50 feet	≤130 feet		
Thin 3-phase primary	≤25 feet	≤65 feet	≤130 feet	
First-span secondary		≤50 feet	≤130 feet	
Other secondaries			≤130 feet	

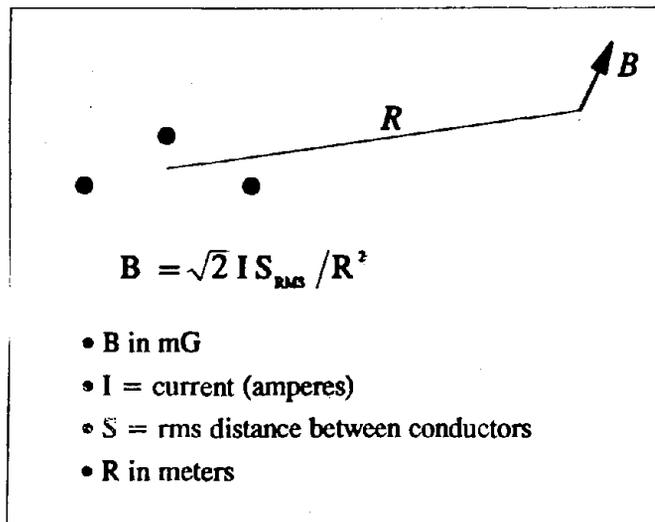
Modified Wertheimer-Leeper Wire Code

	High	Medium	Low
Transmission line Three-phase primary	≤65 feet	≤150 feet	
Open secondary		≤85 feet	

Methods of Exposure Assessment

- Wire Codes
- • Calculated Magnetic Fields
- Spot Magnetic-Field Measurements
- Longer-Duration Magnetic-Field Recordings
- Personal Exposure Measurements
- Measurement of Geomagnetic Fields
- High-Frequency Electric Fields

Stata graph showing wire codes and measured fields



Methods of Exposure Assessment

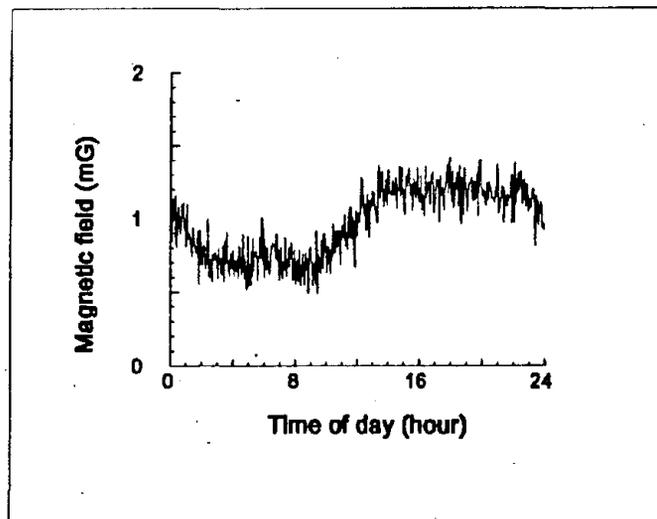
- Wire Codes
- Calculated Magnetic Fields
- • Spot Magnetic-Field Measurements
- Longer-Duration Magnetic-Field Recordings
- Personal Exposure Measurements
- Measurement of Geomagnetic Fields
- High-Frequency Electric Fields

Methods of Exposure Assessment

- Wire Codes
- Calculated Magnetic Fields
- Spot Magnetic-Field Measurements
- • Longer-Duration Magnetic-Field Recordings
- Personal Exposure Measurements
- Measurement of Geomagnetic Fields
- High-Frequency Electric Fields

Spot Magnetic-Field Measurements

- Usually at standardized locations in rooms, but sometimes at locations most frequently used by subjects
- Three vector components or resultant measured
- Temporal sample ~ 1 second through about 30 seconds



Methods of Exposure Assessment

- Wire Codes
- Calculated Magnetic Fields
- Spot Magnetic-Field Measurements
- Longer-Duration Magnetic-Field Recordings
- • Personal Exposure Measurements
- Measurement of Geomagnetic Fields
- High-Frequency Electric Fields

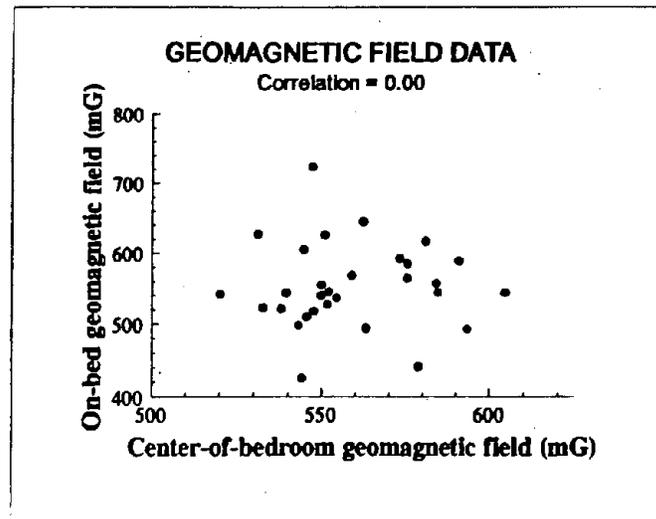
Geomagnetic-Field Measurements

- Flux-Gate Magnetometers
- Vector Components Measured
- Usually At Standardized Locations In Rooms
 - poor correlation between fields measured at different locations

Methods of Exposure Assessment

- Wire Codes
- Calculated Magnetic Fields
- Spot Magnetic-Field Measurements
- Longer-Duration Magnetic-Field Recordings
- Personal Exposure Measurements
- • Measurement of Geomagnetic Fields
- High-Frequency Electric Fields

Geomagnetic Field Data



Methods of Exposure Assessment

- Wire Codes
- Calculated Magnetic Fields
- Spot Magnetic-Field Measurements
- Longer-Duration Magnetic-Field Recordings
- Personal Exposure Measurements
- Measurement of Geomagnetic Fields
- • High-Frequency Electric Fields

Exposure Assessment For Epidemiology

- Exposure Measure Must Be Reduced To A One, Or Perhaps A Few, Numbers
- Exposure Will Likely Be Categorized

High Frequency Electric Fields

- Positron Meter Being Used In Canadian Study Of Childhood Leukemia
- Measures Fraction Of Time 5-20 MHz
Electric Field Is > 200 V/m

EMF Exposure Assessment Issues from the Occupational Studies

Jan Erik Deadman, McGill University, Montreal, Canada

Dr. Deadman reviewed exposure assessments from past occupational studies. Dr. Deadman's viewgraphs are as follows:

Recent Occupational Studies: Measurement of EMF Exposure

- Non electrical utility
 - Floderus, 1993 (gen. populat.)
 - Matanoski, 1993 (tel. workers)
 - London, 1994 (electr. workers)
- Electrical Utility
 - Sahl, 1993 (S. Cal. Edison)
 - Thériault, 1994 (Canada-France)
 - Loomis, 1994 (5-utilities)

Recent Occupational Studies: Exposure Assessment Issues

- Meters
 - E / B fields
 - frequency resp.
 - dynamic range
- Exposure indices
- Measurement strategies

Non Electric Utility Studies Meters		
Floderus	Matanoski	London
EMDEX 100/C interval: 1 sec	EMDEX C interval: 10 sec	EMDEX P/100/C interval: 2.5 sec
Non Electric Utility Studies Indices / Strategies		
Floderus	Matanoski	London
- subject/proxy -AM, MED, SD, P>.2 uT - no past recon. - 169 job categ. - 1015 wkr-days	- job title - AM, MED, PK, 95, P>32uT,SD,AASD,FLAC - partial - 9 job categ. - 204 wkr-days	- job title - AM, P>.25uT, P>2.5uT - past reconst. - 27 job categ. - 383 wkr-days
Electric Utility Studies Meters		
Sahl	Loomis	Thériault
EMDEX 2 B 40-400 Hz +/-3dB +/- 3 dB (0.1-300 µT) interval: 1.5 sec	AMEX 3-D B 30-1kHz +/-3 dB (0.2-15 µT) interval: shift	POSITRON B/E 50/60 Hz 40-400 Hz -9/-28 dB (.01-300 µT) (.3-15000 V/m) interval: 60 sec.

Electric Utility Studies Indices / Strategies		
Sahl	Loomis	Thériault
- job-title 770 days 16 JEM rows AM, GM Med, 95%, 99% F> .5, 1, 5, 10, 100 uT	job-title (rndm) 2196 days 28 JEM rows AM, GM	job-title (rndm) 2066 weeks EDF37 HQ32 OH17 rows AM, GM
Exposure Assessment Issues Meter Differences		
<ul style="list-style-type: none"> • Harmonics <ul style="list-style-type: none"> - EMDEX/AMEX include - POSITRON excludes • Dynamic range <ul style="list-style-type: none"> - EMDEX/POSITRON similar - AMEX upper limit (15 uT) - at HQ: 3% readings > 12.5uT • Meter comparisons <ul style="list-style-type: none"> - EMDEX vs AMEX (Kaune) - EMDEX vs POSITRON? 		
Exposure Assessment Issues - Exposure Indices		
<ul style="list-style-type: none"> • Savitz: indices correlated at < .8 - .9 not redundant • Little overlap of E&B indices <ul style="list-style-type: none"> - PM corr. HQ: r=.1 (AM), r=0.4 (GM) - Rank corr. Savitz r=.4 (AM), r=.3 (GM) - Rank corr. HQ: r=.4 (AM), r=.17 (GM) • Armstrong (1990) <ul style="list-style-type: none"> - AM and GM overall best choices • Sahl (1993) <ul style="list-style-type: none"> - also consider MED, F>.5µT, 1µT - F>.5µT, 1µT [corr. r=.5 (AM) .8 (GM)] • Savitz (1994) <ul style="list-style-type: none"> - AM/GM & lower threshold, eg: 20 V/m, 0.2µT 		

**Exposure Assessment Issues
Measurement Strategies**

- Sampling interval (Sahl):
 - compared 7 intervals (1.5-90s)
 - similar results for summary measures
 - time-dependent measures not analyzed
- Historical Adjustment: (HQ data)
 - 14 job. categ. differed in past
 - No diff. In ORS with/without past adj.

**Exposure Assessment Issues:
Job-Title / Individual Exposure Assignment**

- Average value from job title -> n-d misclassification
 - may distort exp-resp. Trend (Delpizzo)
- Combination of job-title and location
 - Guénel: EDF thermal plant workers
 - Wenzl: Uranium enrichment workers
 - Agnew: OH electric utility workers
- Floderus-style study designs
 - don't assume typical exposure for title
 - visits to worksite essential
- Determinants of variability (Kromhout)
 - increase contrast in exposure groups
 - increase homogeneity of groups

Diseases and Populations for Future EMF Studies
Richard Stevens, Pacific Northwest Laboratory

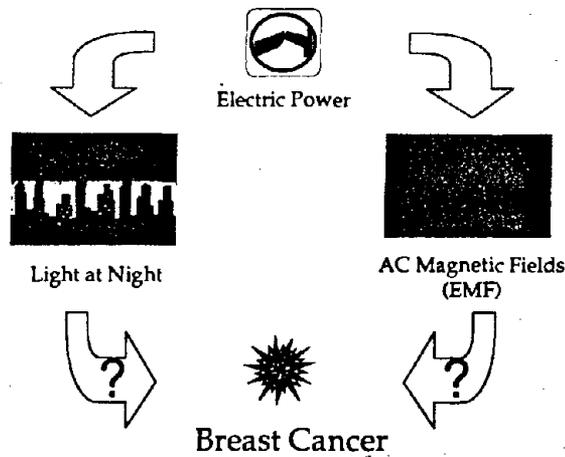
Dr. Stevens discussed diseases and populations, and study designs for testing etiological hypotheses, in future EMF studies.

Dr. Stevens viewgraphs are as follows:

Diseases and Populations for Future EMF Studies	
<ul style="list-style-type: none">• Biological Mechanisms<ul style="list-style-type: none">– oxidative stress - calcium– hormone rhythms - melatonin• Chronic Disease<ul style="list-style-type: none">– cancer - hormone related– other - e.g., Alzheimer's• General Settings<ul style="list-style-type: none">– experiments with "electric sensitive"– Swedish power-line population - breast cancer– buildings - role of lighting and EMF in performance and health	<ul style="list-style-type: none">• Occupational Settings<ul style="list-style-type: none">– women's work environments - new definitions– other exposures in "electrical work"– what do findings mean for common diseases?• Acute Disease<ul style="list-style-type: none">– "electric sensitive"– depression
Electric Sensitive	
<ul style="list-style-type: none">• Symptoms - often VDT users<ul style="list-style-type: none">– skin rash– headache– burning sensation– vertigo• Detection Experiments in Sweden<ul style="list-style-type: none">– 50 Hz at 20 mG– 30 to 120 seconds exposure over 30 minutes– subjects unable to detect field	

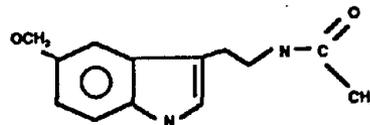
Depression

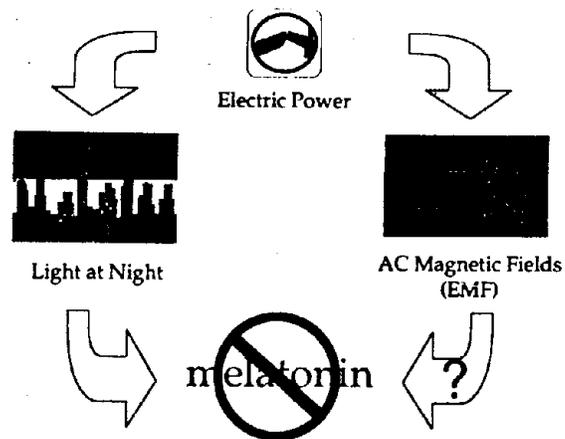
- Biological Rationale
 - disruption of Melatonin Rhythms
- Early Soviet Reports
 - suicide, depression
 - uncontrolled
- New Evidence
 - Poole et al. (AJE, 137:318, 1993)
- Important and Difficult



Melatonin

- Monoamine Hormone
 - pineal gland
 - strong daily rhythm
 - low during day
 - high at night
- Fights Breast Cancer?
 - inhibits breast cancer in rats
 - stops human breast cancer cells in culture
- Mood and Depression
 - Reproductive Physiology





Electric Power and Breast Cancer

- Sweden
 - Karolinska Institute
 - complete in late 1995
- Washington State
 - Davis & Stevens, FHCRC & Battelle
 - \$3M grant from the National Cancer Institute
 - complete in late 1996
- Many Others
 - e.g., breast cancer on Long Island; NCI/NIEHS
 - cellular & animal studies

Buildings and Health

Industrialized Societies:

most people work in buildings
~ all people sleep in buildings

- **Electric Power**
 - lighting effects on hormone rhythms
 - AC magnetic field effects on hormones

- **Buildings**
 - indoor light (flux density and spectral content)
 - electricity flow in buildings (magnetic fields)

LRC Study

- **LAN and Cognitive Performance**
 - ~ 10 male volunteers
 - shift work - midnight to 8 a.m.
 - four exposure conditions:
 - * constant 2,800 lux or constant 200 lux
 - * from 2,800 to 200 or from 200 to 2,800

- **Results**
 - 2,800 better than 200
 - decreasing similar to constant 2,800
 - increasing similar to 200

Questions

Are melatonin rhythms affected?
Does EMF play a role?

Implications

for standards: provide dimmable lighting
for operations: implement the dimming regime on night shift

Design Issues in Residential EMF Studies

Duncan C. Thomas, University of Southern California

Dr. Thomas discussed diseases and populations, and study designs for testing etiological hypotheses, in future EMF studies. Dr. Thomas's viewgraphs are as follows:

Design Issues in Residential EMF Studies

- What are the hypothesis?
- The VHCC question: efficient designs
 - Cohort studies versus case-control studies
 - Two-stage and alternative designs
- Practical issues
 - Past residences
 - What to measure, where, when, and how long?
 - Measurements vs. predictions
- Multicenter studies and meta-analysis
- Testing biological hypotheses
 - Laboratory → Epidemiology
 - Epidemiology → Laboratory

Hypotheses in Residential Studies

- Wiring is a surrogate for a causal effect of mean magnetic field
 - Associations with measured fields due to variability
- Wiring is a surrogate for a causal effect of other aspect of magnetic field
- Wiring is a surrogate for a non-EMF confounder
- The wiring association is an artifact of selection bias

**Testing the Wire Code Association
Cohort vs. Case-Control Approaches**

- Cohort Approach
 - Identify cohorts of subjects with VHCC and “control” residences
 - Look for cases and compare disease rates
 - Exposure measurements can be limited to cases and subset of cohort
 - Large cohorts and long follow-up required
 - Practical difficulties defining cohort and tracing, esp. migrants
- Case-Control Approach
 - Compare exposures between cases and “controls”
 - Population-based selection of cases and controls essential
 - Smaller sample sizes required
 - Further design efficiency by two-stage sampling

Two-Stage Design

(White E. et al, *Am J Epidemiol* 1982; 115: 119-28).

- Select potential cases and controls
- Obtain wiring configurations
- Subsample cases and controls based on wiring
- Obtain magnetic field measurements on subsample
- Use both samples in analysis

Counter-Matched Design

(Langholz and Clayton, *Environ Health Persp*, 1994)

- Select and wire-code potential subjects, as above
- Subsample cases based on wiring
- Mismatch cases to controls on wiring
 - e.g., match OHCC case to UG, VLCC, OLCC, VHCC controls
- Use control sampling fractions as offsets in matched analysis
- Great improvement in statistical efficiency can result

Quota Matched Design with Case Sampling

- If surrogate exposure is rare (e.g. VHCC wiring), retain all “exposed” cases and sample “unexposed” cases
- Select and wire-code potential controls, as above (first stage sample)
- Continue sampling controls until each matched set contains two “exposed” and two “unexposed” subjects
- Obtain magnetic field measurements on second stage sample only
- Use sampling fractions as offsets in logistic regression
- Efficiency gains due to
 - optimal distribution of exposure in cases
 - no uninformative case-control sets

Measurements Versus Predictions

- Rationale:
 - Predictions have shown stronger associations than measurements
 - Predictions are more stable than measurements
 - Only prediction models available are for mean field
- Predictions have Berkson rather than classical error structure
 - Hence, no attenuation of dose-response relationship
- Prediction model built on subsample with complete measurements
 - used to predict exposures for all houses
 - particularly useful for unmeasured past residences
- Two-stage designs ideal for this purpose
- Analysis must include both samples together and allow for uncertainties

Model for Predicting Magnetic Fields from Wiring Configurations
(Thomas, Bowman, *et al.*, *Bioelectromagnetics*, in press)

$$\begin{aligned} \hat{B}^2 = & \sum_f \left(\frac{1012}{D_f^2} \right)^2 && \text{transmission lines} \\ & + \sum_f \left(\frac{8.3 \times 8.2^{ph}}{D_f} \right)^2 && \text{overhead neutral primary lines} \\ & + \sum_f \left(\frac{140 \times 13^{ph}}{D_f^2} \right)^2 && \text{overhead non-neutral primary lines} \\ & + \sum_f \left(\frac{1.5 \times 14^{tw}}{D_f} \right)^2 && \text{overhead secondary lines} \\ & + (\sum_f \beta_f x_f)^2 && \text{ground current sources} \end{aligned}$$

ph = number of phases - 1
 tw = 1 if two-wire, 0 otherwise

Multi-Center Studies and Meta-Analysis

- Multiple centers with different exposure distributions can enhance power
- Essential to allow for center effects in analysis
- Multi-level analysis:
 - Between-center and between-individual comparisons
- More informative than meta-analysis

Some Lessons for Other Studies

- Consider efficient two-stage and multicenter designs
- Measurements
 - Need not be made on every house
 - But obtain at least surrogate information on as many as possible
 - Consider personal dosimetry with concurrent diaries
 - Measure as many EMF attributes as possible
 - Use to build exposure models
- Develop analysis strategy to make maximum use of all data

WORKING GROUP PRESENTATIONS

The following sections provide the presentation materials and summaries for each of the four working groups. For each working group, summaries of the presentations (including the speakers' viewgraphs) are presented first, followed by the group recorders' notes on the discussion and the group's summary.

Resonances Group 1

COORDINATOR: Joseph Bowman, NIOSH

CHAIR: Gerri Lee, California Department of Health

PRESENTATIONS:

Exposure Metric Combinations from the Ion Parametric Resonance Model
Janie P. Blanchard, Bechtel Corporation

Ion Magnetic Resonance and Quantum Coherence Mechanisms
Joseph Bowman, National Institute for Occupational Safety and Health

Some Mechanisms for the Interactions of Weak EMF with Biologic Materials
Frank Barnes, University of Colorado

REPORTER: William H. Bailey, Bailey Research Associates, Inc.

Introduction

Joseph Bowman, coordinator

Mechanisms which result in resonances have often been proposed to explain the frequent reports of "windows" in EMF biological effects (Postow and Swicord, 1986). This working group considered several kinds of resonance mechanisms. Drs. Blanchard and Bowman presented two variants of the ion resonance mechanisms originated by Liboff (1994) and Lednev (1994). A common feature of the ion magnetic resonances is their response to specific characteristics of the AC and DC magnetic fields, including the spatial orientation of the field vectors. Dr. Barnes presented three other resonance mechanisms: stochastic resonances, phase-locking, and adaptive processes with neural networks. A unifying theme in Dr. Barnes' presentation was the simulation of these three mechanisms by electric circuits with some supporting evidence from neurologic experiments.

References

- Lednev, V. V. 1994. "Interference with the Vibrational Energy Sublevels of Ions Bound in Calcium-Binding Proteins as the Basis for the Interaction of Weak Magnetic Fields with Biological Systems," In: Frey A. H. (ed.) *On the Nature of Electromagnetic Field Interactions with Biological Systems*, R.G. Landes, Austin, TX.
- Liboff, A. R. 1994. "The Electromagnetic Field as a Biological Variable," In: Frey A. H. (ed.), *On the Nature of Electromagnetic Field Interactions with Biological Systems*, R. G. Landes, Austin, TX.
- Postow, E., and M. L. Swicord 1996. "Modulated Fields and "Window" Effects," In: Polk C., Postow E. (eds.), *CRC Handbook of Biological Effects of Electromagnetic Fields*. 2nd ed. CRC Press, Boca Raton, FL.

Summary of Speakers' Presentations

William H. Bailey, Reporter

Exposure Metric Combinations from the Ion Parametric Resonance Model

Janie P. Blanchard, Bechtel Corporation

Dr. Blanchard described the ion parametric resonance model (IPR) that she and Dr. Blackman had developed based upon an earlier model proposed by Lednev and other Soviet investigators (Blanchard and Blackman, 1994). The model postulates that static magnetic fields split the energy levels of ions and that alternating magnetic fields of parallel orientation frequency modulate the energy levels. Specific resonance conditions are predicted by the frequency index $\eta = f_c/f_{ac}$ where $f_c = qB_{dc}/2\pi m$. The IPR model corrects mathematical errors in the Lednev model and extends the model to predict that the probability that an ion shifts to a different energy level near resonance is $p = K_1 + K_2 \cdot (-1)^\eta \cdot J_\eta(\eta \cdot 2 \cdot B_{ac}/B_{dc})$ for integer values of η . Otherwise, $p = K_1 + K_2$. Unlike other resonance models, this model predicts that biological responses will vary with the intensity of B_{ac} , and that increases and decreases in responses may occur. The relevant biological responses are assumed to be alterations in enzymatically controlled reactions where ions serve as cofactors.

The second part of Dr. Blanchard's presentation focused upon describing the results of tests of the ion parametric model. These tests involved exposing PC-12 cells incubated with nerve growth factor to specific combinations of alternating and static fields and observing the frequency of cells exhibiting neurite outgrowth. The output of the Bessel function J_1 for cells exposed to a 366 mG static field and 45 Hz magnetic field for variations in B_{ac} intensity from 200 to 468 mG (rms) provided rough estimates of the percent of cells showing neurite outgrowth. The agreement between predicted and experimental values was poorest for low B_{ac}/B_{dc}

ratios. In post hoc analyses, this agreement was improved considerably by assigning a special role to hydrogen ions as a trigger ions. When the static field was adjusted to 20 mG to produce an "off resonance" condition, similar variations in B_{ac} relative to B_c did not inhibit the percent of cells with neurite outgrowth. These experiments are summarized by Blackman et al. (1994) and Trillo et al. (1994).

Dr. Blanchard's viewgraphs are as follows:

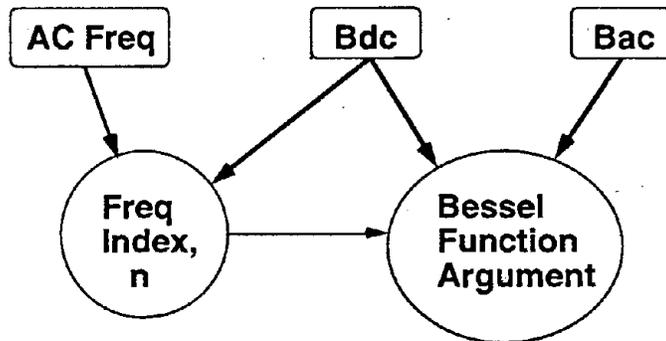
Key Parameters of IPR Model

with:	fac	Bac	Bdc
fac	non-specific resonance and response form	argument to selected Bessel function	selects frequency index, n, if at near resonance
Bac	argument to selected Bessel function	non-specific resonance	apparent argument to selected Bessel function
Bdc	selects frequency index, n, if at near resonance	apparent argument to selected Bessel function	non-specific response vs. control value

Key Parameters of IPR Model

with:	fac	Bac
Bac	argument to selected Bessel function	
Bdc	selects frequency index, n, if at near resonance	apparent argument to selected Bessel function

Key Parameters of IPR Model



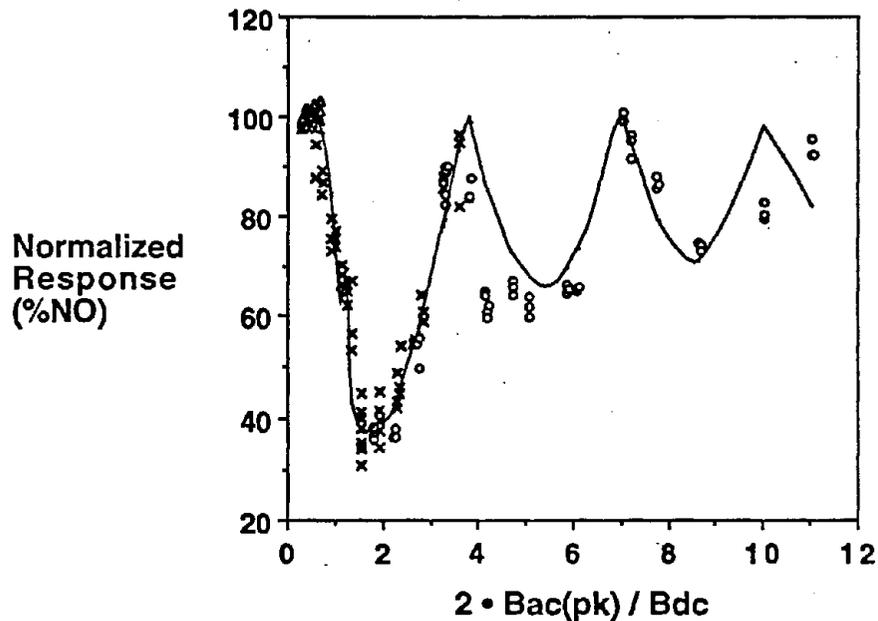
Critical Contributions of IPR Model

- Multiple Ion Resonances
- Corrected Bessel function argument
- Specific inclusion of $(-1)^n$ term
- Defines interrelationship of key exposure parameters

With PC-12 cell tests:

- Unique role of hydrogen
- Rectification of response function

Extended Tests of IPR Model



Experimental Support of IPR Model

First Cycle of Bessel function predictions:

Blackman, et al., "Empirical Test of an Ion Parametric Resonance Model for Magnetic Field Interactions with PC-12 Cells," *Bioelectromagnetics* 15, 239-260, 1994.

Single Ion Resonance, Independent Investigators:

Trillo et al., "Magnetic Fields at Resonant Conditions for the Hydrogen Ion affect Neurite Outgrowth in PC-12 Cells: A Test of the Ion Parametric Resonance Model," *Bioelectromagnetics*, 17:10-20, 1996.

Extended Tests, cycles 2 &3 of Bessel function predictions:

Blackman et al., "The Ion Parametric Resonance Model Predicts Magnetic Field Parameters that Affect Nerve Cells," *FASEB Journal*, 9:547-551, 1995.

References

Blackman, C. F., S. G. Benane, and D. E. House. "Evidence for Direct Effect of Magnetic Fields on Neurite Outgrowth," *FASEB Journal*, 7:801-806, 1993.

Blanchard, J. P., and C. F. Blackman. "Clarification and Application of Ion Parametric Resonance Model for Magnetic Field Interactions with Biological Systems," *Bioelectromagnetics*, 15:217-238, 1994.

Blackman C. F., J. P. Blanchard, S. G. Benane, and D. E. House. "Empirical Test of an Ion Parametric Resonance Model for Magnetic Field Interactions with PC-12 Cells," *Bioelectromagnetics*, 15:239-260, 1994.

Blanchard, J. P., D. E. House, and C. F. Blackman. "Evaluation of Whole Animal Data Using the Ion Parametric Resonance Model," *Bioelectromagnetics*, 16:211-215, 1995.

Blackman C. F., J. P. Blanchard, S. G. Benane, and D. E. House. "The Ion Parametric Resonance Model Predicts Magnetic Field Parameters That Affect Nerve Cells," *FASEB Journal*, 9:547-551, 1995.

Blackman, C. F., S. G. Benane, and D. E. House. "Frequency-Dependent Interference by Magnetic Fields of Nerve-Growth-Factor-Induced Neurite Outgrowth in PC-12 Cells," *Bioelectromagnetics*, 16:387-395, 1995.

Trillo, M. A., A. Ubeda, J. P. Blanchard, D. E. House, and C. F. Blackman. "Magnetic Fields at Resonant Conditions for the Hydrogen Ion Affect Neurite Outgrowth in PC-12 Cells: A Test of the Ion Parametric Resonance Model," *Bioelectromagnetics*, 17:10-20, 1996.

Blackman, C. F., J. P. Blanchard, S. G. Benane, and D. E. House. "Effects of AC and DC Magnetic Field Orientation on Nerve Cells," *Biochemical and Biophysical Research Communications*, 220:807-811, 1996.

Abstracts not yet published

Blanchard, J. P., et al. "Resonance Bandwidth Under IPR Model Exposure Conditions." *The 1994 Annual Review of Research on Biological Effects of Electric and Magnetic Fields from the Generation, Delivery, and Use of Electricity*, November 6-10, 1994, Albuquerque, NM. Also presented as Blackman, C. F., et al. "Experimental Confirmation of IPR Model Bandwidth Hypothesis." *Seventeenth Annual Meeting of the Bioelectromagnetics Society*, June 18-22, 1995, Boston, MA.

Blanchard, J. P., et al. "A Comparison of Theoretical Models for Magnetic Field Interactions with Biological Systems." *Seventeenth Annual Meeting of the Bioelectromagnetics Society*, June 18-22, 1995, Boston, MA.

Blackman, C. F., et al. "An Alternate Assay for Measuring IPR Model Validity." *The 1995 Annual Review of Research on Biological Effects of Electric and Magnetic Fields from the Generation, Delivery, and Use of Electricity*, November 12-16, 1995, Palm Springs, CA. Also presented as Blackman, C. F., et al. "Magnetic Field Alterations of Gap Junction Function." *Eighteenth Annual Meeting of the Bioelectromagnetics Society*, June 9-14, 1996, Victoria, B. C., Canada.

Blackman, C. F., et al. "Double-Blind, and Triple-Blind Tests of the IPR Model." *The 1995 Annual Review of Research on Biological Effects of Electric and Magnetic Fields from the Generation, Delivery, and Use of Electricity*, November 12-16, 1995, Palm Springs, CA. Also presented as Blackman, C. F., et al. "Blinding Procedures Verify Tests of Magnetic Field Influence on NGF-Stimulated Neurite Outgrowth in PC-12 Cells." *Eighteenth Annual Meeting of the Bioelectromagnetics Society*, June 9-14, 1996, Victoria, B. C., Canada.

Ion Magnetic Resonance and Quantum Coherence Mechanisms

Joseph Bowman, National Institute for Occupational Safety and Health

Dr. Bowman reviewed the empirical justification for considering models based upon the hypothesis that exposures involving magnetic resonance affect the interaction of ions with biological substrates. Each model specifies the direct interaction of a charged particle with angular momentum with combinations of static and oscillating magnetic fields. Three magnetic resonance models were reviewed: 1) cyclotron and parametric resonance models; 2) the 'ordinary' magnetic resonance model; and 3) quantum interference models. The ion cyclotron (Liboff, 1994) and parametric resonance (Lednev, 1994) models predict that magnetic fields will affect specific ions according to the formula $f = (q/m)B_0 / 2\pi$ where the static (DC) field B_0 is parallel to the oscillating (AC) field B_1 . These models differ, however, with regard to the locus at which hypothesized ion-substrate interactions occur and the magnetic field characteristics. The ion cyclotron resonance model describes resonance as affecting the energy and trajectory of ions passing through ion channels in cell membranes. Lednev's parametric resonance model predicts resonances in the binding of ions with proteins, thereby affecting their enzyme activity. Both the Lednev model and quantum coherence involve interactions among orbital energy levels which are split by B_0 (the Zeeman effect). The Lednev model is thus a form of quantum interference (see below).

'Ordinary' magnetic resonance effects are utilized in electron spin resonance (ESR), electron orbital motion (spectroscopy), and nuclear spin (NMR, MRI). They occur with perpendicular B_0 and B_1 magnetic fields. For these models, the resonance response peaks as a function of frequency or B_0 intensity and increases the energy of ions, radiation, and quantum coherence. The resonant frequency is determined by the gyromagnetic equation: $2\pi f_0 = n\gamma B_0$, where $\gamma = q/2m$ and $n =$ the harmonic number. Models based upon quantum coherence, i.e. the alignment of magnetic moments, have recently found application in lasers, nanotesla magnetometers, control of chemical reactions, and quantum optics.

Dr. Bowman reviewed the theoretical difficulties and the empirical justification for considering that magnetic resonance models could affect biological substrates. Data from *in vitro* systems (marine diatoms, lymphocytes, enzyme activity, cell proliferation), *in vivo* systems (animal conditioning), and epidemiology (analysis of exposures of leukemia cases and controls in Los Angeles by Bowman *et al*, 1995) have been interpreted according to various resonance models. However, the key laboratory findings have not been replicated and the responses are only indirectly associated with the cancers under investigation by epidemiologic methods.

The major part of Dr. Bowman's presentation focused on his Quantum Coherence Model. In this model, a static magnetic field splits energy levels of ions in excited triplet states (Zeeman effect) while a perpendicular alternating magnetic fields create quantum coherences among the energy levels leading to increased population trapping in excited energy states. This is postulated to lead to an increased probability that ions bound to protein complexes like calmodulin will dissociate. A drawback of this model is that it requires a second coherent energy source.

Dr. Bowman also briefly described exposure assessment strategies for resonant conditions and his use of a Multiwave™ System II portable waveform analyzer to monitor resonance yields predicted by the ion parametric model (Bowman and Engel, 1994; Bowman, 1996).

References

Bowman, J. D. "Pilot Measurements of Ion Magnetic Resonances in Workplaces," Abstract, *Bioelectromagnetics Society Annual Meeting*, Victoria, British Columbia, 1996.

Bowman, J. D., and D. P. Engel. "A Magnetic Resonance Monitor," Abstract, *Bioelectromagnetics Society Annual Meeting*, Copenhagen, 1994.

Bowman, J. D., D. C. Thomas, S. J. London, and J. M. Peters. "Hypothesis: The Risk of Childhood Leukemia May be Related to Combinations of Power-Frequency and Static Magnetic Fields," *Bioelectromagnetics*, 16:48-59, 1995.

Engström, and J. D. Bowman. "Resonances From General Magnetic Fields--A Progress Report," Abstract, *Bioelectromagnetics Society Annual Meeting*, Boston, 1995.

Ionic Magnetic Resonance and Quantum Coherence Mechanisms

by Joseph D. Bowman, NIOSH

ABSTRACT

Resonance from the combination of static and ELF magnetic fields with ions in biological complexes is proposed as a mechanism to account for EMF's reported health effects. Magnetic resonance mechanisms have been considered because of biological experiments which have resonance-like results. Magnetic resonances can produce coherence among a molecule's quantum states, which can affect the course of chemical reactions. In the proposed mechanism, quantum coherence produced by magnetic resonance may be altering the binding of ions to proteins. From this magnetic resonance mechanism, exposure metrics have been derived. Exposure to these resonance metrics can be measured with wave-capture instruments which measure the static and ELF field in three orthogonal directions. Therefore, the magnetic resonance hypothesis can be tested in epidemiologic studies.

OUTLINE

- I. Purpose
 - A. To review ion magnetic resonance mechanisms and the empirical evidence which suggests they might be happening in biological systems.
 - B. To propose the quantum coherence mechanism, a more plausible way for ion resonances to affect biological processes
 - C. To discuss the status of the theory needed to derive quantum coherence metrics and mention an instrument for measuring exposures to ion resonance metrics
- II. Review of magnetic resonance
 - A. Magnetic resonances are due to the direct interaction of a magnetic moment (*e.g.* a charged particle with angular momentum) with the combined static and oscillating magnetic field
 - B. Resonances are found with many magnetic moments -- electron spin (ESR), electron orbital motion (the Zeeman effect in spectroscopy), nuclear spin (NMR and MRI), etc.
 - C. Properties of "ordinary" magnetic resonances:
 1. Resonances obey the gyromagnetic equation: $2\pi f_0 = \gamma B_0$
 2. γ = gyromagnetic ratio = $q/2m$ for orbital angular momentum
 3. B_1 (oscillating field) is perpendicular to B_0 (static field)
 4. B_1 is circularly polarized with plus helicity in the simplest case
 5. Observable results:

- a. increased energy
 - b. radiation
 - c. quantum coherence
6. Lorentzian response with frequency (or B_0)
- D. Properties of parametric resonances:
- 1. The same gyromagnetic equation with $\gamma = q/m$
 - 2. B_1 is parallel to B_0
 - 3. Response with B_0 is a delta-function
- III. Empirical justification for considering magnetic resonance mechanisms in biological systems
- A. narrowband phenomena \implies resonance
 - B. gyromagnetic equation $2\pi f_0 = n(q/m)B_0 \implies$ magnetic resonances with ions
 - C. fit to Bessel function \implies ion parametric resonance (IPR) \implies quantum coherence mechanism
 - D. association of a resonance metric with childhood leukemia \implies hypothetical link to cancer [Bowman *et al.*, 1995]
- IV. Critique of magnetic resonance hypotheses
- A. problems with the experimental base
 - 1. key findings are not replicated
 - 2. resonances from perpendicular B_1 reported only for calcium efflux
 - 3. no direct association with disease outcomes
 - 4. too many reported resonances for an epidemiological test
 - 5. mechanism doesn't explain all the biological effects observed
 - B. implausibilities in the mechanism
 - 1. 1-10 Hz bandwidth from experiments incompatible with thermal noise
 - 2. problems with the theory of ion parametric resonance
 - a. response with frequency is a delta function (unrealistic)
 - b. IPR requires quantum coherence
 - c. IPR's effect might be seen spectroscopically, but its impact on biochemistry is unclear
- V. Hypothesis: These biological effects may be caused by quantum coherence mechanisms due to magnetic resonances with ions in a biological substrate
- A. Definition of quantum coherence
 - 1. The excited quantum states of many target ions in a cell are "in phase"
 - 2. Different from temporal coherence in the Litovitz mechanism
 - B. Applications of quantum coherence in other systems
 - 1. lasers
 - 2. nanotesla magnetometer (at room temperature)
 - 3. coherent population trapping in atomic gases
 - 4. guiding chemical reactions ("coherence chemistry")
- VI. Proposed mechanism
- A. Ion in a protein complex, *e.g.* calmodulin
 - B. If the ion's binding site has sufficient symmetry (tetrahedral or octahedral), some of the ion's excited states will have 3-fold degeneracy. This fulfills the selection rule for magnetic resonance.
 - C. B_0 splits the 3 energy levels of the excited state, *i.e.* the Zeeman effect.
 - D. The oscillating magnetic field creates quantum coherence among these states
 - E. If there is a second coherent energy source, then there can be coherent population trapping in the excited state.

- F. Increased population in the excited state leads to an increased rate of dissociation of the ion from the protein complex.
- VII. Metric for magnetic resonance exposures [Bowman and Engel, 1994]
- A. Gyromagnetic filter to select the resonant harmonic
 - B. Spatial analyzer to get parallel and circularly-polarized perpendicular components of B_1
 - C. Resonance analyzer to get measure of response (*e.g.* dissociation rate)
 - Note: This metric has been derived only for 2-state systems in simple magnetic field exposures. Derivation of the metric for 3-state systems in arbitrary magnetic fields is still in progress. [Engström and Bowman, 1995]
- VIII. Exposure assessment strategy [Bowman and Engel, 1994]
- A. 3D AC/DC probes, *e.g.* 3D flux gate magnetometer for residences and many occupational environments
 - B. Digital waveform capture (stored for future analysis)
 - C. Fast Fourier Transform (both magnitude *and phase* spectra)
 - D. Calculation of resonance metrics (including metric for IPR)
 - E. Pilot measurements of resonance metrics have been taken with the Multiwave II in workplaces [Bowman, 1996]
 - F. Due to the Multiwave's bulk, only body zone measurements are possible now.
- IX. Discussion
- A. Problems with mechanism
 - 1. quantum coherences are generally quenched in condensed media
 - 2. what could be the second coherent energy source in a biological system??
 - B. Exposures for quantum coherence are different from IPR:
 - 1. $\gamma = q/m$
 - 2. B_1 parallel to B_0
 - 3. IPR response to B_1 is a Bessel function
- X. Conclusions
- A. The quantum coherence mechanism addresses some of the theoretical deficiencies with ion magnetic resonances in biologic systems, but others remain.
 - B. Quantum coherence explains some laboratory results, but it has not been really tested.
 - C. Quantum coherence and parametric resonance are different manifestations of Lednev's mechanism of an ion in a symmetric biological complex
 - D. An exposure metric for ion quantum coherence can be derived, but it will be a lengthy calculation, especially for environmental fields.
 - E. With theoretical metrics, the quantum coherence mechanism can be tested in epidemiologic studies.
 - 1. the Multiwave II can measure magnetic resonance conditions in many environments
 - 2. stored waveforms can be reanalyzed as knowledge of resonance metrics is refined

Dr. Bowman's viewgraphs are as follows:

Ionic Magnetic Resonance and Quantum Coherence Mechanisms

Joseph D. Bowman, NIOSH

Acknowledgments

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Prof. James Guinn (Berea College)

Craig Chafin (University of Cincinnati)

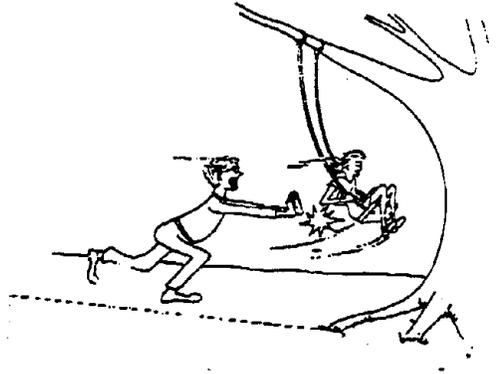
Daniel P. Engel (NIOSH)

Outline

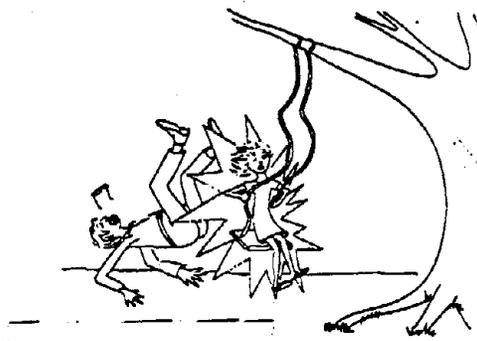
- * Review of magnetic resonance
- * Biological evidence for magnetic resonances
- * Proposed mechanism
- * Exposure metrics
- *****
- * Measuring magnetic resonance exposures

Resonance

Transfer of energy from one oscillating system to another -- *IEEE Dictionary*



Oscillators In Resonance

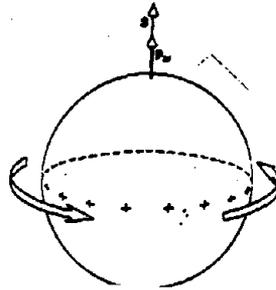


Out of Resonance

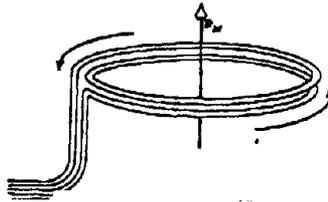
Macomber, *The Dynamics of Spectroscopic Transitions*

Magnetic Moments

Spinning charged sphere



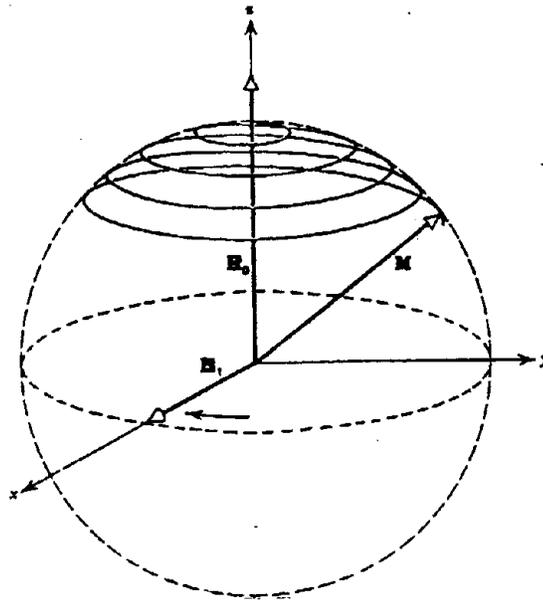
Current in a wire coil



Charged particle in orbit

$$\text{Magnetic Moment} = \left(\frac{q}{2m} \right) \text{Angular Momentum}$$

Magnetic Resonance



- B_0 = static magnetic field
- B_1 = oscillating magnetic field
- M = magnetic moment

Features of Magnetic Resonance

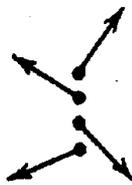
- * seen with many magnetic moments
 - electron spin (ESR)
 - nuclear spin (NMR and MRI)
 - electron & nuclear orbits
- * B_1 is perpendicular to B_0
- * B_1 is circularly polarized with plus helicity
- * response peaks as a function of frequency or B_0
- * resonant frequency f_0 given by the gyromagnetic equation:

$$h \nu = \gamma \hbar B_0$$

- * observable effects:
 - increased energy
 - radiation
 - quantum coherence

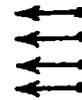
Quantum Coherence

Thermal distribution
of magnetic moments



Coherence

Magnetic
resonance



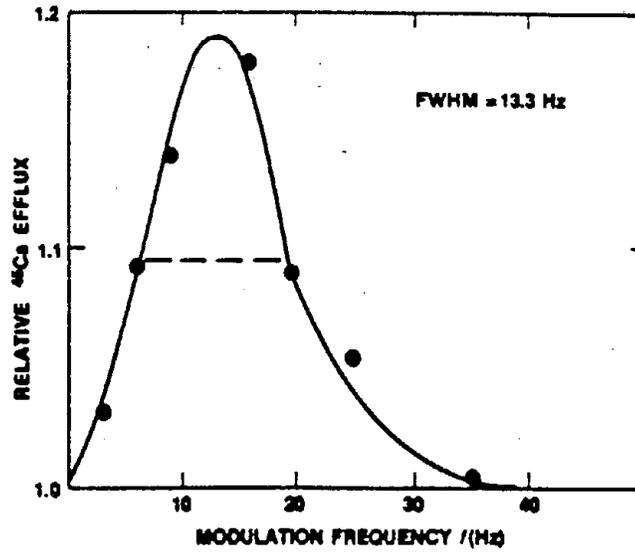
Effects of Quantum Coherence

- * lasers
- * a picogauss magnetometer
(at room temperature)
- * control of chemical reactions
- * coherent population trapping

Empirical Evidence for Magnetic Resonance Mechanisms

Calcium efflux	Blackman <i>et al.</i> , 1985, 1988
Rat conditioning	Thomas <i>et al.</i> , 1986
Diatom mobility	Smith <i>et al.</i> , 1987
Lymphocyte uptake of Ca ²⁺	Liboff <i>et al.</i> , 1987 Yost and Liburdy, 1992
Calmodulin reaction	Shuvalova <i>et al.</i> , 1991
Lymphoma proliferation	Liboff <i>et al.</i> , 1993
Neurite outgrowth	Blackman <i>et al.</i> , 1994
Childhood leukemia	Bowman <i>et al.</i> , 1995

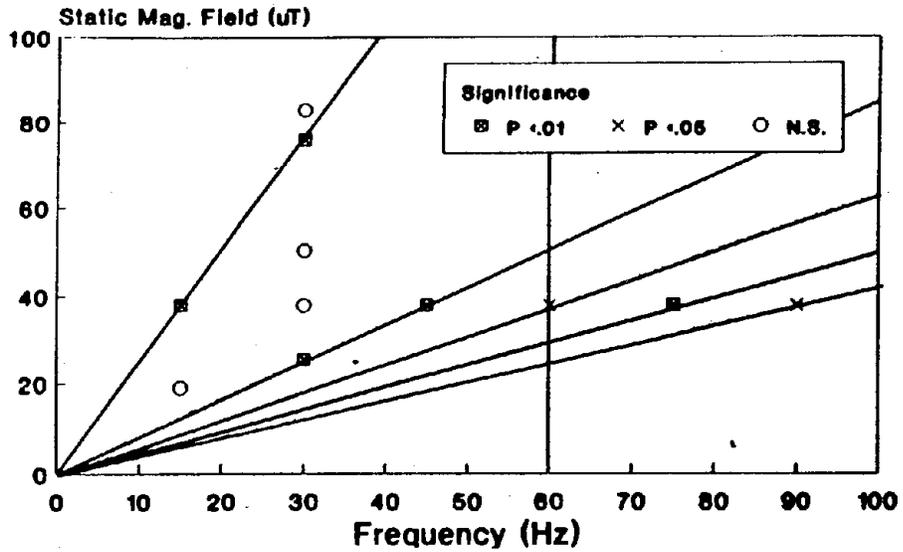
Narrow-band Phenomena
 Example: Lymphocyte uptake of calcium Liboff *et al.* (1987)



Suggest Resonances

Linearity between Static Field and Frequency

Example: Calcium efflux (Blackman *et al.*, 1985, 1987)



Suggests the gyromagnetic equation of magnetic resonance
 $n 2 \pi f_0 = \gamma B_0$

Experimental gyromagnetic ratio \approx Charge-mass ratio for biologic ion

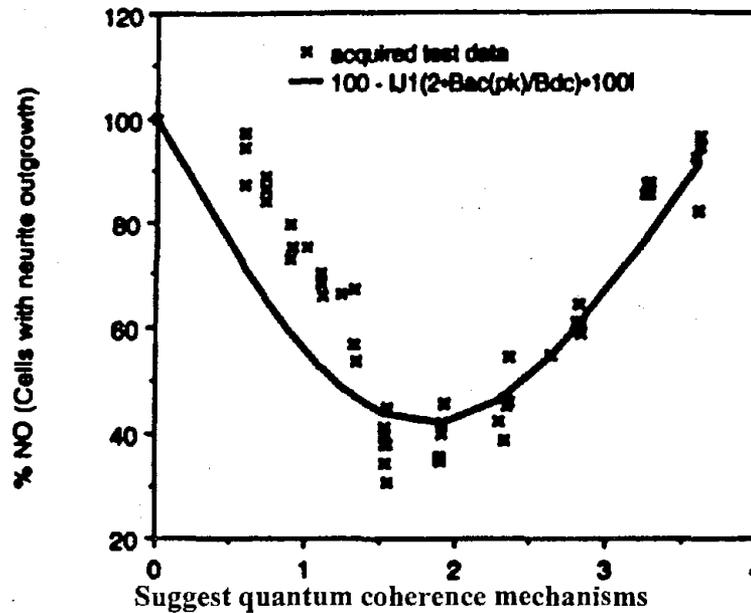
Biological response	Experimental γ (Hz/T x 10^{-6})	Ion	Charge-mass ratio (Coul/kg x 10^{-6})*
Diatom mobility	4.81	Ca ²⁺	4.81
⁴⁵ Ca ²⁺ uptake by lymphocytes	4.29	⁴⁵ Ca ²⁺	4.29
Calcium efflux <i>perpendicular</i> <i>field orientation</i>	2.48	K ⁺	q/m = 2.47
		Ca ²⁺	q/2m = 2.40

*Note: Hz/T = Coul/kg

Suggests resonance with the magnetic moment
due to ion's orbital motion

Bessel Function Responses

Example: Neurite outgrowths
Blackman *et al.* (1995)



**Risk of Childhood Leukemia in Los Angeles County
with an Empirical Resonance Metric for 60 Hz**

Static magnetic field:	Out of resonance	In resonance
ELF magnetic field (μT):		
< 0.07	OR = 1.0	0.5 (0.2 - 1.4)
0.07 - 0.14	0.1 (0.0 - 0.4)	0.7 (0.2 - 2.4)
0.14 - 0.30	0.4 (0.1 - 1.2)	2.3 (0.4 - 12.4)
> 0.30	0.8 (0.2 - 3.0)	3.3 (0.4 - 30.5)
P (test for trend)	0.300	0.041

Reference: Bowman *et al.* (in press)

suggests that ion magnetic resonances are linked to cancer

Problems with the Laboratory Evidence

- * key findings not fully replicated
- * resonances from perpendicular B_1 reported only for calcium efflux
- * only indirect association with diseases
- * too many reported resonances for an epidemiological test

Theoretical Problems with Magnetic Resonance

General criticisms:

- * ELF resonances are destroyed by thermal vibrations
- * Energy from ion magnetic resonance is too small to affect biochemistry

Criticisms of IPR:

- * Requires quantum coherence*
- * Has no observable effect in biology*
- * No clear relation to biochemistry
- * Quantum effects quenched in fluids and solids

* R. Adair (1992)

Hypothesis

Biological effects due to specific combinations
of static and oscillating magnetic fields
may be caused by quantum coherence mechanisms
initiated by magnetic resonances
with ions in a biological complex.

Proposed Mechanism

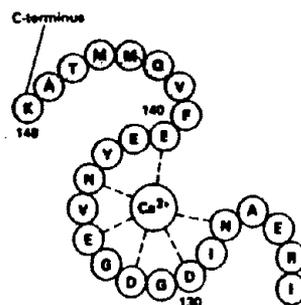
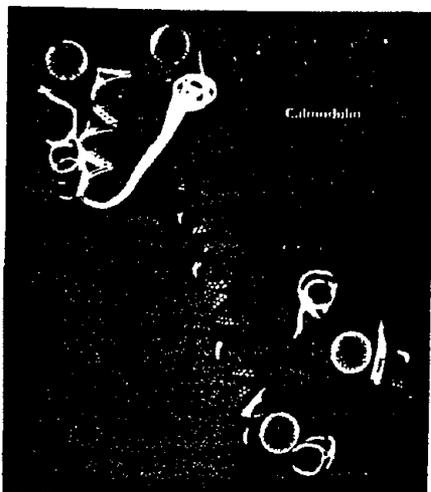
- * the target is an ion in a protein complex
- * protein symmetry gives a triplet excited state
- * B_0 splits the triplet (Zeeman effect)
- * resonant B_1 creates quantum coherence
- * *if there is a second coherent energy source, population can be trapped in the excited states*
- * increased population in the excited states leads to changes in the dissociation rate
- * ion binding affects protein conformation
- * systematic changes in the protein affects its enzymatic role

(Vertical bars indicate Lednev's mechanism)

Quantum Coherence Mechanism

1. The target is an ion in a protein complex.

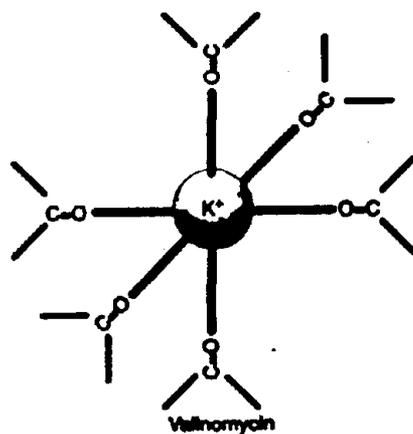
Example: calcium-calmodulin



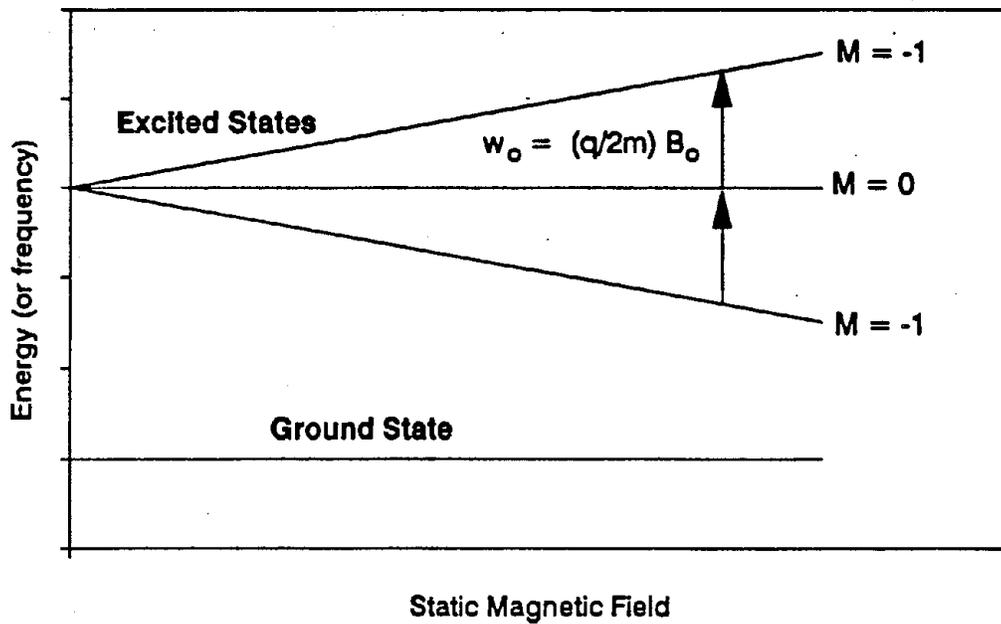
Quantum Coherence Mechanism

2. Protein has enough symmetry for a triplet excited state.

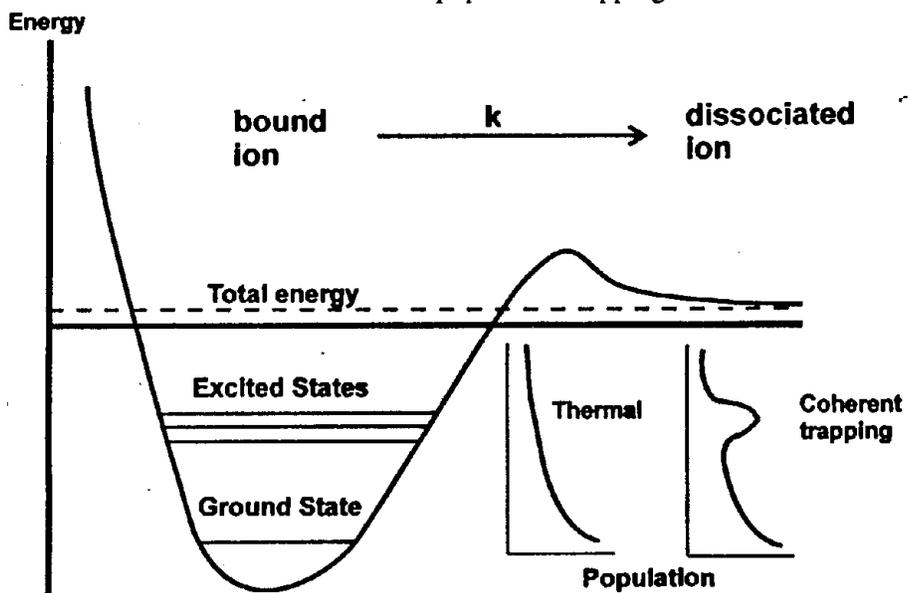
Example: valinomycin with octahedral symmetry



Quantum Coherence Mechanism
 3. Zeeman effect splits the triplet



Quantum Coherence Mechanism
 4. Coherent population trapping



Conclusions on Quantum Coherence Mechanisms

- * Theory deficiencies: some addressed, but others remain:
 - thermal noise
 - second coherent energy source
- * Explains some laboratory results, but not really tested.
- * Magnetic and parametric resonance are different manifestations of the same mechanism.
- * An exposure metric can be derived, but it will be a lengthy calculation, especially for environmental fields.
- * With the metric, the quantum coherence exposures can be measured for epidemiologic studies.

Stochastic Resonance and Phase-Locking Models

Frank Barnes, University of Colorado

This presentation discussed three models that might be applicable to understanding how alternating magnetic fields affect biological systems. They are termed stochastic resonance, phase-locking, and adaptive process models. They describe the response of simple physical systems whose output can be strongly influenced by periodic stimuli at levels significantly below thermal noise levels. The stochastic models are patterned after R-L-C electrical circuits. In addition, there are other examples where the information content of weak signals in non-linear systems can be facilitated by the presence of noise. The phase-locking model is based upon observations that periodic injections of small 0.2 nA currents into *Aplysia* pacemaker cells (Wachtel) can entrain the oscillatory firing of the cells. When part of a feedback loop, such signals can modulate the behavior of cells at S/N ratios less than 1. A biological model of adaptive processes might involve reductions in gap junction resistance or the release of neurotransmitters. Such adaptive processes can be modeled by simple neural network models that can be 'trained' to discriminate signals from noise after many repetitions of the signal even for S/N ratios $\ll 1$.

Recent references

Barnes, F. S. "Interaction of DC and ELF Electric Fields With Biologic Materials and Systems." In: Polk C., Postow E. (eds.), *CRC Handbook of Biological Effects of Electromagnetic Fields*. (Second edition) CRC Press, Boca Raton, FL, 1996.

Pickard, W. F. "Trivial Influences: A Doubly Stochastic Poisson Process Permits the Detection of Arbitrarily Small Electromagnetic Signals." *Bioelectromagnetics*, 16:2-8, 1995.

Pickard, W. F., R. K. Adair, D. J. Welling, J. R. Urani, and A. R. Sheppard. "Comments on "Trivial Influences: A Doubly Stochastic Poisson Process Permits the Detection of Arbitrarily Small Electromagnetic Signals" and the Author's Reply." *Bioelectromagnetics*, 16:9-19, 1995.

Dr. Barnes' viewgraphs are as follows:

**Some Mechanisms for the Interactions of Weak Electric
and Magnetic Fields with Biological Materials**

Outline

1. Stochastic Resonances
2. Parametric Processes
3. Injection Locking
4. Adaptive Processes

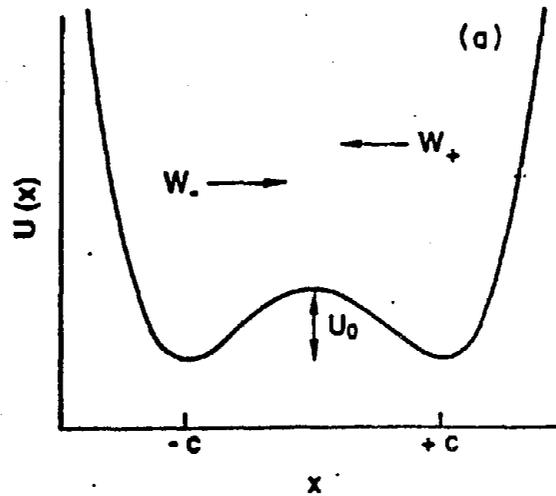
Common Features

1. Nonlinear
2. Gain
3. Coherent or Repetitive Signals
4. Operate with Signal Noise at the input less than one

**Introduction
The Nature of the Problem**

1. We need to look at the size and complexity of the system
 - A. Fluids, Ions, Molecules
 - B. Fluids Plus Membranes
 - C. Cells
 - D. Organs
 - E. Whole Body
2. Time Scales
 - A. Excited State Life Times 10^{-12} -- 10^{-3} sec
 - B. Membrane Transit Times $> 10^{-6}$ sec
 - C. $RC = \tau = 10^{-3}$ sec
 - D. Cell Adaptive Processes Seconds
 - E. Cell Growth Times - Hours, Days
 - F. Health Effects - Genetic Effects
3. Likely Chains of Events
 - A. Force Applied
 - B. Change in Current Flow
 - C. Change in Chemical Reaction Rate or Membrane Binding
 - D. Enhancement or Inhibition of Cell Function

1. Assume bistable system with a potential well



Parametric Processes

1. A means of using nonlinearities to transform energy from one frequency to another.
2. Hypothesis is that 60Hz is not a magically bad number for biological systems.
3. We need to discriminate against larger noise in the same general frequency band.

Injection Locking

1. Postulate. The maximum sensitivity of a biological system occurs at frequencies where the cells can amplify electrochemical signals.
2. For Pacemaker Cells, this occurs near the natural frequency of oscillation and can be measured by determining the minimum signal for injection locking.

Basic Assumptions

- There are experimental observed levels which are dangerous.
- There are levels which may or may not cause biological effects.
- There are levels which are below the natural background or below the level of natural fluctuations. The background level is assumed to be the lowest level which can cause significant biological effects.
- The significance of an electric field, or current can depend on its location in the biological subject, its direction, its frequency, and the length of the exposure.

Discussion

The Group discussed the difficulties in taking the theories under discussion and applying them to the collection of data for epidemiological studies in residential or occupational environments. The greatest problems arose in specifying how attributes or characteristics of magnetic fields* were to be measured in operational terms. For example, it was pointed out that the theories were not sufficiently comprehensive to determine, for instance, over what length of time or how frequently were measurements to be taken. The Group was interested in the observations made by Dr. Litovitz that indicated that uninterrupted (temporally coherent) exposures might be necessary for biological systems to respond to magnetic fields. The deliberations of the Group are summarized in relation to the following key questions.

What theories should be tested?

Of the three kinds of models considered, the Group was most interested in seeing the ion resonance models pursued further. This interest was based upon the relatively comprehensive, yet specific, predictions that could be made and consideration of preliminary experimental reports that interactions of alternating and static (AC and DC) magnetic fields could affect biological systems under some conditions. It was felt that further theoretical and empirical development of the stochastic and phase-locking theories was required. However, even for IPR model that was judged to be the most developed of the theories considered by the Group, it was not considered ready to be tested in an epidemiology study.

*It was pointed out that some of the proposed mechanisms might be affected by electric fields too, but the discussion focused almost entirely on exposures to alternating and static magnetic fields.

What is required to apply biologically-based theories to exposure assessment?

Before implementing any of these theories in any full-scale epidemiology study, more data from three kinds of research will be required. They are theoretical improvements, laboratory tests, and surveys of exposure conditions in residential and occupational environments.

What is the objective of proposed measurement programs?

The objective of the exposure assessment process is to capture enough information to identify resonance conditions in the environment. This objective was based on the assumption that specific AC and DC magnetic field combinations may affect interaction of ions with biological substrates in ways that might influence health and disease processes.

What measurements should be taken to test theory?

There was general agreement that the technology was available to measure any conceivably relevant exposure parameter if cost and time were not limiting factors. The Group felt that the key issue was to narrow down the list of possible attributes so that meaningful surveys and exposure assessment strategies could be developed. Because both the IPR and Quantum Coherence models required similar kinds of measurements, it was felt that any field measurements should be capable of addressing both theories. Table 1 summarizes the attributes of exposures that need to be measured and the Group's estimates of the required tolerances for these measurements. From an epidemiological perspective, the goal would be to obtain measurements that characterize the exposures of individuals rather than just locations. The Group discussed the desirability of assessing exposure conditions both in homes and in work places.

How can the measurements be made in a time and cost effective manner, given the constraints imposed by application in epidemiology studies to large dispersed populations?

The Group did not make much progress in answering this question. However, the Resonance Monitor developed by Dr. Bowman did seem to offer the potential to develop portable monitors to obtain information on both static and alternating fields to test resonance theories under field conditions. One major problem is the tremendous amount of data that must be analyzed and stored. Storage of all measured data with off-site processing is one possibility that was considered. Also promising is the approach used by Bowman to analyze data on-the-fly and store only the resonance metrics.

Table 1. Exposure Attributes and Measurement Tolerances

Attribute	IPR	Quantum Coherence	Stochastic Resonance	Phase-Locking Mechanisms	Adaptive Processes
AC Magnetic Field	<5 G	>0.2 mG	<1 G	x ±10%	x ±10%
DC Magnetic Field	√	√	—	—	—
Frequency	3 kHz	3 kHz	<100Hz	√	±10%
Orientation	±10%	±10%	±10-20%	±10%	—
Time Scale	?	?	10-30 sec	≥30 sec	hours
Phase	√	√	—	x ± 0%	—
Sampling Interval	10 sec	0.10 sec	—	—	—
Data Capture Rate	8 kHz	8 kHz	—	—	—

KEY: √ = measurement required
 x ± 10% = measurement required to specified tolerance

Recommendations

The Group discussed two resonance models, and several models based upon electrical engineering and neurobiology concepts. The recommendations regarding these models were:

1. Resonance Models

The Ion Parametric Model and the Quantum Coherence Model were favored by the Group because these models were fairly well developed and were compatible with some laboratory data (albeit unreplicated). The Group concluded that further laboratory, theoretical, and exposure assessment research is needed to refine the models and develop supporting data before resonance exposure metrics are employed in epidemiological studies. This research should include:

- a. Laboratory studies to assess how changes in the interactions of biological ions with substrates might relate to specific diseases, e.g. cancers;
- b. Exposures surveys of residential and occupational environments to identify combinations of AC and DC magnetic fields that meet resonance criteria;
- c. Exposure surveys to identify residential and occupational settings that differ in the prevalence of 'resonance-on' and 'resonance-off' conditions; and
- d. Testing of a Magnetic Resonance Monitor, or similar device, in appropriate environments to define the minimum data collection needed to construct reliable and manageable resonance exposure metrics.

2. Electrical Circuit/Neurobiology Models

Several innovative models were discussed by the Group that were theoretically capable of

detecting signals at signal/noise ratios < 1 . The focus of these models is on hypothesized characteristics of a biological mechanism. No particular exposure metrics are prescribed by these except that the exposure be repetitive. The Group judged these models as not being sufficiently well developed to be considered as a basis for constructing exposure metrics.

Coherence and Intermittency

Group 2

COORDINATOR: Gregory Lotz, NIOSH

CHAIR: Gene Sobel, University of Southern California Medical School

PRESENTATIONS:

The Coherence Model

Theodore Litovitz, Catholic University

The Kinetic Model

Charles Montrose, Catholic University

Chronobiological Considerations

Ken Groh, Argonne National Laboratory

REPORTER: Asher Sheppard, Asher Sheppard Consulting

Introduction

Gregory Lotz, coordinator

The temporal pattern of EMF exposures has affected laboratory studies on biological outcomes such as ornithine decarboxylase (ODC), messenger RNA transcription, and cancer promotion. These investigations have reported that intermittent exposures or time "windows" of exposure could have a stronger biological impact than continuous exposures of the same magnitude.

To explain such phenomena, Litovitz, Montrose and co-workers published in 1991 their "kinetic hypothesis." This mechanism was the subject of the Case Study presented at the Workshop's opening plenary session because it had been tested in an epidemiologic study. Since then, Litovitz and colleagues at Catholic University of America have developed the concept that temporal coherence or constancy of exposure is a key to biological responses. At the same time, Groh and co-workers at Argonne National Laboratory have been performing experimental investigations of chronobiological mechanisms. The working group considered which of these mechanisms were sufficiently developed to be the basis for exposure measurements in future epidemiologic studies. In this group, the discussion on both days also dealt with the parameters that would need to be measured in field studies to address these temporal characteristics of exposure, as well as the engineering feasibility to make such measurements, and the practical constraints of experimental design in collecting that data.

Working Group Report

Asher R. Sheppard, Reporter

The working group on coherence and intermittency was chaired by Eugene Sobel, Ph.D., Professor, Department of Preventative Medicine, USC Medical School, Los Angeles, California. The group was coordinated by W. Gregory Lotz, Ph.D., Chief, Physical Agents Effects Branch, NIOSH, Cincinnati, Ohio.

Following a brief introduction by the chairman, the working group heard three presentations of models to describe biological responses to electric and magnetic field (EMF) exposures. Two of the presentations concerned a physico-chemical model based on the postulate that EMFs affect chemical rate constants. The third paper discussed alteration of chronobiological rhythms in EMF-exposed animals and the perspective in which such changes may be fundamental biological response to EMF exposure.

The presentations were "The Coherence Model" by Theodore Litovitz, Ph.D., Professor, Physics Department, Catholic University, Washington, DC; "The Kinetic Hypothesis," by Charles Montrose, Ph.D., Professor, Physics Department, Catholic University, Washington, DC; and "Chronobiological Considerations," by Kenneth Groh, Ph.D., Assistant Biologist, Argonne National Laboratory, Argonne, Illinois. During each presentation and after the set of three presentations the group engaged in critical discussions for the purpose of evaluating each model's predictions about the temporal and amplitude properties of biologically active EMFs.

Summary of Speakers' Presentations

Sobel introduced the working group session with the observation that, in addition to cancer, epidemiologic studies now indicate that other diseases were also potentially associated with exposures to ELF fields. The combined results of four studies by Sobel and his colleagues indicated that the risk of Alzheimer's disease is about 3 to 4 times greater among persons occupationally exposed to elevated levels of power frequency EMFs. Amyotrophic lateral sclerosis was associated with EMF exposures in one small study. In relation to Alzheimer's Disease, Sobel indicated that one of the biochemical pathways by which beta amyloid protein is synthesized was calcium dependent, thereby suggesting a possible linkage to the body of laboratory research that indicates an EMF effect on calcium in tissues and cells.

The Coherence Model,

Theodore Litovitz, Ph.D., Catholic University

Litovitz discussed a body of data obtained from various laboratory studies, many of which involved measurements of the activity of the enzyme ornithine decarboxylase (ODC) in cells grown in culture. Material presented to the whole workshop was directly relevant to the discussion group as well. From experiments on "coherence properties" of the applied waveform, Litovitz drew the conclusion that events spanning a period of approximately ten seconds were important to the fundamental transduction step. Laboratory data from in vitro studies showed that the increase in ODC activity did not occur if the frequency, phase, or amplitude of the applied field was altered more often than about once every ten seconds. This result occurred even in the case where the only alteration was a shift of frequency from 55 to 65 Hz and even though both 55 and 65 Hz were each effective in changing ODC activity if the field was left on without interruption. In various experiments both ELF magnetic fields and ELF-modulated radio frequency fields caused the same results. The ten second period was found to be characteristic of each of the cell systems tested. The ten second coherency requirement has not been tested in an animal experiment.

Calculations showed that the ten second period was too brief for a signal averaging process to be effective in overcoming the low signal-to-noise ratio typical of many experimental and environmental exposures to weak ELF fields. Hence, the ten second period did not seem to reflect an underlying critical step involving signal averaging. Litovitz suggested that the processes occurring during the ten second period were analogous to the charging of a capacitor.

Litovitz presented a model in which it was necessary to simultaneously activate ("fire") an array of sensors. These sensors were identified as a group of perhaps several hundred membrane protein receptor molecules of a single cell. In discussion of questions from workshop participants (R. Savage, B. Wilson, and R. McGaughy) it was suggested that the receptor activation affected, for example, hormone affinities, by changing either binding/off-binding energetics and kinetics (q.v. Patton's model) or receptor occupancy in a group of perhaps 150 to 200 receptor molecules of a cell. Litovitz suggested the binding energy change may be a result of a physical mechanism involving pericellular electric currents (induced by a time-varying magnetic field in the case of magnetic field exposures). McGaughy expressed interest in seeing data to support these receptor-related effects, but none is known.

A second category of experiments indicated the inhibitory influence of imposed noise on EMF biological effects (including developmental abnormalities in chicken embryos). The data from experiments with both sinusoidal and pulsed magnetic fields were interpreted as evidence that a spatially coherent noise field about equal to the amplitude of the signal was capable of masking the signal. This was so even though there was also a much larger amplitude noise field generated by intrinsic thermodynamic and physiologic

processes. The two types of noise, imposed and intrinsic--and their different influences on receptor binding--were distinguished by their spatial coherence and incoherence, respectively. The cooperative group of receptors was postulated to respond to a signal or noise which was coherent over the dimensions of the group.

Litovitz drew inferences from other sensitive physiologic processes such as chemotaxis wherein cells can respond to concentration gradients that are one one-thousandth as great as the "noise." This suggested a mechanism based on "temporal sensing" such that the cell could detect a gradient by a comparison of concentrations remembered from some earlier time.

In contrast to the ten second time period, the fact that cells respond to sinusoidal signals at frequencies of about 60 Hz suggests an averaging process that operates over times of about 10 ms. In response to a question (Wilson), Litovitz indicated the fundamental dielectric relaxation time for cell surface ions was the Debye relaxation time of about 10 ms. Experimental evidence for the existence of an averaging process that occurs at about the frequency of applied 60 Hz fields was developed from experiments on ODC activity enhancement. The signal was modified by introduction of gaps of various durations (10 to 200 ms) in the waveform. The gaps were introduced once per second. The short gaps had little or no influence, but gaps of about 100 ms severely attenuated the ODC effect. The relaxation time obtained from studies with L929 murine cells exposed for 4 h was 40 ms. In response to a question (D. Driscoll) Litovitz indicated that the foregoing data indicate that any future exposure meter should be designed to resolve gaps of this duration or longer.

The Kinetic Hypothesis

Charles Montrose, Ph.D., Catholic University

EMF exposures may cause transient increases in the whole cell level of messenger RNA (mRNA). Such an effect would perhaps be the direct result of a change in the rate constant for one of the biochemical steps that leads to transcription of the mRNA from the DNA template. Montrose identified the "kinetic index" as the integrated mRNA concentration during the transient, i.e., the area under a curve of mRNA concentration as a function of time. Montrose cautioned that the details of the model were only one example of many and that in view of the many unspecified parameters, the details were "not to be taken seriously."

Chronobiological Considerations

Kenneth Groh, Argonne National Laboratory

Unlike the preceding talks, Groh presented data and ideas from experiments with whole animals. He also provided possible explanations in terms of principles and data from biologic research in gene expression and cell biochemistry. As an overview of the complexity and integration of the biochemical processes underlying the rhythms in physiological parameters, Groh emphasized that at any time of the day one or another process is at a peak or valley in its activity while numerous others are in either increasing or declining phases. Groh illustrated the physiological importance of circadian physiologic changes by reference to a major shift in animal survival rates (from 50 to 100%) depending on when the subjects were irradiated with a large dose (550 gray) of x-radiation.

EMF effects on circadian function have involved a variety of neurophysiologically regulated functions

including activity, arousal, neurotransmitter levels in rat brain, pineal and serum levels of melatonin, CO₂ and O₂ concentrations. EMF effects on melatonin were placed in context with Loewy's well-known studies of the influence of light on human melatonin and its relation to seasonal affective disorder.

Chronobiologic parameters such as the light-to-dark ratio are of critical importance to experimental outcome. For example, animals acclimated to a 12:12 light-dark cycle prior to EMF exposure showed no effects, but circadian phase advanced if the animals were acclimated to a 8:16 schedule. Groh tied the animal data to both epidemiologic and cell biologic research with the observation that gene expression varies with circadian phase for entrained cell cultures and therefore epidemiologic studies may need to account for the time of day as a major factor in whether an exposure would be biologically effective.

Questions and comments by Wilson and Goodman drew out the information that despite the impression that in vitro experiments had mostly shown enhancements of gene expression whereas animal studies of melatonin involved inhibition, there were data from in vitro studies for which inhibition was also observed.

Finally, Groh noted that in his experience with animal EMF experimentation it was common for 20 to 40% of a group to be "non-responders." This fact has obvious effects on the sensitivity of animal assays and interpretation of data based on averaged responses.

The hypotheses needing tests in epidemiological studies were stated in terms of EMF exposure conditions that might be required in order that adverse health outcomes occur. These hypothetical conditions were: (1) EMFs must be constant over periods of 10 seconds or longer and there should not be gaps lasting more than 100 milliseconds. These properties were those identified by Litovitz and co-workers in research with cell cultures and chick embryos; (2) EMF exposures must occur in coincidence with stressors, particularly repetitive stresses such as those from exposures to toxic chemicals; and (3) EMF exposures must be evaluated with reference to the influences of chronobiologic variations in human physiology.

The following viewgraphs were written to present the working group's conclusions at the final plenary session.

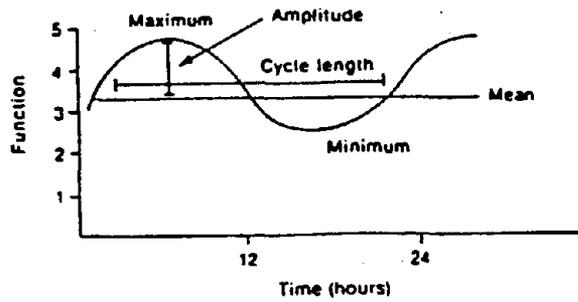
Chronobiological Influences on EMF Exposure and Biological Effects

K. R. Groh
Argonne National Laboratory

Electromagnetic Field (EMF) Characteristics Which Influence Biological Effects

1. Field Type:
Magnetic, Electric, or Both
2. Static or Time-Varying Field
3. Field Frequency
4. Field Intensity
5. Pulse Shape and Rise Time
6. Length of Exposure
7. Ambient Background Field:
Level and Orientation
8. Circadian Phase of Exposure
9. Biological Species Sensitivity

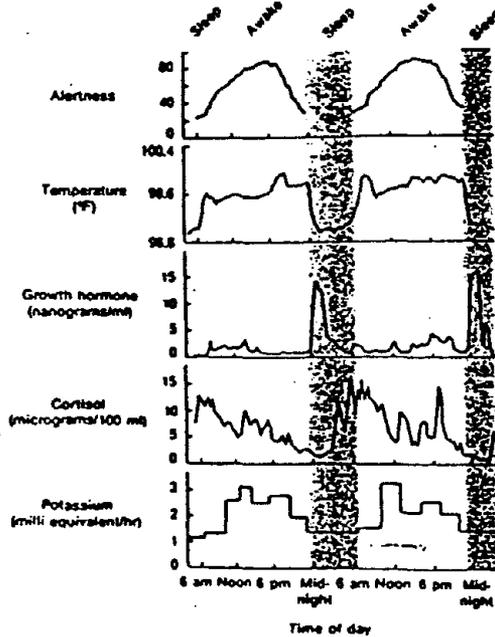
Figure 1-1—Circadian Rhythm



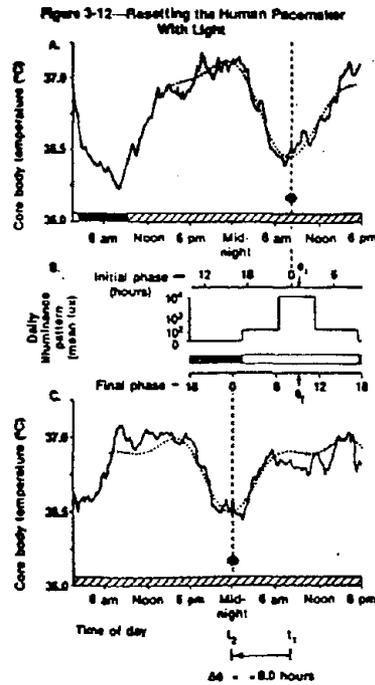
Circadian rhythms have a single cycle length of approximately 24 hours. The amplitude, a measure of the degree of variation within a cycle, is the difference between the maximum value and the mean.

SOURCE: Office of Technology Assessment, 1991.

Figure 1-2—Circadian Timing of Various Functions



The timing of some functions that cycle with a circadian rhythm.
 SOURCE: Adapted from R.M. Coleman, *Awake at 3:00 a.m. by Choice or by Chance* (New York, NY: W.H. Freeman, 1968).



The first graph (A) illustrates the original circadian rhythm of body temperature. Following exposure to bright light, as illustrated in B, the rhythm of body temperature was significantly shifted (C).
 SOURCE: C.A. Czeisler, R.E. Kronauer, J.S. Allan, et al., "Bright Light Induction of Strong (Type 0) Resetting of the Human Circadian Pacemaker," *Science* 244:1328-1332, 1999.

Chronobiological Effects of Electromagnetic Fields

1. Behavioral
 - Arousal
 - Avoidance
2. Neurotransmitter Effects
 - Pineal
 - Melatonin
 - Snat
 - Serotonin
 - Brain Neurotransmitters
3. Phase Shifts of the Entrained Circadian Rhythm
4. Amplitude Decrease of the Entrained Circadian Rhythm
5. Analgesic Effectiveness Responses

Following the morning plenary sessions on Tuesday, September 27, there was extended discussion on the roles for intermittency and chronobiological factors. Wilson and Groh pointed to the absence of any effort to take chronobiology into account for epidemiologic purposes. Thomas suggested utilization of personal dosimeters rather than room measurements for such a study. The remainder of the discussion was directed to specification of potential EMF exposure metrics based on laboratory data from cell culture research and other mechanistic laboratory research.

Lotz noted that the National Toxicology (NTP) Study now in progress was purposefully designed to achieve highly uniform and temporally invariant magnetic fields. Thomas said it appeared to him that the laboratory data gave a much better justification for an intermittent exposure protocol than for the constant exposure protocol adopted by the NTP. Litovitz noted that certain temporal features (involving coherence times in cell culture ODC assays) were identical for experiments with ELF and amplitude modulated-radio frequency fields. Thomas thought this observation was so significant that there should be direct tests of the effective exposure protocols in experiments on animal carcinogenesis. In contrast, Wilson believed animal studies were too expensive to proceed without first obtaining evidence for acute effects in animals.

Lotz turned the discussion to exposure measurements in the next generation of epidemiologic studies. Replies by Wilson, Montrose, Lotz, Gauger, Thomas, Driscoll, Sobel, and Yost identified the value and characteristics of an ideal waveform capture device. Ideally the retained information could be used to analyze exposures according to any model, including those associated with Litovitz and Montrose et al., Kirschvink, Liboff, Lednev and Blackman. There was extended discussion of the engineering feasibility of a device capable of capturing all useful exposure data, especially in the context of occupational exposures. Identification of worker tasks was identified as important to successful occupational epidemiology of EMF exposures. During discussion, the focus of interest was in capturing evidence for continuity such that no gaps of 100 ms or more would go undetected.

In addition, the field amplitude, phase and frequency should be monitored to identify epochs over which they were constant for 10 seconds or more. In order to avoid creation of extraordinarily large databases, various schemes for compression of the stored information were offered. A typical scheme (suggested by Gauger) was to sample at a relatively high rate, such as at 100 ms intervals, but to merely retain a running total for the duration over which these repeated samplings met the criteria for constancy.

During the final plenary session Sobel indicated that personal dosimetry was to be a last resort and that information on the static magnetic field was not needed. In contrast, Driscoll spoke in opposition and to deny that this was a conclusion of the group. A. Sastre and S. Cleary each took issue with the idea that a 10 second constancy period could be adopted on the basis of the relatively narrow range of studies so far done by Litovitz and colleagues and that any one hypothesis could be adopted as if it would apply to all possible biological subsystems. Lotz agreed and emphasized that there was a strong need for more laboratory data which illuminated mechanisms. J. Sahl though it preposterous that epidemiology be considered a suitable means for testing hypotheses, arguing that epidemiology by its nature was too blunt a tool for such purposes.

The discussion of means to implement the hypotheses of item 3 above into future epidemiology brought out these ideas:

- Polarization, phase and static field information are also of significance for mechanistic approaches to exposure.
 - Light levels, light cycles and season may be useful or crucial data.
 - Spectral information is also needed. It is simplistic to assume the 60 Hz field is the correct etiologic factor.
 - Amplitude changes of 20% may be a suitable criterion for identification of an amplitude-change event.
 - If a metric is defined to be too restrictive there will not be sufficient numbers of exposed cases to gain good statistics.

The working group recommendations follow.

- Based on hypotheses discussed by the group, protocols and instrumentation should address three factors that may be important in the expression of biological effects. These are:
 - constancy of frequency, phase, and amplitude over periods of greater than 10 seconds
 - interruptions as short as 100 ms
 - repetition of exposures meeting the above two criteria in a manner that produces repetitive stress
- EMF exposures may be more or less stressful depending on the phase of the chronobiological cycle relevant for a particular biochemical, neurophysiological or physiological process

No one element of the hypothesis was identified as more important than another. The bulk of group discussion time was focused on elements I) and ii) above.

The group did not develop particular exposure metrics that would include all important factors. The consensus of discussion appeared to be that a new dosimeter could be designed so that detailed waveform information would be captured at a high sampling rate. In order to avoid unrealistic volumes of data and a huge data analysis problem, the instrument would (in real time) reduce most of the raw waveform data into a number of indices. For example, temporal constancy could be measured in terms of a sequential list of the durations of periods meeting the criteria for constancy and the associated times at the end of each of the periods of constancy. An index for the number of waveform gaps exceeding a criterion length such as 100 ms would be maintained, for example, as an hour-by-hour tally for the number of such events. Presumably analyses for chronobiologic coincidences and the repetition index would not be represented by pre-programmed functions in the instrument.

Exposure assessment strategies were assumed above where it is indicated that a newly designed waveform-sensitive dosimeter would be needed and that some aspects of analysis would be done following data acquisition.

The following viewgraphs were written to present the working group's conclusions at the final plenary session.

<p style="text-align: center;">Coherence and Intermittency</p> <p style="text-align: center;">Coherence Model Kinetic Model Chronobiological Considerations</p> <hr/> <p style="text-align: center;">Hypotheses</p> <p>1. Coherence</p> <ul style="list-style-type: none">A. Constancy in the EMF field for longer than 10 seconds induces a biological responseB. A change in the EMF field over a 0.1 second or more duration prior to 10 seconds prevents a responseC. A large number of constancy periods in the EMF field leads to the disease under investigation <p>2. Homeostatis Disruption</p> <ul style="list-style-type: none">A. A large number of changes in the EMF field, especially in time periods less than 10 seconds leads to the disease under investigation <p>3. Effect Modifiers to Consider</p> <ul style="list-style-type: none">A. Chronobiological: light; sleep-wake cycle; season; activityB. Associated diseasesC. Sensitivity, stress, genetic predisposition
--

Exposure Metrics

1. RMS
2. Frequency
- + DC Fields Not Needed

Exposure Assessment

1. Personal dosimetry -- As a last resort
2. Task-specific dosimetry --
Specific types of equipment
Specific usage patterns
Whole-body exposure
Measurements taken in actual working situation
Area measurements
3. Interview / Field Observations
Lifetime Exposure Information --
Occupational / electrical equipment
Residential / electrical equipment
Hobby / electrical equipment

Other Peculiar Sources of Exposure in Environments

Study Design

1. Dosimeters which can measure as much as possible
2. Use task-specific measurements so as to maximize the number of different parameters of EMF recorded
3. Observe occupational, residential and hobby task-specific Exposures
4. Personal dosimetry as necessary
5. Case-control study for rare diseases
6. Combination of case-control and longitudinal Study for common diseases
7. Consider genetic predisposition, e.g., look at family members, and other possible effect modifiers

Induced Currents, Transient and Otherwise Group 3

COORDINATOR: Paul Gailey, ORNL

CHAIR: Richard Stevens, Battelle, Pacific Northwest Laboratory

PRESENTATIONS:

Transients

Antonio Sastre, A. S. Consulting and Research

Gap Junctions, Tissue Dielectrics, Ion Binding, and EMF Bioeffects

Art Pilla, Mount Sinai School of Medicine

Induced Currents

Charles Polk, University of Rhode Island

REPORTER: Peter Valberg, Gradient Corporation

Introduction

Paul Gailey, coordinator

Although much of the EMF laboratory research has focused on 60 Hz exposures, it is well known that the “real world” electric and magnetic field environment is far more complex. Devices such as electric motors and dimmer switches, for example, produce fields with a broad range of temporal characteristics and frequency spectra. While it is unknown which, if any, characteristics of field exposure may be harmful, currents induced in the body by electric and magnetic fields are the most basic and obvious mechanism to investigate. Such currents induce changes in membrane potentials, and may directly or indirectly affect excitable tissues or cell receptors which are sensitive to the local field environment around cells.

Part of the mission of this working group was to identify important differences in microdosimetry issues associated with the various types of field exposure. For example, transients may exhibit very short durations, but have large amplitudes. Because the higher frequency components of these transients couple better with the body than 60 Hz frequency components, the induced internal electric fields (and consequently, induced membrane potentials) will be higher. Such issues complicate questions about which exposure conditions may be important, but these issues must be addressed to adequately relate exposure assessment studies to the biological studies performed in the laboratory.

Summary of Speakers’ Presentations

Peter A. Valberg, Reporter

One of the key motivations for the overall workshop was the question of why the wire-code association with childhood cancer exists side by side with a lower association when time-weighted average (TWA) 60 Hz magnetic fields are used as the exposure metric. One possibility is that the truly appropriate EMF metric, which has a better association with wire codes than with TWA fields, has not heretofore been measured. What might this more biologically relevant metric be?

The working group on “Induced Currents, Transients, and Otherwise” began their work by identifying the following four questions:

- (1) What are the pros and cons of transients as a EMF interaction mechanism?
- (2) What is the best theoretical choice for a “transient” metric, and what ought to be measured based on our best understanding of the biophysics?
 - Is it the pulse *per se* that is important (rise times, duration), or the pulse's frequency spectrum?
 - Are bioeffects due to induced fields, currents, or voltages?
 - How can beneficial effects (*e.g.*, bone healing) be separated from potentially adverse effects (*e.g.*, chromosome breaks)?
 - How do the biological effects of short but intense pulses differ from pulses less intense but chronic? It was pointed out that some reported bioeffects go away shortly after field application, yet others do not manifest themselves until substantial time has elapsed since initiation of EMF exposure.

- (3) What are our best guesses as to a quantitative, empirical “transient” parameter for the next generation of epidemiologic studies?
- What measurements need to be taken to capture “transients”, if we assume that they are biologically effective?
 - Transients consist of high dB/dt , high B_{peak} , “ringing”, short time duration, variable repetition rate, variable power content, and unique characteristics (“no two are alike”). Can we take a multi-parameter, complex exposure, such as “transients”, and reduce it to a single number that encompasses the risk of an adverse health outcome?
- (4) What further experimental and theoretical work needs to be done? What suggestions can be made for new experiments in the laboratory?

What distinguishes Transients from Intermittency?

At our initial meeting, we grappled with the question of what exactly defines a “transient”. It was decided that there was potential for overlap with the “Coherence and Intermittency” work group. The following distinctions were made, although it was acknowledged that the potential for overlap would continue, and necessarily so.

Transients

We can define “transients” as time variations faster than the fundamental (60 Hz) frequency, with the “size” of the transient being determined by the time rate of change of the magnetic field (dB/dt). Magnetic field transients are different in amplitude and in frequency from the basic 60-Hz signal, ranging from about 100 Hz on up in frequency content. In this sense, the higher harmonics of the 60-Hz signal could be considered transients.

Transients on distribution lines derive from switching of loads in homes and in substations. Bill Feero presented measurements of transients having a dB/dt of 6 G/s, that he had measured on substation lines due to the presence of harmonics. Many appliances have turn-on and turn-off current fluctuations, and these current fluctuations result in transient magnetic fields being generated. Robert Kavet pointed out that turning off a 450 Watt light fixture can produce a transient with a dB/dt of 400,000 G/s, which may occur over 10 nanoseconds.

Dimmer switches, motors with brush commutators, and other appliances that interrupt current flow as part of their normal function, are a continuous source of transients. Dimmer switches can in fact saturate any transient-measuring system that has not specifically tuned out this source.

Early in our deliberations, it was noted that background static electricity discharges can also give rise to large transient currents in body tissues. These transients are fundamentally different from what are normally considered as transients in E and B fields, since they involve contact currents. However, such “microshocks” might actually have greater health implications than electric fields induced by non-contact EMF transients.

Intermittency

Intermittency refers to longer-term variations that encompass anywhere from several to many 60-Hz cycles. That is, whereas transients occur over time scales shorter than $1/60^{\text{th}}$ s, intermittency occurs over time scales much longer than $1/60^{\text{th}}$ s. For example, if we determined the number of times per day that a certain level was exceeded for a period of 10 s or more, this would be an “intermittency” metric. In fact, the “Coherence and Intermittency” group stated that an intermittent fluctuation not lasting longer than 0.1 s was unlikely to have a biological effect; almost all transients occur in time scales shorter than this.

Large and periodic changes in field strength (Intermittencies) derive from:

- fluctuating power consumption
- changes in EMF as a function of body movement
- residential room heaters, bed heaters, and intermittent appliance use
- workers making regular, discontinuous use of electrically-operated tools

Some exposure paradigms used in human experiments have, in fact, utilized intermittency (*e.g.*, fields turned on and off periodically) because some investigators feel that this is a biologically more effective EMF exposure than continuous-wave.

Transmission Lines *versus* Distribution Lines

The working group also discussed the sources of transients, and made some interesting comparisons between EMF exposure from transmission lines and distribution lines.

SIMILARITIES: The 60-Hz fundamental, sinusoidal fields predominate in terms of the time-weighted average. The EMF from both types of lines are generally circularly (or elliptically) polarized, although transmission lines tend to contain a greater proportion of circular polarization.

DIFFERENCES: Harmonic content is higher on distribution lines. Distribution lines are characterized by larger step changes in load. Distribution lines are more prone to transients due to load and capacitor-bank switching. Transmission lines are steadier over the long term (months to years), whereas distribution lines exhibit dramatic variations over the longer term as old lines become overloaded and new lines are built.

Expert Reports

Several investigators presented their views to the working group, and the following notes by reporter Peter Valberg are a simplified summary of what was said.

Transients

Antonio Sastre, A. S. Consulting and Research

Reporter's Notes:

As a mechanism potentially affecting biological processes, transients do not have a “below *kT*” problem. Transients generate larger signals in the body than low-level rms (*i.e.*, TWA) EMF signals, which are buried in the noise. With transients, you do not have to invent a new brand of physics when proposing

mechanisms of interaction. Also, transients are “real world” EMF phenomena, whereas, some of the other metrics being discussed require a stability or combination of exposure conditions that seem suitable only to the laboratory environment.

In the experimental work that was discussed, transient-capture records for a large number of residences were scanned. For each residence, the 10 largest transients were selected and digitized to a resolution of 5 ns. The frequency ranges examined for transient capture were:

40 Hz to 5 kHz (low frequency B)
5 kHz to 12.5 MHz (high frequency B)

Fourier transforms of transient signals were filtered to limit the peak frequency to 160 kHz because of the expected frequency response of the cell membrane is expected to cut off at this point. The Fourier components below this level were applied to a biophysical model of a single cell.

The target cell system utilized the following parameters, which were chosen to take on one of a range of plausible values: cell-membrane conductance, cell radius, body radius, capacitance of the cell membrane, and resistivity of extra and intracellular medium. Nyquist-Johnson noise in the cell membrane was calculated for a bandwidth of 160 kHz, and was compared to the signal induced by the “transient.”

The results of the analysis showed that conditions favoring better signal-to-noise ratios included large radius, high membrane conductance, and low resistivity of intracellular and extracellular medium. However, it was not necessary to always assume extreme values to achieve a $S/N > 1$ for a large number of cell and transient parameters.

The study did not address any relationship between transients and wire code classification. Dr. Sastre concluded that development of a credible metric is going to be very difficult because of the heterogeneity in the nature of transients.

Dr. Sastre's viewgraphs are as follows:

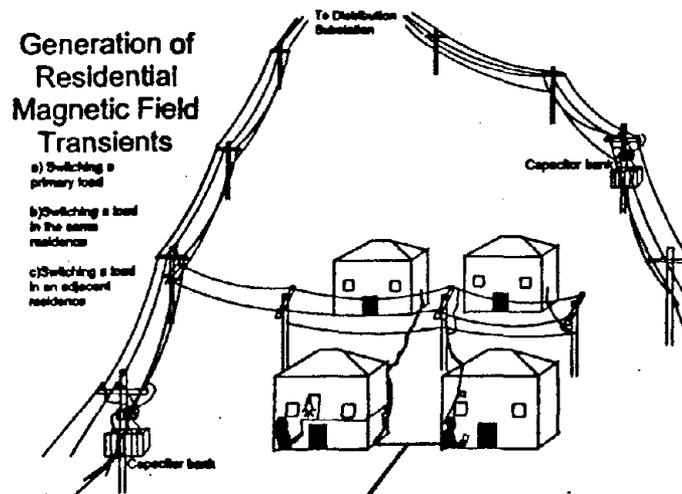
Residential Magnetic Field Transients (RMFT): Induced Signals Versus Thermal Noise

Antonio Sastre, A. S. Consulting & Research
Robert Kavet, EPRI
Jeffrey L. Guttman, Enertech Consultants
James C. Weaver, Harvard-MIT DHST

Supported by Electric Power Research Institute under RP3349

Background

- Research has been initiated under EPRI sponsorship to characterize transient electric and magnetic fields in residential environments
- A key goal of the original research plan was to assess the relationship between the properties and occurrence of RMFT and wire codes
- This investigation's objective is to examine the magnitude of transient induced transmembrane voltage in relation to membrane noise



Objective of this Analysis

To evaluate how the transmembrane voltages induced from among the largest of sampled RMFT compare to thermal (Nyquist-Johnson) noise in a single cell model.

Primary Data Acquisition

- Measurement program conducted by EnerTech in northern CA in 21 residences across W-L wire code spectrum
- Instrumentation, featuring LeCroy 7200 oscilloscope with 8-channel input, deployed for 24 hours per residence

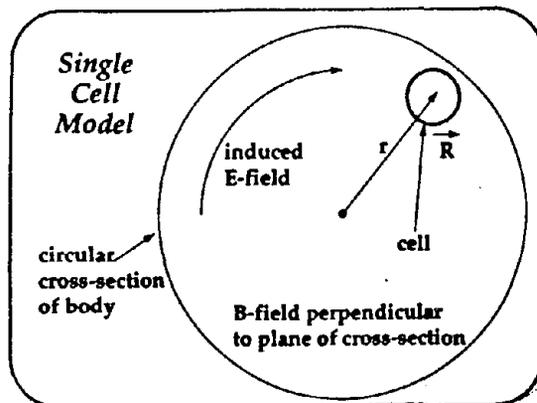
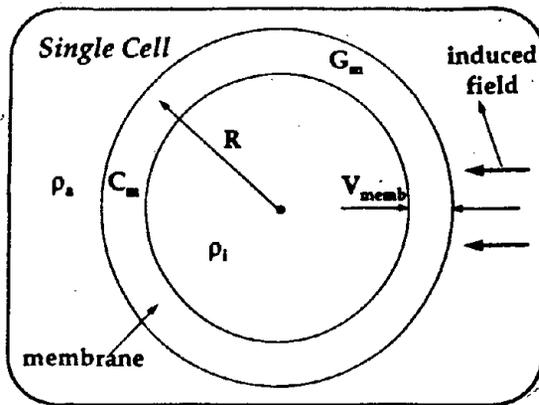
<u>Channel type</u>	<u>No. channels</u>	<u>Bandwidth</u>
Hi freq B	3	5 kHz - 12.5 MHz
Hi freq I_{NS}	1	1 kHz - 20 MHz
Lo freq B	3	40 Hz - 5 kHz
Lo freq I_{NS}	1	10 Hz - 10 kHz

I_{NS} = neutral service current

Transient: Operational Definitions

A transient event was triggered when trigger threshold (as defined by background level, e.g., noise, AM radio) was exceeded in the high frequency x-channel, which was oriented horizontally in the north direction

- Internally generated transient:
"Large" simultaneous 60 Hz I_{NS}
- Externally generated transient:
"Small" simultaneous 60 Hz I_{NS}



Induced Membrane Voltage, V_{memb}

$$V_{memb}(\omega) = \frac{jB(0.75\omega rR/A) \cdot \{1/[1+j\omega RC_m(\rho_i+0.5\rho_a)/A]\}}{A}$$

where,

$$A = 1 + RG_m(\rho_i+0.5\rho_a)$$

$B = B_{real}(\omega) + j B_{imag}(\omega)$
 $\omega = 2\pi f$
 $r =$ loop radius
 $R =$ cell radius

$C_m =$ membrane capacitance
 $G_m =$ membrane conductance
 $\rho_i =$ intracellular resistivity
 $\rho_a =$ extracellular resistivity

Based on: Foster & Schwan, 1989

Transient Selection

For each residence with eligible data (16 residences), the 5 largest “internal” and 5 largest “external” signals, $B(t)$, were selected

- all signals collected digitized to a resolution of 5 nsec
- waveshapes were screened for magnitude without antenna correction
- magnitude based on maximum peak-to-peak flux density

Transient Analysis: Basic Procedure

For each signal:

- Discrete Fourier Transform (DFT) used to extract frequency/phase content
- Each frequency component corrected for antenna sensitivity
- Outputs were filtered to 160 kHz
- Each complex DFT component fed to cell model
- Output of model fed to inverse DFT to produce $V_{\text{memb}}(t)$
- Peak-to-peak $V_{\text{memb}}(t)$ compared to V_{noise} \equiv signal-noise ratio (S/N)

Results

- For all transients (160) and cell model permutations (81), S/N ratios ranged from 3.0×10^{-4} to $8.2 \times 10^{+1}$
- All 160 events resulted in $S/N > 3$ for at least one set of cell parameters
- Most events (144/160) satisfied a criterion of $S/N > 10$ for at least one set of cell parameters
- Conditions that favored larger V_{memb} included large R , high G_m , and low ρ_i and ρ_a ; extreme values of these parameters were not necessarily required to satisfy $S/N > 3$

Discussion

- Some of the largest RMFT recorded in the pilot study induce transmembrane voltages in our cell model that exceed thermal noise
- $S/N > 1$ implies only that a given signal above noise occurred; we do not believe inferences may be drawn regarding possible biological activity of such signals

Perspective to DOE/NIOSH Workshop

- **Residential magnetic field transients**
 - are very heterogeneous in terms of amplitude, frequency content and other defining parameters
 - require relatively bulky state-of-the-art equipment for accurate waveform capture
- **Our preliminary results**
 - reflect a highly simplified dosimetric model
 - are based on a limited sample size of residences and signals
 - do not address possible relationships between RMFT and residential wire codes
 - do not permit the development of a credible exposure metric without intrinsic ambiguity relative to both biological activity and exposure classification

Gap Junctions, Tissue Dielectrics, Ion Binding, and EMF Bioeffects
Art Pilla, Mount Sinai School of Medicine

Reporter's Notes

A cell-array, distributed-parameter model can be shown to be responsive to low levels of induced E-field, but frequency response drops off dramatically for large arrays (a 10 mm cell array only has good response down below 1 Hz). If an inductance element is put in, you can get membrane voltage perturbations that are tenfold higher than the baseline case, at "resonant" conditions.

Cell-free, myosin phosphorylation systems are affected by DC magnetic fields over the 0-300 μ T range. This effect occurs only over a very narrow window of Ca^{++} concentrations. On the other hand, you need about 100 mT to have any effect on ion exit from a molecular binding site.

One of Dr. Pilla's observations is that EMF effects may be quite dependent on the previous state of the system. For example, in the damped, double-well oscillator, he showed that the binding dynamics exhibit high sensitivity to small changes. A 0.02% change in the static magnetic field caused a dramatic change in the phase-space orbits of the oscillator. He predicts that "preexisting state of the system" will be very important in determining the EMF response.

Because the EMF effect will depend so critically on the current biological state of the exposed system, Dr. Pilla recommended that "everything" be measured.

Bioelectrochemistry and Bioenergetics **35**: 63-69 (1994)

**Gap junction impedance, tissue dielectrics and thermal noise limits
for electromagnetic field bioeffects**

A. A. Pilla, P. R. Nasser, J. J. Kaufman

*Bioelectrochemistry Laboratory, Department of Orthopaedics, Mount Sinai School of Medicine,
New York, NY 10029, USA*

Abstract

The model presented in this study quantitatively examines the effect of gap junctions and gap junction impedance on electromagnetic field (EMF) dosimetry in a tissue target. A simple linear distributed-parameter electrical model evaluates the effect of tissue structure on the thermal threshold (signal-to-thermal-noise ratio) for detectable induced transmembrane voltage. Analysis of the angular frequency response of the array model, using a membrane impedance which includes ion binding and coupled surface chemical reaction kinetics, suggests that the frequency range, over which maximum detectable induced transmembrane voltage could be achieved, is orders of magnitude lower than that for a single cell. Gap junction impedance has negligible effect on both the frequency response and the increased transmembrane voltage due to a cell array unless its value becomes as high as that of an artificial bilayer lipid membrane. This results in a threshold for induced electric fields bioeffects of approximately $10 \mu\text{V cm}^{-1}$ at the target site for a 1-10 mm cell array. Physiological variations in gap junction impedance appear to have little effect on this threshold. Thus, cells in gap junction

contact in developing, repairing or resting state tissue structures would be expected to be able to detect significantly weaker EMF signals than isolated single cells. The lowered frequency response of a cell array reinforces the suggestion that the spectral density of the input signal should be adjusted to the bandpass of the detector pathway for dose-efficient and selective EMF bioeffects.

Induced Currents

Charles Polk, University of Rhode Island

Reporter's Notes

Dr. Polk predicted that since electric field in the body couples only poorly to the cell interior, it is unlikely that the induced currents produced by transients are responsible for the bioeffects we see at low EMF levels. On the other hand, for more sophisticated metrics, the biological and physical models very quickly become too complicated to be able to zero in on a simple hypothesis suitable for an epidemiologic study.

The heterogeneity of the body with regard to electric conductivity makes it difficult to know in detail the size of the electric fields induced by changing magnetic fields.

In the case of bone glycosaminoglycan content, having an exposure duration of 2 hrs/day gives an optimum effect, while a longer exposure, 8 hrs/day gives a minimal effect. This observation points to the necessity of carefully monitoring the time domain of exposure and outcome determination. For systems where the induced current depends on the orientation of the system, the difference between linearly-polarized magnetic fields and circularly-polarized magnetic fields can be dramatic.

In summary, we do not know at present if it is changes in transmembrane potential, or changes in electric field effects elsewhere in the organism, that make the important difference in causing EMF bioeffects.

Dr. Polk's viewgraphs are as follows:

Induced Currents

- Induced currents are probably not the mechanism through which low intensity magnetic fields produce biological effects.
- Biological/Physical models are not yet well enough developed by *In Vitro* research to be epidemiologically testable.

AT DC or ELF:

$$E_{\text{outs}} \gg E_{\text{INS}}$$

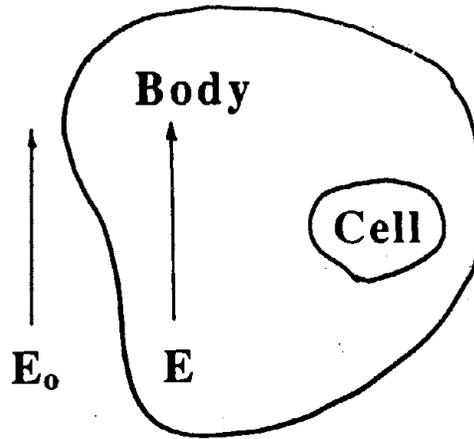
$$\omega \epsilon_0 E_0 = \sigma_i E_i$$

$$B_{\text{OUTS}} \approx B_{\text{INS}}$$

AT RF:

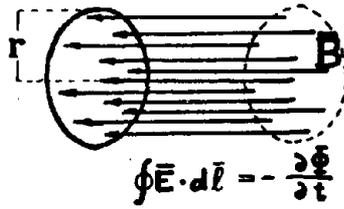
$$P_{\text{ABS}} = \Phi(f, L, \epsilon, \sigma)$$

$$\frac{E}{H} = \sqrt{\frac{\mu_0}{\epsilon_0}} = 377 \text{ (free space, far field only!)}$$



$$E_0 \gg E \quad E = E_0 \frac{\omega \epsilon_0}{\sigma} K$$

$$\text{At } f \leq 60 \text{ Hz} \quad E \leq 10^{-7} E_0$$



$$\Phi = \iint \bar{B} \cdot d\bar{s}$$

$$\text{IF } B = B_0 e^{j\omega t}$$

$$\oint \bar{E} \cdot d\bar{l} = -j\omega \iint \bar{B} \cdot d\bar{s}$$

FOR PERFECTLY HOMOGENEOUS
MEDIUM AND UNIFORM \bar{B}

$$2\pi r E = -j\omega B \pi r^2$$

$$|E| = \frac{\omega B r}{2}$$

$$|\bar{J}| = \sigma E = \frac{\sigma \omega B r}{2}$$

Electric Field Action



TRANSLATION



DIPOLE FORMATION



DIPOLE ORIENTATION



IONIZATION



DESTRUCTION OF DIELECTRICS

ELF and Pulsed E-Field Effects

	V/m Inside Tissue or Fluid
Transient ELECTROPORATION Depends on E (Δt) Permanent	10^5
CELL ROTATION IN INSULATING FLUID	10^4
initiation of firing NERVE / MUSCLE STIMULATION alteration of f rate	10^3
alteration of f rate 10	10
SUBTLE "LONG TERM" ($t > 10$ min) EFFECTS (Bone / soft tissue repair, Ca-efflux, transcription)	$10^{-3} - 10^{-5}$

- Is exposure to field vectors with many different orientations (so as to induce circulating currents in many different organs) important?
- Compare populations exposed to linearly polarized fields with populations exposed to circularly/elliptically polarized fields (discriminate accordingly between different homes).
- Is intermittent (i.e., frequent, but frequently interrupted) exposure particularly likely to produce biological effects?
- Look at occupations that are characterized by this type of exposure:

Welders? Street car operators?
 People near electric railroad corridors?

General Discussion

The suggestion was made that an appropriate “metric” for transients might, for a start, be taken to mimic the same pulse characteristics that have been reported to be effective in bone healing. If there is some evidence that repeated pulses at, say 5 kHz, cause biological changes, maybe it is these types of transients that we need to look for when conducting exposure surveys for epidemiologic studies.

Peculiar shapes of magnetic field exposure are caused by hand-held electric drills, by substations, and even by people jogging in the earth's magnetic field. Do these sources of “transient” field exposure have any implications with regard to adverse health effects?

From the information presented, the interim conclusions of the working group were:

- (1) Transients, even below 160 kHz, can produce $S/N \gg 1$ without need for “new physics.”
- (2) Small (100 μV) changes in membrane potential may modulate the firing of excitable cells and may modify function of non-excitabile cells.
- (3) The complexity of transient exposures may preclude, at this time, deciding which transients are most important, and determining how exactly they may be linked to health risk.

The group then tackled the question we were charged with:

- (4) Is there a logical candidate for the next epidemiologic study that requires quantification of transients?

Overall Conclusions

Metrics Involving Transients

Biological activity (aside from bone healing) has not been explored specifically for transients, but transients are real-world events that have the capability of producing signals in the body that are above noise. Extrapolating from the expectation that the intensity, duration, and frequency of transients would be related to biological effects, the group proposed the following list of candidate metrics suitable for epidemiologic studies:

- Transient duration
- Transient repetition rate (also, repetitive *versus* singular transients)
- Peak B
- Peak dB/dt
- Average dB/dt to peak
- Frequency spectrum, or histogram of dB/dt (*i.e.*, rise time) content
- Signal-noise ratio (S/N) from cell membrane models

Several key considerations need to be kept in mind if one or more of these metrics is to be applied. If some correlation to wire codes is envisioned, it will be necessary to contrast internally (within-home) generated *vs.* externally (outside-the-home) generated transients. Working group members pointed out that the variability of the baseline, steady state is an important adjunct measurement; they recommended that intermittency in the baseline AC and DC fields be characterized.

The time scales to be monitored cover 1 to 10 seconds. Even though transients can be recorded that have frequency spectra up to the GHz range, biological systems are unlikely to respond to anything shorter than 10 μ s. Hence a 1 Hz to 100 kHz frequency bandwidth would be appropriate. If all of the above parameters cannot be sampled simultaneously, then sampling of different parameters could be carried out at slightly different times (*e.g.*, back-to-back).

Finally, there was a consensus that static electricity discharges may be a confounding factor for epidemiologic studies that focus on transients. It may be necessary to monitor microshocks (which have been reported to produce chromosome breaks). There seemed to be a general agreement that microshocks might more effectively be quantified by questionnaire than by actual measurements of current transients through people.

Instrument Needs

The first step in identifying instrument needs is to define the transient "event". Since transients come in so many different flavors, threshold values for the metrics discussed above will need to be identified. Again, because transients are so heterogeneous, some computer software will be needed to collect, sort, and quantify transient exposure. Three areas where software development might be important are:

- discrimination capability (to avoid lock-up on dimmer-switch signals)
- signature analysis (on-the-fly transient recognition)
- coincidence testing (correlation to in-home currents or to intermittency in baseline EMFs)

This software development will be important not only for focusing in on biologically relevant transients, but also to discriminate among sources of transients. For example, current work on transient exposure classification has looked at the synchrony between transients and return current sources (residential grounding circuits).

A range of instruments was envisioned, ranging from simple devices that utilize transient recognition at a "hardware" level, up to complex, signal-processing devices that measure multiple parameters.

The following three categories were identified:

- The simplest device might consist of a ringing (resonant) R-L-C circuit. Since transients deliver power over a broad spectrum, any high-Q, inductor-capacitor circuit could be expected to be set into oscillation by a transient. This simple device would merely count the number of such events on a data logger and note their time of occurrence. The metric developed from this would be either total number of transients per day or number of times the repetition rate of transients exceeds a preset value.
- A device of moderate complexity would use a computer to calculate only summary parameters on the fly; no attempt would be made to record pulse waveshapes. Again, this device would include a data logger and time stamp.

An example of this type of device was discussed at length. There would be one such sensor per home, it would be a 3-axis device, and it would be an add-on to a baseline study which would be recording average *B*-fields. (It appeared that Paul Gailey was involved in developing such a device for the epidemiologic study being conducted by Richard Stevens and collaborators). The device would not monitor polarization

information. It would digitize for one second whenever you trigger; it would not save all the data on the digitized waveform, but would run a summary statistics program for 0.2 seconds after the 1 second of digitization. The parameters kept for each pulse would be: peak B , plus about 20 bins of dB/dt values (*i.e.*, keep a spectrum of rise times). For a trigger level, a dB/dt corresponding to the dB/dt of a continuous-wave 100-mG, 60-Hz signal was suggested. Such a device would typically run for 24 hrs in each of about 400-500 homes, and the collected data would be correlated with wire codes for those homes.

A higher complexity device might be based on the transient study undertaken by Sastre and colleagues. Here, one would calculate the biological effectiveness of transients on a event-by-event basis and the program could be tailored to seek transients effective for specific cells, *e.g.* bone marrow or breast cells. This device also used coincidence testing to determine if the transients were deriving from current pulses on the grounding circuits. An effectiveness metric would have to be developed. Again, this device would include a data logger and a time stamp.

Populations of Interest

Our basic suggestion here was to measure the transient exposure for several candidate exposed groups, and then pick most exposed populations for epidemiologic study. The working group discussed the manner in which we might identify candidate populations.

Features of desirable groups would involve the following considerations:

- ability to evaluate residential stability *versus* job stability
- high exposure due to use of switched motors (seamstresses, tailors, dressmakers, barbers, carpenters, . . .)
- ability to control or quantify the population for their exposure to microschocks. It was suggested that control of possible confounding in this area might best be accomplished with a questionnaire

There already is available at least one study on residential transients and exposed residential groups (Sastre, Kavet, Guttman, and Weaver). Therefore, future data on transient exposures could be compared to this "baseline" case. It was suggested that occupational, but non-utility populations be studied, because it was felt that the utility environment is well controlled, and transients may be rare. There may likely exist specific populations (welders, telephone workers, Swedish occupational cohorts. . .) with high, quantifiable transient exposure and pre-existing health data.

Summary Recommendations

The following list of summary recommendations were offered by the "Transients" working group as answers to the indicated questions:

How should an epidemiologic study of transient exposure be undertaken?

- The initial "transient studies" should be add-ons to ongoing epidemiologic studies.
- For these "add-on" studies, transients should be measured with a stationary instrument and should be linked to activity data (home, occupation, travel, *etc.*) and to measured personal TWA B -field exposure and intermittency.
- In addition to any association with disease, these studies should also address:

- Is intermittency a surrogate for transients?
- What is the correlation of transients with wire codes? (As mentioned earlier, studies will need to discriminate between transients that are generated by the distribution lines outside the home vs. the transients generated by wires and appliances inside the home and in nearby houses.)

How should the question of developing a “transient metric” be approached?

- We should first collect a taxonomy of transients, and identify the “signature” of transients.
- Studies should be undertaken to determine what EMF attributes of transients are related to each other; this will allow investigators to measure only the key, independent descriptive parameters.
- We should use existing transient exposure assessment studies to identify design needs for dosimeter-type instruments.
- Finally, in order to control for a possible confounder, we need to investigate the prevalence of microshocks from electrical equipment and from static discharges.

What other information might be necessary to develop meaningful epidemiologic studies?

- An effort needs to be launched to determine what laboratory data would help identify biologically relevant transients. At the present time, we have little information on which to base decisions choosing those transients potentially important to disease causation.
- A suggestion was made that performing laboratory experiments utilizing exposure to recorded, real-world transients would help identify biological endpoints. However, some individuals felt that this could turn out to be a poorly-controlled and ineffective approach.

The following viewgraphs were written to present the working group's conclusions at the final plenary session.

Metrics Involving Transients

- Transient duration
- Transient repetition rate
- Peak B
- Peak dB/dt
- Average dB/dt to peak
- Frequency spectrum
- Signal-noise ratio (S/N) from cell membrane models

Considerations

- Contrast internally (within-home) generated vs. externally (outside-the-home) generated transients
- Determine variability of the steady state; identify intermittency in the baseline AC and DC fields
- Monitor microshocks (which may produce chromosome breaks); i.e., measure current transients through people
- Monitor a 1 to 10 second window, 1 Hz to 100 kHz frequency bandwidth
- Sample different parameters at different times (back-to-back)

Instrument Needs

- Need to define “event”
- Need to develop necessary software:
 - discrimination (avoid lock-up on dimmer-switch signals)
 - signature analysis (transient recognition)
 - coincidence testing (correlation to intermittency or to transients in grounding currents)
- Synchronize transients with return current sources (residential). Discriminate among source transients.
- Simplest: Ringing (resonant) R-L-C circuit; include data logger and time stamp
- Moderate complexity: Computer calculates only summary parameters on the fly; include data logger and time stamp
- Higher complexity: Calculate effectiveness of transients on a event-by-event basis for specific cells, e.g., bone marrow or breast cells; include data logger and time stamp

Populations of Interest

- Identify candidate populations.
Considerations:
 - evaluate residential stability *versus* job stability
 - switched motors (seamstresses, tailors, dressmakers, barbers, carpenters, . . .)
 - microshocked population (confounding or controlled for by questionnaire ?)
- Next, measure the transient exposure for the candidate groups, and pick most exposed groups for epidemiologic study

Also:

- Residential transients and exposed residential groups - we already have some exposure data here (Sastre, Kavet, Guttman, and Weaver)
- Occupational, but non-utility populations (utility environment is well controlled, transients may be rare)
- Other, esoteric groups (welders, telephone workers?)

Recommendations

- The initial “transient studies” should be add-ons to ongoing epidemiological studies
- Determine what EMF attributes of transients are related to each other, pick the key descriptive parameters
- Collect taxonomy of transients; identify the “signature” of transients
- Correlate transients, measured with a stationary instrument, to activity data and to measured personal B-field exposure and intermittency (EMDEX meter); Is intermittency a surrogate for transients?
- Use existing transient exposure assessment studies to identify design needs for dosimeter-type instruments
- Determine what laboratory data would help identify biologically relevant transients; i.e., after identifying taxonomy, which transients are the important ones?
- Explore correlation of transients with wire codes; discriminate between transients that are generated by the distribution lines outside the home vs. the transients generated by wires and appliances inside the home and in nearby houses.
- Investigate prevalence of microshocks from electrical equipment, and microshocks from static discharges.
- Perform laboratory experiments with real-world transients to help identify biological endpoints.

Magnetic Moment Effects

Group 4

COORDINATOR: Lynne Gillette, DOE

CHAIR: Jack Sahl, Southern California Edison Company

PRESENTATIONS:

Free Radicals

Jan Walleczek, Jerry L. Pettis Memorial Veterans Administration Medical Center

Magnetosomes

Joseph Kirschvink, California Institute of Technology

REPORTER: Robert Banks, Robert S. Banks Associates, Inc.

Introduction

Lynne Gillette, coordinator

Our working group explored two very different biological mechanisms with the potential to explain how power frequency EMFs may effect the human body. We considered first the hypothesis that cellular radical pair recombination rates may be altered by field exposure thereby increasing the number of free radicals, which are linked to cancer. Our group also considered the hypothesis that magnetite crystals in cell systems could be conveying energy or signals to alter cell signals that initiate a variety of biological processes.

After much discussion and debate, the group concluded that both of these hypothesis were feasible. Both hypothesis have similar strengths and weaknesses. For instance, neither potential mechanism is dependent on a signal or energy that is greater than the thermal noise of the body. On the flip side, neither hypothesis can offer anything in the way of an explanation of why wire codes have shown a better correlation with disease that measured fields in many residential epidemiological studies. Since neither hypothesis could be dismissed, the group developed a list of exposure measurement parameters to collect in future epidemiological studies if researchers wanted to be able to test these hypotheses.

Summary of Speakers' Presentations

Robert S. Banks, Reporter

Working Group 4 considered two distinct molecular-level biophysical mechanistic hypotheses for power-frequency magnetic field biological effects: alteration of cellular radical-pair recombination rates (Radical-Pair Mechanism Hypothesis), and mechanical motion of magnetite crystals (Magnetosome Hypothesis).

The Working Group did not deliberate the two hypotheses in parallel, but considered the Radical-Pair (RP) Mechanism Hypothesis singularly in its first meeting, followed by the Magnetosome Hypothesis during its second meeting. Conclusions and recommendations were developed during the second meeting.

Radical-pair Mechanism Hypothesis

Free Radicals

Jan Walleczek, Jerry L. Pettis Memorial Veterans Administration Medical Center

Dr. Walleczek presented an overview of the RP Mechanism Hypothesis.

The RP mechanism involves magnetic-field coupling to non-thermal molecular states in biological tissue. In summary, the hypothesis is that magnetic fields influence RP reaction product yields, affecting cellular signaling events—with a gain of perhaps 20,000—which in turn may result in cellular-level effects.

Understanding the role of electron spin states in chemical reactivity is key to broader understanding of the RP Mechanism Hypothesis. Radicals are atoms or molecules with one or more unpaired electrons, which usually makes radical species highly chemically reactive. However, their reactivity is determined by the spin state of their outer-shell electrons. Static or time-varying magnetic fields can modify electron spin states during free-radical formation steps and thus alter radical-dependent biochemical reaction rates and product yields. In principle, these altered reaction kinetics could give rise to effects on cellular function and regulation.

Dr. Walleczek pointed out that radical reactions in biological systems can have the following effects:

1. Production of free radical species with *adverse* biological activity (e.g., lipid peroxidation).
2. Production of free radical species that have *necessary functions* in biological systems such as potential cell signaling functions and cytotoxic activity (e.g., reactive oxygen species, nitric oxide).
3. Function as *reaction intermediates* in enzyme reaction cycles (e.g., cytochrome P-450s, lipxygenases).

With respect the NIOSH/DOE Workshop's objectives, salient features of the RP Mechanism Hypothesis include:

1. The RP mechanism provides a physical explanation of how magnetic interactions, involving energies that are several orders-of-magnitude lower than the background thermal energy (kT), can affect living systems.
2. Thermodynamic laws are *not* violated because during the field interaction; only non-thermal, biochemical reaction kinetics are affected. For this reason, RP mechanism-mediated magnetic field effects are termed "magnetokinetic" effects.
3. For some biochemical reactions, predictions based on mathematical modeling have been verified in the laboratory with magnetic field levels as low as 0.5 mT.
4. The RP mechanism may be involved whenever radical species are generated, during biological processes that either create free radicals or operate via formation of transient radicals.

While there is insufficient experimental evidence that the RP mechanism plays a role in the mediation of magnetic field effects on biological systems, Dr. Walleczek emphasized the following observations in his concluding remarks:

1. No biophysical model of magnetic field interaction can neglect *a priori* the possibility of RP mechanism-mediated effects.
2. The RP mechanism is the only proposed mechanism to describe the interaction of weak magnetic fields (below $100 \mu T$) with biochemical reactions.
3. Resonance effects in accord with the RP mechanism are known.

Hypothesis Statement

From Dr. Walleczek's presentation, the Working Group formulated the following statement of the Radical-Pair Mechanism Hypothesis:

Cellular radical-pair recombination steps—which are coupled to signal transduction/amplification mechanisms—are affected by magnetic field exposure, including resonance-type interactions. Since free-radical processes are linked to carcinogenic processes, magnetic field radical-pair impacts could impact cancer development, including leukemia and breast cancer.

Discussion

The Working Group's discussion centered on the strengths and weaknesses of the Radical-Pair Mechanism Hypothesis in five areas:

1. **Does the Radical-Pair Mechanism Hypothesis address the thermal noise (kT) limit issue?** Since the applied magnetic field's influence is on non-thermal, biochemical reaction kinetics, thermal noise does not impose a limit on the interaction. This is the greatest strength of the Radical-Pair Mechanism Hypothesis.
2. **Is the Radical-Pair Mechanism Hypothesis biologically plausible?** Biologic plausibility has not been satisfactorily demonstrated in whole organisms. Research needs to be conducted into the influence of radical-dependent biochemical reaction rate changes on signal transduction and amplification pathways.
3. **Does the Radical-Pair Mechanism Hypothesis describe a mechanism that lies on the cancer initiation or promotion pathway?** Free radicals have been shown to be involved with carcinogenic processes, which strengthens the hypothesis. However, further research by mainstream cancer researchers is needed to establish whether EMF-induced radical-dependent biochemical rate changes can in fact influence cancer induction.
4. **Is the Radical-Pair Mechanism Hypothesis relevant to environmental field levels and characteristics?** There has been some experimental verification of the mechanism for static magnetic flux densities as low as 0.5 mT. This is, however, three orders of magnitude above levels associated with increased risk of childhood cancer. Additional research is needed to establish that the mechanism is operative 1) at these lower field levels; and 2) at the 60-Hz power frequency. The latter point is likely moot as the mechanism has time constants in the nanosecond range; on this time scale, a 60-Hz field is essentially static. Field polarity is irrelevant to the mechanism.
5. **Is the Radical-Pair Mechanism Hypothesis relevant to resolution of the measured magnetic field vs. residential wire code issue?** The question here is whether the mechanism addresses the disparity between childhood cancer relative risks when using measured magnetic fields versus wire codes as the exposure index. Since the mechanism is at the molecular level, it is inherently incapable of directly addressing this issue.

These issues need to be evaluated in the context of all other biophysical mechanistic hypothesis considered by the Workshop.

Magnetosome Hypothesis

Magnetosomes

Joseph Kirschvink, California Institute of Technology

Dr. Kirschvink provided background information on the Magnetosome Hypothesis.

The discovery of biogenic magnetite (Fe_3O_4) in human brain tissue (levels range from 5–10 nG/g up to 100 nG/g) suggests that these single-domain magnetic crystals (called, “magnetosomes”) may be responsible for some of the reported effects of weak extremely-low-frequency (ELF) magnetic fields. For this hypothesis, energy flux is not a factor at microwave frequencies and below—which addresses the thermal noise limit (kT) issue—rather, absorption is.

Dr. Kirschvink identified and described four possible magnetosome-mediated biological mechanisms of interaction:

1. **Mechanical Motion.** In the ELF range, two possible mechanical motion mechanisms may be involved:
 - **Magnetoreception**
 - **Ion channel activation**

Results from tissue culture experiments suggest that magnetosome crystals may be activating transmembrane calcium channels. A simple model has been proposed that connects a spherical magnetosome crystal to a mechanically sensitive ion gate via a cytoskeletal filament. Rotation of the crystal in response to the external field activates the gate.

Opening the gate requires a force of one piconewton acting through four nanometer, work of $\approx 4 \times 10^{-21}$ J, which equals the thermal noise limit, kT. A 0.1-mT rms 60-Hz magnetic field acting on a 0.1- μm spherical magnetite crystal can contribute this level of energy each half cycle, based on some assumptions regarding membrane viscosity. This is not the biological limit, with lower strength fields activating the mechanism at energy levels below kT.

Gating calcium into a cell via this mechanism could induce some rather strong effects. For example, in a dividing cell, the chromosome is being pulled apart by spindle fibers. If the local calcium concentration is increased, the spindle fibers can be broken, possibly leading to chromosome dysfunction.

2. **Radical-Pair Mechanism.** This is an application of the Radical-Pair Mechanism Hypothesis. The biological membrane surrounding the magnetosome is subject to a localized strong magnetic field of up to ~ 0.5 T. Rotation of the magnetosome under the influence of a 60-Hz magnetic field could alter the field resulting in changes in radical-pair reaction product yields.

3. **Membrane Poration.*** The idea is that under the influence of a magnetic pulse, magnetosomes located on the cell membrane could “rip” the membrane, which is equivalent to opening an ion channel. However, this mechanism is not likely to be of interest to the Working Group, as it is relevant to frequencies in the microwave range.
4. **Ferromagnetic Resonance.** Resonance and absorption of microwave electromagnetic energy are well established properties of all ferrites. Magnetite is one of the best broadband absorbers of microwave energy known, used in many industrial applications for heating. Theoretical analysis predicts that the spin resonance for single-domain magnetic crystals is in the 100 MHz–10 GHz range, depending upon crystal shape, crystallographic orientation and packing density.

Sub-thermal levels of microwave energy (i.e., below 10 mW/cm²) still contain a significant amount of energy. Because the background thermal energy, kT, is $\approx 4 \times 10^{-21}$ J, a 10-mW/cm² energy flux translates to 2.5×10^{-18} kT/cm²s. For the area of a typical 10- μ m² cell, this corresponds to $\approx 10^{12}$ kT/s; for the area of a single 0.1- μ m spherical magnetite crystal, $\approx 10^8$ kT/s. Thus, even a small amount of this energy, if absorbed through ferromagnetic resonance, can readily exceed the kT thermal limit.

Dr. Kirschvink stressed that energy should always be used in EMF exposure assessment, which is proportional to the square of the magnetic flux density.** This can be derived as follows: For plane-polarized fields, the magnitude of the Poynting vector, used in far-field analysis, is

$$\langle S \rangle = E_m B_m / 2\mu_0,$$

where E_m and B_m are the time-average values of the electric and magnetic fields and μ_0 is the permeability of free space (1.26×10^{-6} m/s). But because $E_m = cB_m$, where c is the speed of light (3×10^8 m/s), this becomes

$$\langle S \rangle = cB_m^2 / 2\mu_0 \text{ (W/m}^2\text{)}$$

Note should be made that this analysis is *not* frequency dependent, allowing consistent exposure assessment metrics across the ELF–microwave frequency range. Dr. Kirschvink stressed that this analysis is applicable to both far-field and near field situations. Circularly polarized fields have *twice* the energy content of linearly polarized fields.

*Vaughan, T.E. and J.C. Weaver. Energetic constraints on the creation of cell membrane pores for magnetic particles. *Biophysics J.* 71:616-622, 1996.

**Adair, R.K. Biological responses to weak 60-Hz electric and magnetic fields must vary as the square of the field strength. *Proc Natl Acad Sci* 91:9422-9425 1994.

Dr. Kirschvink's viewgraphs are as follows:

Magnetite and EMF Dosimetry

- I. Energy flux not a problem - Absorption is. Magnetite solves this one, both ELF and Microwave.
- II. Pretty Pictures of Biogenic Magnetite
- III. Possible Magnetite - Mediated Mechanisms
 - A. Mechanical Motion - ELF
 - (1) Magnetoreception
 - (2) Ion Channel Model
 - B. Radical Pair Effects in Magnetosome Membranes
 - C. Membrane Poration (Weaver)
 - D. Ferromagnetic Resonance at microwave frequencies

How to convert your field measurements to units of energy (or Power)

For plane-polarized waves, calculate the magnitude of the Poynting Vector ($\langle S \rangle$). The basic relationship is:

$$\langle S \rangle = E_m B_m / 2\mu_0$$

where E_m and B_m are the time-average values of the electric and magnetic fields, and μ_0 is the permeability of free space (1.26×10^{-6} henry/meter). But because $E_m = c B_m$, where c is the speed of light (3×10^8 m/s), this becomes:

$$\langle S \rangle = c(B_m)^2 / 2\mu_0 \quad (\text{W/m}^2)$$

Thus,

100 μT (1 G) rms field becomes	$1.19 \times 10^8 \mu\text{W/cm}^2$	or	$3 \times 10^{22} \text{ kT/cm}^2\text{-sec}$
10 μT (0.1 G) rms becomes	1.19×10^6		3×10^{20}
1 μT (10 mG) rms becomes	1.19×10^4		3×10^{18}
0.1 μT (1 mG) rms becomes	119		3×10^{16}

(Circularly Polarized waves have twice the energy density).

Not frequency dependent

All you need is on an "Antenna"

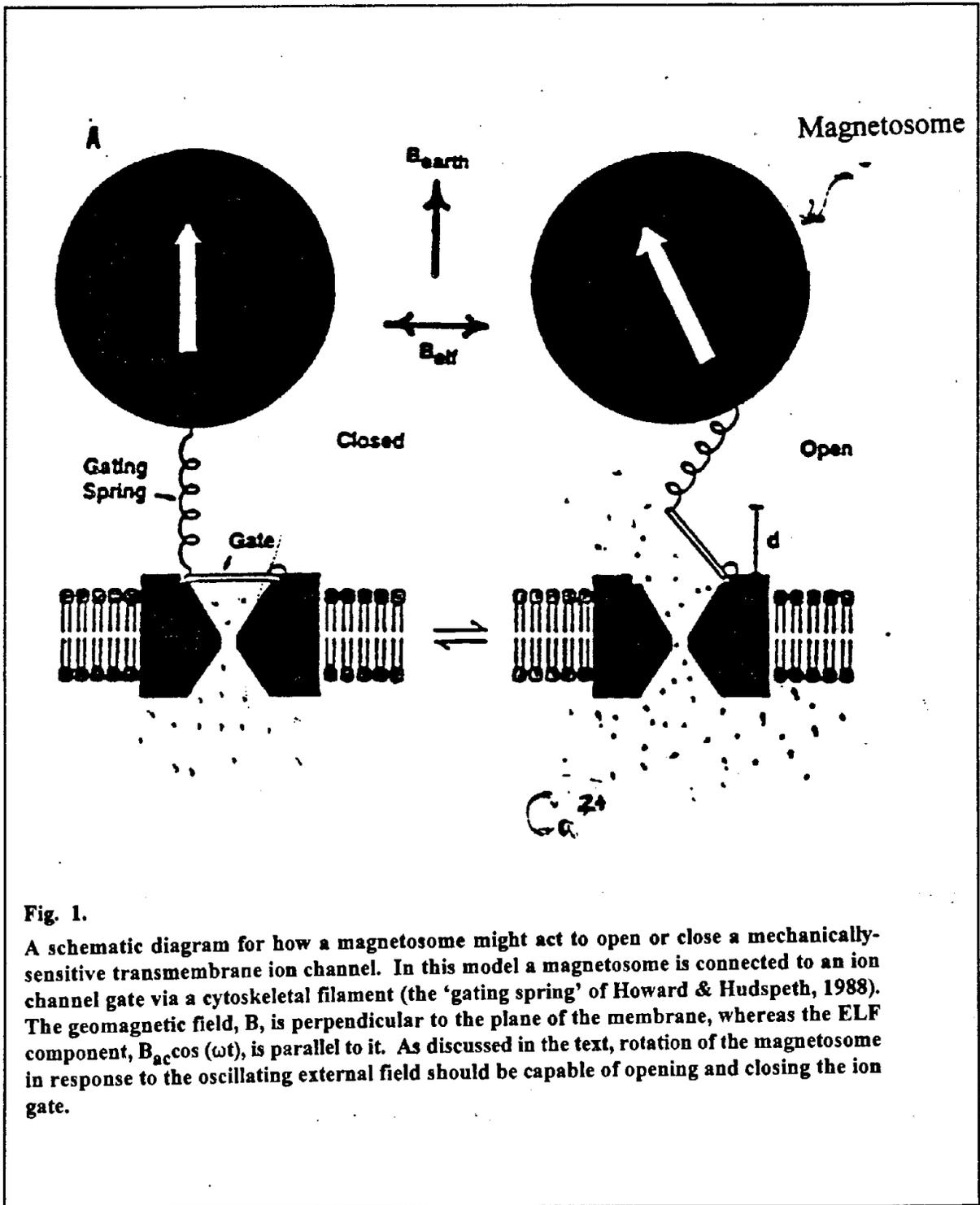


Fig. 1.

A schematic diagram for how a magnetosome might act to open or close a mechanically-sensitive transmembrane ion channel. In this model a magnetosome is connected to an ion channel gate via a cytoskeletal filament (the 'gating spring' of Howard & Hudspeth, 1988). The geomagnetic field, B , is perpendicular to the plane of the membrane, whereas the ELF component, $B_{ac} \cos(\omega t)$, is parallel to it. As discussed in the text, rotation of the magnetosome in response to the oscillating external field should be capable of opening and closing the ion gate.

Always use the ENERGY in Dosimetry

- Virtually all biological processes are governed by Einstein-Boltzmann relationships of the form

$$r = a e^{-\Delta E/kT}$$

where r is the reaction rate, a is a rate parameter, ΔE is the energy difference between two states, and kT is the thermal background energy.

- For any potential field (e.g., electric or magnetic), the energy density is proportional to the SQUARE of the field strength.
For example,

$$E(\omega) = \int_V B^2 dv(\omega)$$

Hence, for ELF epidemiology, something related to B^2 should be a better metric than simply B .

- Use of the energy at ELF frequencies makes dosimetry consistent with shorter wavelengths.

The following viewgraphs were used in Dr. Kirschvink's presentation:

Magnetokinetics, Mechanistics, and Synthesis

Keith A. McLauchlan
Physical Chemistry Laboratory, Oxford

Chemistry in Britain, September 1989, pp. 895-898.

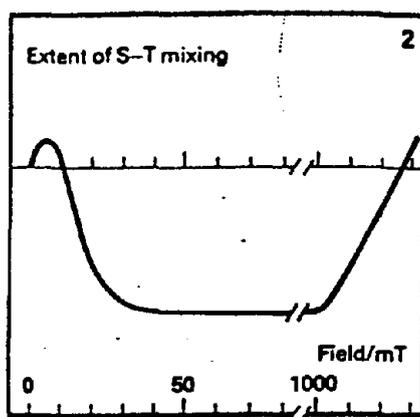


Fig. 2. The extent of S-T mixing in a typical radical pair is shown as a function of the applied field strength.

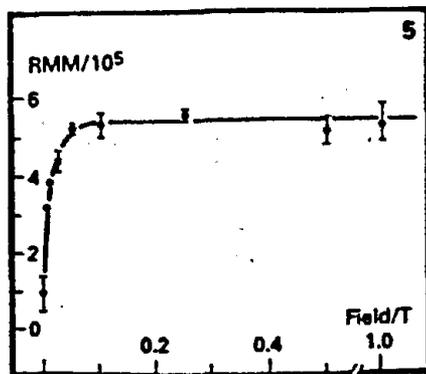


Fig. 5. The variation in the relative molecular mass of polystyrene, produced by photoinitiation of an emulsion polymerisation, with magnetic field. (Redrawn and reproduced with permission from N. J. Turro¹⁶)

Energetics of 'Sub-Thermal' levels of EMF Radiation

- The 1992 ANSI standard for maxim human exposure to microwave radiation was set at 10mW/cm² (It has recently been revised to vary with frequency).
- As the thermal background energy, kT, is $\sim 4 \times 10^{-21}$ Joule, the 10 mW/cm² translates to 2.5×10^{-18} kT/cm²-sec.
- For the area of a typical 10 μm^2 cell, this energy is $\sim 10^{12}$ kT/cell-sec.
- For the area of a single 0.1 μm magnetite cube, it is $\sim 10^8$ kT/s.
- Magnetite is one of the best, wide-band absorbers of microwave radiation through the process of **ferromagnetic resonance**, particularly in the 500 MHz to 10 GHz band (which includes cellular telephones, microwave ovens, police radar, ...).
- If 'sub-thermal' levels of microwave radiation actually do have biological effects, the most likely site of action is in a magnetite-containing cell (a **magnetocyte**).
- Magnetite crystals could separate low-frequencies from a microwave carrier wave.

Hypothesis Statement

From Dr. Kirschvink's presentation, the Working Group formulated the following statement of the Magnetosome Hypothesis:

Mechanical motion of magnetite crystals in a cellular environment has the ability to transduce energy efficiently from ELF magnetic fields to cellular processes. This could influence biology either through a sensory process (e.g., magnetoreception) or through direct action of magnetosomes on adjacent cellular structures, causing a change in cellular signal transduction/amplification events.

Discussion

The Working Group's discussion centered on the strengths and weaknesses of the Magnetosome Hypothesis in the same five areas as in the discussion of the Radical-Pair Mechanism Hypothesis.

1. **Does the Magnetosome Hypothesis address the thermal noise (kT) limit issue?** Since the applied magnetic field produces mechanical motion of magnetite crystals with very large magnetic moments, the resulting energy is within reach of the thermal noise limit. This is the greatest strength of the Magnetosome Hypothesis.
2. **Is the Magnetosome Hypothesis biologically plausible?** Biologic plausibility has not been satisfactorily demonstrated in human tissues although the mechanism has been demonstrated with magnetotactic bacteria with very large magnetosomes. Research needs to be conducted into the influence of the mechanical motion of magnetite crystals on signal transduction and amplification pathways.
3. **Does the Magnetosome Hypothesis describe a mechanism that lies on the cancer initiation or promotion pathway?** Mechanical motion of magnetite crystals has not presently been linked to carcinogenic processes. Research is needed to establish whether EMF-induced magnetite crystal mechanical motion can in fact influence cancer induction.
4. **Is the Magnetosome Hypothesis relevant to environmental field levels and characteristics?** Theoretical analysis suggests that the magnetosome-mediated biological mechanisms may be operative with ELF magnetic fields as low as 0.1 μT , and assemblages of magnetite-containing cells can have even lower thresholds.
5. **Is the Magnetosome Hypothesis relevant to resolution of the measured magnetic field vs. residential wire code issue?** The question is whether the mechanism addresses the disparity between childhood cancer relative risks when using measured magnetic fields versus wire codes as the exposure index. Since the mechanism is at the molecular level, it is inherently incapable of directly addressing this issue.

These issues need to be evaluated in the context of all other biophysical mechanistic hypothesis considered by the Workshop.

Conclusions and Recommendations

After considering each hypothesis independently, the Working Group discussed them in context with each other, finding both to be viable with some quite similar characteristics. With respect to exposure measurements necessary to test both hypotheses in future epidemiologic research, the Working Group had two general conclusions:

1. The total frequency range from DC to microwave—wherever the spectral content is—needs to be considered, not just power frequencies.
2. Measurement data needs to be collected in such a way that the total energy content of the field can be reconstructed.

The Working Group developed the following recommendations with respect to an exposure metric and measurements:

1. **Exposure Metric.** Total magnetic field energy content across the DC–microwave frequency range.
2. **EMF Measurements.** The following measurements need to be made simultaneously:
 - **Geomagnetic field amplitude and orientation.**
 - **Time-varying magnetic field amplitude, orientation and polarization.** In view of the frequency response of presently available exposure meter, the frequency spectrum can be divided in two parts: 3–800 Hz, which is covered by present instrumentation; and 800 Hz–microwave.
 - **Integration of magnetic field amplitude spectral content.**
 - **Markers for temporally relevant (duration, chronobiologic and stage-of-life factors) exposure characteristics.**
3. **Co-Factor Measurements.** The following need to be measured concurrently:
 - **Exposure variables for other mechanisms that may enhance risk.**
 - **Confounding variables.**

The following viewgraphs were written to present the working group's conclusions at the final plenary session.

Radical-Pair Mechanism Hypothesis

Cellular radical-pair recombination steps—which are coupled to signal transduction/amplification mechanisms—are affected by magnetic field exposure, including resonance-type interactions. Since free-radical processes are linked to carcinogenic processes, magnetic field radical-pair impacts could impact cancer development, including leukemia and breast cancer.

Magnetosome Hypothesis

Mechanical motion of magnetite crystals in a cellular environment has the ability to transduce energy efficiently from ELF magnetic fields to cellular processes. This could influence biology either through a sensory process (e.g., magnetoreception) or through direct action of magnetosomes on adjacent cellular structures, causing a change in cellular signal transduction/amplification events.

Radical-Pair and Magnetosome Mechanism Hypotheses

(should be evaluated with respect to all other mechanistic hypothesis)

	STRENGTH	WEAKNESS	NEEDS
KT	XXX		
Biologic Plausibility	X		Radical-pair/ magnetosome signal transduction/ amplification pathways
Cancer Pathway	XX		Mainstream cancer issues/research
Relevant to Environmental Field Levels and Characteristics		XX	Refined research
Relevant to Wire- Code Benchmark		X	

Conclusions

- Consider total range from DC to microwave; wherever energy is; don't focus on 50/60 Hz.
- Collect data in such a way that the total energy content of the field can be reconstructed.
- Both radical-pair mechanism and magnetosome hypotheses are viable.

Exposure Metrics and Measurement Methods

Physical Quantity

- Vectoral sum of magnetic field energy over the DC-microwave frequency range

Measurements

- DC magnetic field amplitude and orientation
- AC magnetic field (3-800 Hz; 800 Hz-microwave) amplitude, orientation and polarization
- Spectral analysis to integrate field amplitude
- Temporal relevance

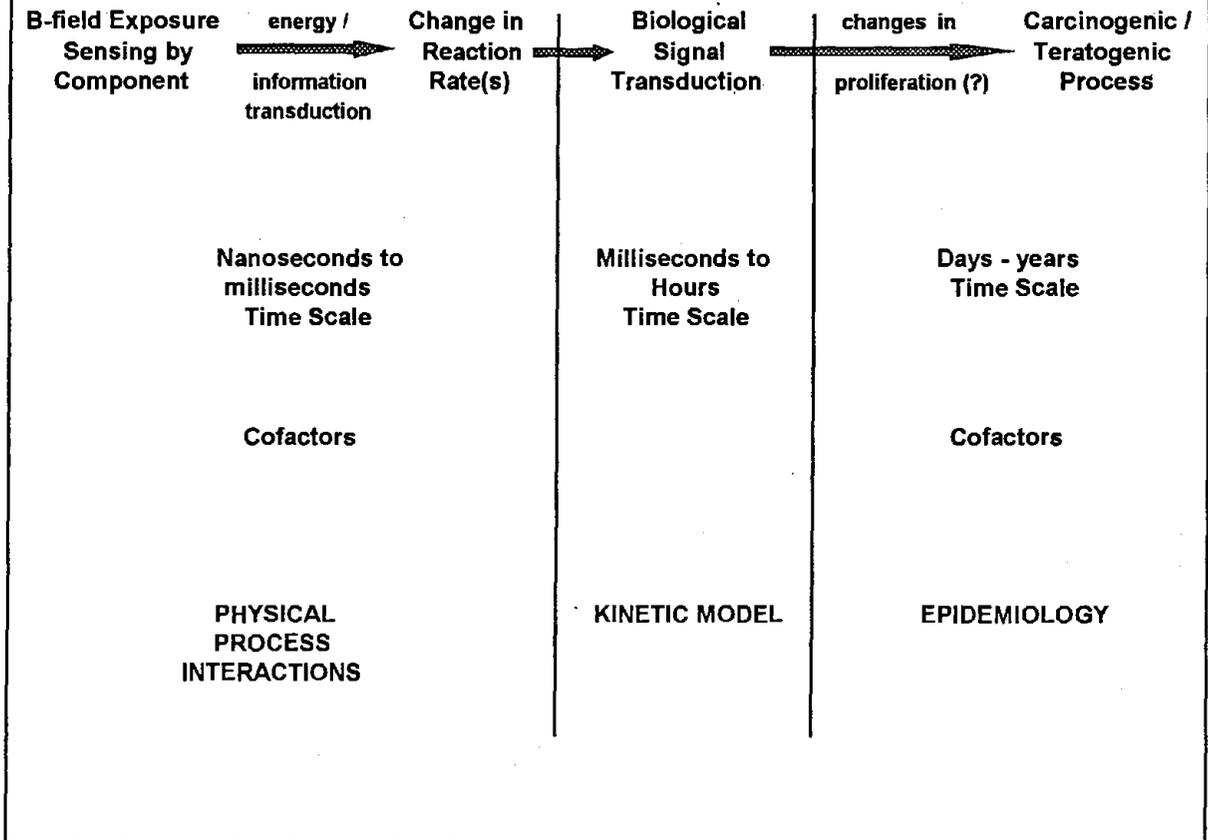
Co-factors

- Enhancing mechanisms
- Other risk factors

Time-Related Exposure Characteristics

- Duration characteristics
- Chronobiologic characteristics
- Life-cycle

**Processes, Mechanisms and Time Scales for EMF Interaction
with Biological Systems**



FINAL PLENARY SESSION

WORKING GROUP REPORTS:

Resonances

Gerri Lee, California Department of Health

Coherence and Intermittency

Gene Sobel, University of Southern California

Transients

Richard Stevens, Battelle Pacific Northwest Laboratory

Magnetic Moments

Jack Sahl, Southern California Edison

CONCLUDING DISCUSSION

Chair: Paul Gailey, Oak Ridge National Laboratory

Recorder: Robert Patterson, Temple University

REFLECTIONS ON THE WORKSHOP

Joseph Bowman, NIOSH

Lynne Gillette, DOE

Paul Gailey, ORNL

Gregory Lotz, NIOSH

Working Group Reports

The final plenary session on Wednesday morning began with the presentation of conclusions and recommendations by the chairs of the four working groups.

I. Resonances

Chair: Gerri Lee, California Department of Health

A. Electrical Circuit Models

Hypothesis: specific coherent or repetitive signals affect biological substrates which may be associated with adverse health

Features:

- * signal / noise < 1
- * focus on signal integrator not exposure metric
- * Low Priority: Innovative but still in abstract form

Conclusion: Not applicable to issues at workshop

B. Ion Resonance Models

Hypothesis: Specific AC/DC field combinations affect interactions of ions with biological substrates which may be associated with adverse health

Ion Parametric Resonance

Quantum Coherence

* Response peaks at: $n 2\pi f = \text{const.} \times B_{dc}$

* Resonance const. = q/m

* Resonance const. = $q/2m$

* B_{ac} parallel to B_{dc}

* B_{ac} perpendicular to B_{dc}

* Response varies with B_{ac} intensity (Bessel func.)

* No prediction with B_{ac} intensity

C. Biological Support

Laboratory:

- * Calcium Transport
- * Conditioning of Rat Behavior
- * Diatom Mobility
- * Calmodulin Reaction
- * Neurite Outgrowth

Epidemiology:

- * Childhood Leukemia
- * Based on different mechanisms
- * Variety of Resonance Parameters
- * Findings not confirmed

D. Measurement Requirements

Objective: To accurately discriminate “resonance” environments from “non-resonance” environments in a variety of residential and occupational settings

Essential Components:

- * B_{dc} (3-axes)
- * B_{ac} (3-axes, frequency)
- * B_{ac} - to - B_{dc} orientation
- * Defined period of time to maintain resonance
- * Preselected resonance parameters

Instrument: Monitor requires a wave capture function
(modified Multiwave System II)

E. Proposed Metric

Resonance Yield (Y): Predicted change in a physical property (*e.g.* a reaction rate) resulting from the MF exposure under a resonance mechanism

Output:

Time of measurement
Y
 B_{dc}
 B_{ac} - parallel to B_{dc}
 B_{ac} - perpendicular

F. Recommendations

Refinement of metric components needed before using metric in epidemiologic studies:

- a. Lab studies to assess ions related to disease
- b. Exposure surveys to define residential and occupational AC/DC combinations that may predict resonance
- c. Exposure surveys to identify residential and occupational settings with both “resonance-on” and “resonance-off” conditions
- d. Test meter in appropriate environments to define the minimum data collection needed to construct reliable and manageable metric components

G. Summary

Need to assess laboratory, theoretical, and exposure assessment survey results together to:

1. Determine what resonance parameters to use for Y
2. Refine the meter capabilities for epidemiologic exposure environments
3. Select which environments are appropriate to test the resonance hypothesis
4. Test the resonance hypothesis using these environments

II. Coherence and Intermittency

Chair: Gene Sobel, USC

A. Mechanisms considered

1. Coherence model
2. Kinetic model
3. Chronobiological considerations

B. Hypotheses

1. Coherence

A. Constancy in the EMF field for longer than 10 seconds induces a biological response

B. A change in the EMF field over a 0.1 second or more duration prior to 10 seconds prevents a response

C. A large number of constancy periods in the EMF field leads to the disease under investigation

2. Homeostasis Disruption

A large number of changes in the EMF field, especially in time periods less than 10 seconds leads to the disease under investigation

3. Effect Modifiers to Consider

A. Chronobiological: light; sleep-wake cycle; season; activity

B. Associated diseases

C. Sensitivity, stress, genetic predisposition

C. Exposure Metrics

1. RMS magnetic field magnitude
2. Frequency

Note: DC Fields Not Needed

D. Exposure Assessment

1. Personal dosimetry -- As a last resort

2. Task-specific dosimetry --
 - Specific types of equipment
 - Specific usage patterns
 - Whole-body exposure

- Measurements taken in actual working situation
- Area measurements

3. Interview / Field Observations

- Lifetime Exposure Information --
 - Occupational electrical equipment
 - Residential electrical equipment
 - Hobby electrical equipment

- Other Peculiar Sources of Exposure in Environments

E. Study Design

1. Dosimeters which can measure as much as possible
2. Use task-specific measurements so as to maximize the number of different parameters of EMF recorded
3. Observe occupational, residential and hobby task-specific exposures
4. Personal dosimetry as necessary
5. Case-control study for rare diseases
6. Combination of case-control and longitudinal study for common diseases
7. Consider genetic predisposition, e.g., look at family members, and other possible effect modifiers

Discussion

Some participants took issue with the idea that a 10 second constancy period could be adopted on the basis of the relatively narrow range of studies so far done by Dr. Litovitz and colleagues. They also commented that any one hypothesis should not be adopted as if it would apply to all possible biological subsystems. In reply, Dr. Litovitz said that he would not want an epidemiologist to rush out and take measurements based on his model. Others from the Coherence group emphasized the strong need for more laboratory data which can illuminate mechanisms.

III. Transients

Chair: Richard Stevens, PNL

A. Metrics Involving Transients

- Transient duration
- Transient repetition rate
- Peak B
- Peak dB/dt
- Average dB/dt to peak
- Frequency spectrum

B. Considerations

- Contrast internally (within-home) generated vs. externally (outside-the-home) generated transients
- Determine variability of the steady state; identify intermittency in the baseline AC and DC fields
- Monitor microshocks (which may produce chromosome breaks); i.e., measure current transients through people
- Monitor a 1 to 10 second window, 1 Hz to 100 kHz frequency bandwidth
- Sample different parameters at different times (back-to-back)

C. Instrument Needs

- Need to define "event"
- Need to develop necessary software:
 - discrimination (avoid lock-up on dimmer-switch signals)
 - signature analysis (transient recognition)
 - coincidence testing (correlation to intermittency or to transients in grounding currents)
- Synchronize transients with return current sources (residential) to discriminate among source transients.
- Simplest: Ringing (resonant) R-L-C circuit; include data logger and time stamp
- Moderate complexity: Computer calculates only summary parameters on the fly; include data logger and time stamp
- Higher complexity: Calculate effectiveness of transients on an event-by-event basis for specific cells, e.g., bone marrow or breast cells; include data logger and time stamp

D. Populations of Interest

- Identify candidate populations.
 - Considerations:
 - evaluate residential stability *versus* job stability

- switched motors (seamstresses, tailors, dressmakers, barbers, carpenters, . . .)
- microshocked population (confounding or controlled for by questionnaire ?)
- Next, measure the transient exposure for the candidate groups, and pick most exposed groups for epidemiologic study

Also:

- Residential transients and exposed residential groups - we already have some exposure data here (Sastre, Kavet, Guttman, and Weaver)
- Occupational, but non-utility populations (utility environment is well controlled, transients may be rare)
- Other, esoteric groups (welders, telephone workers?)

E. Recommendations

- The initial “transient studies” should be add-ons to ongoing epidemiological studies
- Determine what EMF attributes of transients are related to each other, pick the key descriptive parameters
- Collect taxonomy of transients; identify the “signature” of transients
- Correlate transients, measured with a stationary instrument, to activity data and to measured personal B-field exposure and intermittency (EMDEX meter); Is intermittency a surrogate for transients?
- Use existing transient exposure assessment studies to identify design needs for dosimeter-type instruments
- Determine what laboratory data would help identify biologically relevant transients; i.e., after identifying taxonomy, which transients are the important ones?
- Explore correlation of transients with wire codes; discriminate between transients that are generated by the distribution lines outside the home vs. the transients generated by wires and appliances inside the home and in nearby houses.
- Investigate prevalence of microshocks from electrical equipment, and microshocks from static discharges.
- Perform laboratory experiments with real-world transients to help identify biological endpoints.

IV. Magnetic Moments

Chair: Jack Sahl, Southern California Edison Company

Radical-Pair Mechanism Hypothesis

Cellular radical-pair recombination steps—which are coupled to signal transduction/amplification mechanisms—are affected by magnetic field exposure, including resonance-type interactions. Since free-radical processes are linked to carcinogenic processes, magnetic field radical-pair impacts could impact cancer development, including leukemia and breast cancer.

Magnetosome Hypothesis

Mechanical motion of magnetite crystals in a cellular environment has the ability to transduce energy efficiently from ELF magnetic fields to cellular processes. This could influence biology either through a sensory process (e.g., magnetoreception) or through direct action of magnetosomes on adjacent cellular structures, causing a change in cellular signal transduction/amplification events.

Radical-Pair and Magnetosome Mechanism Hypotheses

(should be evaluated with respect to all other mechanistic hypothesis)

	STRENGTH	WEAKNESS	NEEDS
KT	XXX		
Biologic Plausibility	X		Radical-pair/ magnetosome signal transduction/ amplification pathways
Cancer Pathway	XX		Mainstream cancer issues/research
Relevant to Environmental Field Levels and Characteristics		XX	Refined research
Relevant to Wire- Code Benchmark		X	

Conclusions

- Consider total range from DC to microwave; wherever energy is; don't focus on 50/60 Hz.
- Collect data in such a way that the total energy content of the field can be reconstructed.
- Both radical-pair mechanism and magnetosome hypotheses are viable.

Exposure Metrics and Measurement Methods

Physical Quantity

- Vectorial sum of magnetic field energy over the DC-microwave frequency range

Measurements

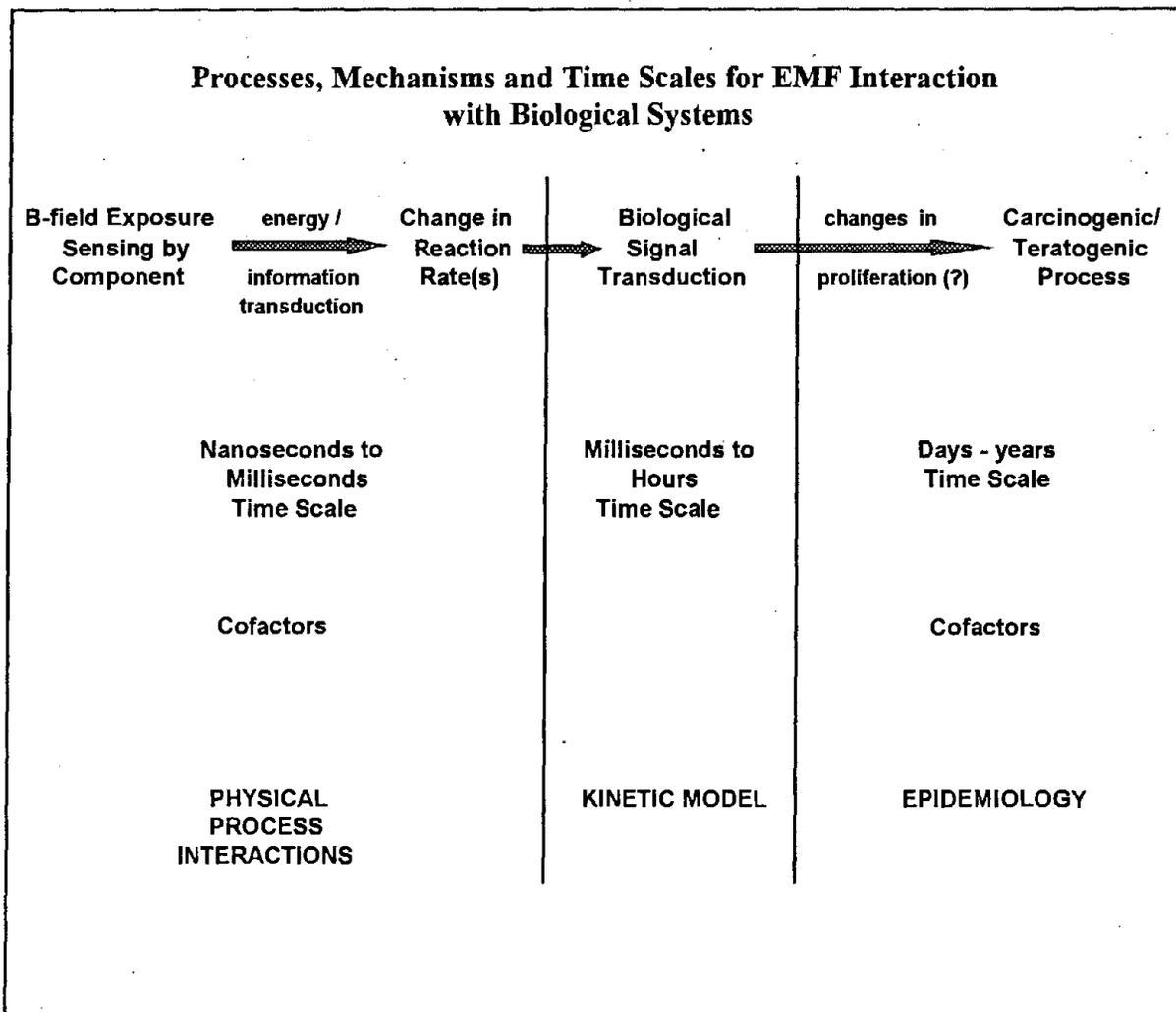
- DC magnetic field amplitude and orientation
- AC magnetic field (3-800 Hz; 800 Hz-microwave) amplitude, orientation and polarization
- Spectral analysis to integrate field amplitude
- Temporal relevance

Co-factors

- Enhancing mechanisms
- Other risk factors

Time-Related Exposure Characteristics

- Duration characteristics
- Chronobiologic characteristics
- Life-cycle



Discussion

Dr. Litovitz objected to the working group's suggestion of energy as the metric, saying that the same energy deposition with different modulation can produce different effects. Dr. Kirschvink responded that the occurrence of an effect or no effect with the same energy deposition was a function of the mechanism.

Concluding Discussion

The workshop concluded with a guided discussion with the goal of identifying:

- a) the most plausible hypotheses,
- b) the best research strategies for testing these hypotheses
- c) exposure assessment methods valid for several hypotheses

These objectives were not entirely met. Although there was advocacy for some biological hypotheses, the participants were not able to rank them on the basis of plausibility. Working groups were able to quantify their exposure metrics only partially. Discussion of exposure assessment protocols was limited. In the end, the principal product from the final plenary session was Table 1 summarizing the EMF measurements needed to test the four hypotheses.

EMF Exposure Measurements for Evaluating Biological Mechanisms

Requirements for calculating the metrics recommended more than one working group

Measurement	Mechanism			
	Resonances	Coherence	Transients	Magnetic Moments
B_{DC}				
Magnitude	X			X
Orientation	X			X
B_{AC}				
Magnitude	X	X*	X†	X
Orientation	X			X
Frequency spectra	X	X*	X**	X††
Duration	X	X	X	

* exposure must be constant over 0.05-0.10 sec sampling period

† peak magnitude of B_{AC}; also the peak and RMS magnitudes of the magnetic field derivative dB/dt

** 1-100 kHz bandwidth

†† bandwidth from DC to microwave

Here are some remarks from the concluding discussion:

On designing laboratory studies:

- "The epidemiological evidence should now be used to help design the next generation of lab experiments."
- "I think the meeting is a big disappointment. I thought there would be more discussion between the laboratory and epidemiological scientists."
- "This was a great meeting for me. I got many ideas for new experiments."

- "Experimentalists should study the kinds of fields that exist in the environment, that is, fields that are highly variable and involve transients."

On epidemiologic tests of mechanism hypotheses:

- "More biological studies are needed to confirm these mechanisms before launching new epidemiological studies."
- "The working groups gave us several practical ways that mechanisms can be tested right now, especially by add-on exposure measurements with existing epidemiology studies."
- "It is preposterous to consider epidemiology for testing these EMF hypotheses. By its nature, epidemiology is too blunt a tool."
- "This workshop gave me several ideas for hypotheses which I can test with my epi study right away."
- "Would an epi study to test one of the Workshop's hypotheses have any chance at all of getting funded?"

On measuring everything about EMF exposures:

- "There are a variety of possible EMF mechanisms, and we will never understand their biology well enough. Therefore we must proceed and measure everything about the fields. The data sets can then be analyzed to find out what metrics might be different between cases and controls."
- "When you talk about measuring everything, do you how much data that is? You would never use all the data you collect."
- "Some may argue that such an approach is hypothesis generation rather than hypothesis testing, and EMF research is beyond that. We are not."
- "It is important to measure everything possible in an epidemiological study -- it may be useful later."

Reflections from the Workshop Organizers

Joseph Bowman, NIOSH

Although the workshop did not produce the desired blueprint for new EMF epidemiologic studies, these proceedings are a gold mine of promising ideas for future research. For exposure assessment experts, the working groups specified new kinds of monitors needed for epidemiologic tests of EMF mechanisms. The big unresolved issue was whether these monitors should store the voluminous waveform data or just keep the calculated metrics which possibly relate to biological mechanisms. I feel that epidemiologic investigations in the foreseeable future will need both kinds of instruments: personal dosimeters for long-term monitoring of the most important metrics, and portable monitors to capture waveforms and transients over briefer periods.

For epidemiologists, the workshop brought out two new approaches for future EMF studies: the two-stage designs described by Duncan Thomas for testing hypotheses, and generating new hypotheses by measuring "everything" to which the cases and controls are exposed. During the workshop's concluding discussion, participants were deeply split on whether hypothesis testing or hypothesis generation is the best strategy for future epidemiologic studies.

An important postscript to this debate appeared a few months after the workshop when David Savitz and Dana Loomis published their massive study of electric utility workers. In discussing the contradictions between their findings and other occupational EMF studies, Savitz and Loomis said: "Lacking a clear biologic rationale for selecting magnetic field indices ..., each set of investigators makes a series of informed but arbitrary choices ... [which] may all contribute to divergent results," a state of affairs remarkably similar to the wire code paradox with childhood cancers. Their final sentence strikes me as an appropriate summation for the Workshop on EMF Exposure Assessment and Epidemiology:

Future investigations of these diseases in relation to magnetic field exposure should be driven ... by more specific, testable hypotheses regarding biologically relevant exposure metrics that could test with more precision whether there is a causal link between exposure and disease.

-- Savitz & Loomis, *Am. J. Epidemiol.* 141:123-134, 1995

Lynne Gillette, DOE

This workshop was pivotal for the EMF RAPID Program on many levels. It helped to shape the exposure measurement work being carried out under the program. It strengthened our resolve to collect as many exposure parameters as feasible in a given study, since there are viable mechanisms for all the parameters we have imagined. I believe that this workshop also helped some of the biological researchers see the undeniable value in a variety of types of exposure and how these exposures might be produced and/or documented in the laboratory.

During the workshop I was continually impressed with the willingness of EMF researchers to share information and ideas and let others openly question and scrutinize them. I think this workshop was not only a forum for people to absorb new information, but an invitation to think about "old" information in new ways and to take the first baby steps toward defining a plan for systematically evaluating for all these possible biological mechanisms.

Paul Gailey, ORNL

Part of the value of this workshop was the fact that it brought attention to the difficult question of EMF exposure metrics. In the attempt to determine whether or not EMF exposure affects human health, lack of knowledge about appropriate exposure metrics is one of the key stumbling blocks. This deficiency limits our ability to design both laboratory and epidemiologic studies that will help clear up the controversy about possible biological and health effects of EMF exposure. Fortunately, a number of researchers are now attacking this problem from opposite directions - the physics of EMF energy coupling to biological systems on one side, and careful analysis of real-world field environments on the other.

Through this workshop, we were able to bring both groups together with researchers from the EMF biology and epidemiology communities to discuss progress and to benefit from each others' findings. In addition to advancing knowledge in this area, the workshop helped to insure that the health effects researchers are able to take advantage of the latest advances in our understanding of EMF exposure metrics.

Gregory Lotz, NIOSH

The workshop was a success in stimulating intense dialog among epidemiologists, laboratory biologists, and physical scientists, both exposure assessment experts and theoreticians. These specialties don't always take the time to interact, but the opportunity to do so was both stimulating and fruitful, both individually and collectively. I observed that many laboratory scientists left the workshop with a new awareness of the need to test the biological effects of EMF beyond 50/60 Hz sinusoidal fields. The workshop also influenced subsequent exposure assessment studies, such as the measurements made in 1995 in Scandinavia by DOE and Battelle Pacific Northwest Laboratory scientists.

Another success of the workshop was in better defining questions important to assessing EMF health effects and developing practical methods for answering these questions. Workshop deliberations often led to the suggestion that exposure assessments should measure "everything" about EMF, in order to maximize the potential to evaluate many metrics. In reply, engineers and epidemiologists pointed out the technical and logistic problems in doing so. From these exchanges, participants left the workshop with ideas for new instruments and study designs.

The workshop failed to reach consensus on the goal of determining the most important hypotheses to test. When we undertook this workshop, we knew that these were challenging questions, and they proved to be so. Nevertheless, the interdisciplinary dialog and ideas that were exchanged were significant and timely in advancing our consideration of these important questions.

We thank the workshop participants for their contributions.

Appendix A

“NIOSH/DOE Workshop on Exposure Assessment and Epidemiology”

Article from *EMF Health and Safety Digest*, October 1994

NIOSH/DOE Workshop on Exposure Assessment for Epidemiology

The National Institute for Occupational Safety and Health (NIOSH) and the U.S. Department of Energy (DOE) co-sponsored a three-day workshop in Cincinnati on September 26–28 that brought together approximately 100 epidemiologists, exposure assessors, biophysicists and biologists interested in EMF health effects. According to W. Gregory Lotz, PhD, NIOSH, the workshop was successful in focusing attention from many disciplines on how to design exposure assessment protocols to get the most useful information for epidemiologic investigation.

Goals of the workshop were threefold:

- identify the two or three most plausible biological hypotheses for how occupational and residential exposure may lead to reported associations with adverse health effects—leukemia and breast cancer in particular—that might be tested in future NIOSH epidemiologic studies;
- develop quantitative exposure metrics from these hypotheses for assessing exposures in occupational and residential settings;
- propose exposure assessment strategies that will collect data needed to assess future hypotheses with various study populations.

"What can laboratory scientists do to help epidemiologists with their exposure assessment methods?"

— Carl Blackman, U.S. EPA

One of the opening presenters, Carl Blackman, PhD, U.S. Environmental Protection Agency, summarized well the workshop's task, "What can laboratory scientists do to help epidemiologists with their exposure assessment methods?"

He noted that a number of years ago, epidemiologist David A. Savitz, PhD, University of North Carolina-Chapel Hill, predicted that as methods improved, epidemiologic results would become clearer—relative risks would move toward one, or above ten. "That hasn't happened," Blackman said. "The relative risk is still hovering around two or three. Is epidemiology not using the correct metric? Or is the human system so complex that we cannot see effects?... Are the easiest metrics to measure the ones that will tell us about health effects?"

The Kinetic Model

The kinetic model of EMF effects was discussed by Theodore A. Litovitz, PhD, Catholic University, on the first afternoon, followed by Reba Goodman, PhD, Columbia University, who applied it to her own work. The two presentations set the tone for much of the meeting, with working group chairs referring to the kinetic model in several instances. The Litovitz kinetic model:

- attempts to account for "window" effects; i.e., ranges (field strength, frequency, duration) in which biological systems exhibit increased sensitivity to EMF exposure;
- assumes that the direct effect of EMF exposure is to increase the rates of production and degradation of messenger RNA or proteins;
- is a multi-step chemical reaction model; each step with a distinct reaction rate constant, with EMF exposure affecting the second rate constant;
- demonstrates that "window" effects can be accounted for by recognizing the transient character of the response of biological systems; and
- predicts that the maximum biological effect occurs at some intermediate (relatively short) time duration of exposure, at any given field strength.

There are a number of epidemiologic implications of the kinetic model. For example, for a given field strength, there would be a time duration that induces a maximum biological effect. It also implies that for a given time duration, there would be a field strength that induces a maximum biological effect. Finally, if the model is correct, in epidemiologic studies, effect measures will probably *not* correlate well with time-averaged field strength exposure measures in either homes or workplaces. A better measure might be times per day that a subject enters a space of known field strength and the duration of that exposure.

Small Group Format

Participants chose one of four working groups, each of which considered a different mechanistic hypothesis:

Resonances; coherence and intermittency; induced currents, transients and otherwise; and magnetic moments. Each group was charged to develop a mechanistic hypothesis to be presented as part of its report in the final plenary session. The resulting hypotheses were:

Resonances—There are specific AC/DC magnetic field combinations (perpendicular and parallel respective orientations) that affect the interaction of biologically important small ions with biological substrates in a manner that may lead to disease.

Coherence and Intermittency—The applied magnetic field must be “constant” for periods longer than 10 seconds, as sensed by membrane receptors, in order to induce a biological response. A “change” longer than 0.1 second will prevent the response. A large number of constancy periods may lead to disease.

Induced Currents, Transient and Other—One or more of the following metrics characterizing transient events may be predictive of disease: transient duration, transient repetition rate, peak magnetic field (B_{max}), maximum time-rate-of-change of magnetic field (dB/dt_{max}), ratio of average to peak time-rate-of-change of magnetic field ($dB/dt_{avg}/dB/dt_{max}$), spectral content.

Magnetic Moments—I. Radical pair formation. Cellular radical pair recombination steps—which are coupled to signal transduction/amplification mechanisms—are affected by magnetic field exposure, including resonance-type interactions. Since free-radical processes are linked to carcinogenic processes, magnetic field radical pair impacts could affect cancer development, including leukemia and breast cancer.

II. Magnetosomes. Mechanical motion of magnetite crystals in a cellular environment has the ability to transduce energy efficiently from ELF magnetic fields to cellular processes. This could influence biology either through a sensory process (e.g. magnetoreception) or through direct action of magnetosomes on adjacent cellular structures, causing a change in cellular signal transduction/amplification events. (See sidebar for a list of presenters by group.)

Some Surprising, Interesting Recommendations

In addition to developing a statement of its hypothesis, each group deliberated and reported on various issues. All groups made specific measurement recommendations.

An area of general consensus was the need for simultaneous measurement of broadband AC spectral content and the geomagnetic field, in apparent preference to further investigation of wire-codes.

Group 1 **RESONANCES**
Coordinator: Joseph D. Bowman, NIOSH
Chair: **Geraldine Lee**, California Department of Health Services
Recorder: **William H. Bailey**, Bailey Research Associates
Speakers: **Janie Page Blanchard**, Bechtel Corporation
Exposure Metric Combinations from the Ion Parametric Resonance Model
Joseph D. Bowman, NIOSH
Ionic Magnetic Resonance and Quantum Coherence Mechanisms
Frank Barnes, University of Colorado
Stochastic Resonances and Phase Locking

Group 2 **COHERENCE AND INTERMITTENCY**
Coordinator: W. Gregory Lotz, NIOSH
Chair: **Eugene Sobel**, University of Southern California
Recorder: **Asher R. Sheppard**, Asher Sheppard Consulting
Speakers: **Theodore A. Litovitz**, Catholic University of America
The Coherence Model
Charles J. Montrose, Catholic University of America
The Kinetic Model
Ken Groh, Argonne National Laboratory
Chronobiological Considerations

Group 3 **INDUCED CURRENTS, TRANSIENT AND OTHERWISE**
Coordinator: Paul Gailey, Oak Ridge National Laboratory
Chair: **Richard G. Stevens**, Pacific Northwest Laboratory
Recorder: **Peter Valberg**, Gradient Corporation
Speakers: **Antonio Sastre**, A.S. Consulting & Research
Transients
Art Pilla, Mt. Sinai School of Medicine
Gap Junctions, Tissue Dielectrics, Ion Binding and EMF Bioeffects
Charles Polk, University of Rhode Island
Induced Currents

Group 4 **MAGNETIC MOMENTS**
Coordinator: Lynne Gillette, DOE
Chair: **Jack D. Sahl**, Southern California Edison Company
Recorder: **Robert S. Banks**, Robert S. Banks Associates, Inc.
Speakers: **Jan Walleczek**, Jerry L. Pettis Memorial VA Medical Center
Free Radicals
Joseph Kirschvink, California Institute of Technology
Magnetosomes

Metric Measurement Requirements Identified By More Than One Working Group

	Resonances	Coherence	Transients	Magnetic Moments
B _{DC}				
Magnitude	X			X
Orientation	X			X
B _{AC}				
Magnitude	X	X*		X
Orientation	X			X
Broadband Spectral Content	X	X	X**	X***
Duration	X	X	X	

* 0.05–0.10 second sampling period ** 1–100 kHz *** DC–GHz

Specialized Metrics Of Interest To Individual Working Groups

- Resonances—Y = probability that the defined resonance condition was obtained during sampling period.
- Transients—transient repetition rate, peak magnetic field (B_{max}), maximum time-rate-of-change of magnetic field (dB/dt_{max}), average time-rate-of-change of magnetic field (dB/dt_{avg}), $dB/dt_{avg}/dB/dt_{max}$.
- Magnetic Moments— B_{ac} polarization, spectral energy content.

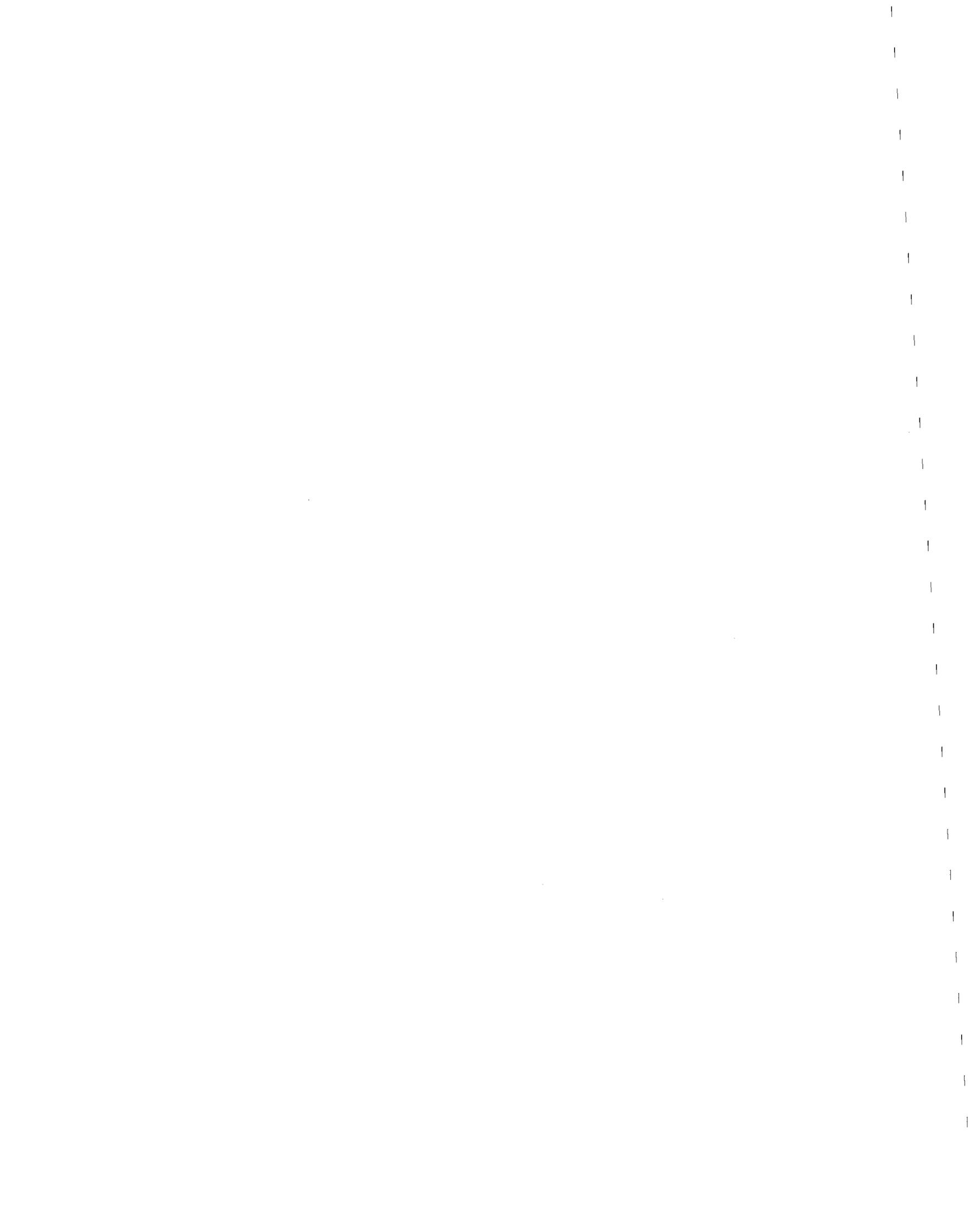
A number of workshop participants urged de-emphasizing personal exposure measures, in favor of task- or environment-specific measurements. Other researchers, noting the long time and high cost of epidemiologic studies, urged “measuring everything” in future studies, because appropriate data could be later extracted to test new mechanistic hypotheses. Some engineers present challenged this recommendation, asking how all the collected data could feasibly be used by epidemiologists.

The principal work product was a set of general specifications for a new generation of EMF measurement instrumentation (see box), which had a surprising degree of commonality across working groups. However, the organizers’ original objectives were not entirely met: There was some advocacy of specific biological hypotheses, and participants were not able to rank order them on the basis of plausibility; working groups were able only to partially quantify exposure metrics; and exposure assessment protocols were discussed only to a limited extent.

Nonetheless, NIOSH’s Lotz was pleased with the results. “We did not expect a magic answer,” he told workshop participants in the final plenary session. “But we did learn what you people think. We want you to know that NIOSH is an active institute with an interest in these issues.”

NIOSH plans to issue a report before the end of this year on results of the workshop.

BIBLIOGRAPHIC INFORMATION: Litovitz TA, Montrose CJ, Wang W. **Dose-response implications of the transient nature of electromagnetic-field-induced bioeffects: theoretical hypotheses and predictions.** *Bioelectromagnetics* 1992; Suppl 1:237–46.



Appendix B

“NIOSH/DOE Workshop on Exposure Assessment and Epidemiology”

Agenda

**EMF Exposure Assessment and Epidemiology:
Hypotheses, Metrics and Measurements**

A Joint NIOSH / DOE Workshop
September 26-28, 1994
Cincinnati, Ohio

AGENDA

Monday, September 26, 1994

11:30 Lunch for organizers, speakers, recorders and chairs.

Plenary Session -Greg Lotz, Chair

1:00 Welcome, Workshop purpose and structure

**Greg Lotz, NIOSH
Lynne Gillette, DOE**

1:15 Epidemiology and the Current Interest in Exposure Metrics
Laboratory Evidence: Is It Useful To Epidemiologists?

**Bill Kaune
Carl Blackman**

1:45 Case Study of an EMF Hypothesis Tested Epidemiologically
The Litovitz Kinetic Hypothesis

Hypothesis
Biological Evidence For and Against
Exposure Metric and Measurements
Epidemiological Design and Results

**Ted Litovitz
Reba Goodman
Joe Bowman
Duncan Thomas**

Discussion, lead by Joe Bowman

2:45 Directions for Working Groups
(Goals, participants, room locations, etc.)

Joe Bowman

3:00 Break

Working Groups (3:15-5:30)

Session goals:

- 1) Invited speakers summarize their hypotheses and issues
- 2) List additional hypotheses
- 3) Select one hypothesis to focus on
- 4) Make assignments to participants to prepare material on biological evidence, metrics, and measurements for the hypothesis chosen

Tuesday, September 27

Plenary Session

8:00 Summary of Workshop Agendas

Working Group Chairs

EMF Measurement Equipment: State-of-the art - Lynne Gillette, Chair

8:30 The EMF environment

Dan Bracken

8:50 Personal Exposure Monitors

Michael Yost

9:10 Waveform and Transient Capture Devices

Bill Feero

9:30 Discussion

10:00 Break

Epidemiologic considerations in EMF exposure assessments - Joe Bowman, Chair

10:20 Exposure Metrics for Other Toxicants

Bob Spear

10:40 Exposure Assessments in Past Residential Studies

Bill Kaune

11:00 Exposure Assessments in Past Occupational Studies

Jan Deadman

11:20 Discussion

11:50 Lunch

1:20 Diseases and Populations for Future EMF Studies

Richard Stevens

1:40 Epidemiologic Designs for Testing EMF Etiological Hypotheses

Duncan Thomas

2:00 Discussion

2:30 Directions for Working Groups - Lynne Gillette

2:40 Break

Working Groups (3:00 - 5:00)

Session goals:

- 1) Hear and discuss statements on the hypothesis wording, biological evidence, exposure metrics, and measurement methods
- 2) Discuss the priority to be assigned to the two hypotheses
- 3) Select a group member to prepare and present a 15 minute report on the hypothesis to the plenary session.

Wednesday, September 28

Plenary Session - Paul Gailey, Chair

8:00 Reports from each Working Group - recommendations related to the objectives of the workshop:

- a) Identification of hypotheses for consideration
- b) Selection of the hypothesis most plausible for a relationship between occupational and residential EMF exposure and diseases which could be tested in future Epidemiological studies.
- c) Recommendations for quantitative exposure metrics from this hypothesis and strategies for assessing exposures to these metrics in future studies, either epidemiologic or laboratory.
- d) Recommendations for exposure assessment strategies which will collect the data needed to assess future hypotheses with this study population.

10:00 Break

10:20 Continued discussion of the hypotheses and Working Group recommendations

10:50 Guided discussion with the goal to identify:

- a) The most plausible hypotheses
- b) The best research strategies for testing these hypotheses
- c) Exposure assessment methods that would be valid for several hypotheses

11:40 Closing remarks - Paul Gailey

12:00 Adjourn

Organizing Committee:

Joseph Bowman, NIOSH
Lynne Gillette, DOE
Paul Gailey, Oak Ridge National Laboratory
Gregory Lotz, NIOSH

Appendix C

“NIOSH/DOE Workshop on Exposure Assessment and Epidemiology”

Workshop Registrants



DOE EMF Exposure Assessment Workshop
Terrace Hotel Cincinnati
Cincinnati, Ohio
September 26-28, 1994

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