

Assessment of Health Effects from Exposure to Power-Line Frequency Electric and Magnetic Fields



NIEHS Working Group Report

**National Institute of Environmental Health Sciences
of the National Institutes of Health**

Assessment of Health Effects from Exposure to Power-Line Frequency Electric and Magnetic Fields

Working Group Report*

*This report represents the views and expert opinions of the Working Group
which met in Brooklyn Park, Minnesota, 16-24 June 1998

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Preface

The National Institute of Environmental Health Sciences was charged by Congress to prepare and submit an evaluation of the potential human health effects from exposure to extremely low frequency electric and magnetic fields (ELF EMF). To evaluate the quality of the science and the strength of the evidence on EMF, the NIEHS organized a comprehensive review of the data which included three science symposia and a working group meeting. The goal of the Working Group meeting was to perform a critical review and evaluation of the research data on ELF EMF exposures and potential biological and/or health effects.

Scientists both within and outside of EMF research were selected as members of the Working Group representing a wide range of disciplines including, engineering, epidemiology, cellular and molecular biology, medicine, mathematics, neurobiology, pathology, physics, statistics, and toxicology. This diversity helped to ensure a cross-disciplinary discussion of the experimental findings and broad scientific perspective.

The Working Group Report presented here draws conclusions on the strength and robustness of the experimental data related to ELF EMF and its implications for human health and disease etiology. The summaries used to define the strength of the evidence in any one area have definitions which, to properly understand the report, should be read carefully (Appendix A). The Report was completed during the 16-24 June 1998 meeting in Brooklyn Park, Minnesota and the information contained within this report reflects the deliberations and discussions of the Group. Following the meeting, the Report was reviewed and edited by a science writer for clarity and put into a common format. Systeme International (SI) units are used throughout the document. Some attempt was made to check the accuracy of references and data prior to the Report being printed; however, there was only limited time for this prior to its release to the public so there are likely to be some minor technical errors within the document.

The deliberations and summarization of the scientific data regarding possible health effects from exposure to ELF EMF are critical to the NIEHS' hazard evaluation project. This document represents the first step in a risk assessment for potential health effects of ELF EMF in human populations. The final categorizations represent strength of the evidence for a hazard and do not reflect the degree of that hazard. While there is no short summary of the results, the final discussions in Chapter 5 are sufficiently short and informative to give some indication of the overall strength of this evidence. The only way a reader can be

certain they understand these decisions is to read the appropriate sections in the book.

Preparation of the Working Group Report in a nine-day period was a monumental undertaking. There was a vast literature to cover in a short period, and the members responded to this challenge with diligence and long hours. The 30 members of the Working Group contributed approximately 1200 person-hours prior to the meeting and 3000 person-hours while at the meeting. Adding to this, the contribution of NIEHS staff and contractors shows that the document represents approximately 3 person-years of effort focused on this problem in a very short period. This effort was greatly enhanced by the summaries from the three science symposia which would add another 4 person-years to this effort.

We wish to thank the members of the Working Group for their contributions to the meeting, their dedication, and their open-minded approach to preparation of the report. We greatly appreciate the efforts of the participants in the science symposia who highlighted areas of concerns and identified key research findings for the Working Group. We also wish to thank the staff and contractors of the *EMFRAPID* Program for their technical support in preparation of the report. Finally, we also wish to thank our families and friends who have shown us continuing support throughout this effort.

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Contents

PARTICIPANTS	1
1 INTRODUCTION	7
2 OCCURRENCE AND MEASUREMENT OF EXTREMELY LOW FREQUENCY ELECTROMAGNETIC FIELDS	9
2.1 What are electromagnetic fields?	9
2.2 Measurements, unit conventions, and sources.....	14
2.3 Exposure assessment.....	17
2.3.1 Instrumentation.....	17
2.3.2 Exposure metrics.....	19
2.3.3 Exposure environments.....	22
2.3.4 Exposure assessment for epidemiological studies.....	23
2.4 Occupational exposure.....	24
2.4.1 General occupational environments.....	24
2.4.2 Visual display terminal operators.....	31
2.5 Residential exposure.....	32
2.5.1 Direct measurements.....	33
2.5.2 Calculated historical fields.....	39
2.5.3 Wire codes as an exposure surrogate.....	42
2.6 Exposure in transport.....	43
2.7 Exposure in schools.....	44
2.8 Exposure from appliances.....	45
2.9 Laboratory exposure systems.....	47
2.10 Summary.....	49
3 INTERNAL DOSIMETRY.....	79
3.1 Electric field dosimetry for human exposure.....	79
3.2 Low-frequency magnetic field dosimetry.....	80
3.2.1 Magnetic fields induced in the body by external magnetic fields.....	80
3.2.2 Magnetic fields induced in the body by external magnetic fields.....	80
3.3 Scaling between different organisms, assuming that an observed effect is due to induced electric fields.....	81
3.4 Considerations for <i>in vitro</i> dosimetry.....	82
3.4.1 Electric field dosimetry.....	82
3.4.2 Magnetic field dosimetry.....	83
3.5 Summary.....	83
4 BIOLOGICAL DATA RELATING TO THE TOXICITY OF EXTREMELY LOW-FREQUENCY ELECTROMAGNETIC FIELDS.....	85
4.1 Carcinogenicity in animals.....	85
4.1.1 One- and two-year bioassays.....	86

4.1.2 Multistep carcinogenesis.....	89
4.1.2.1 Mammary Cancer.....	89
4.1.2.2 Skin tumor models.....	95
4.1.2.3 Liver cancer models.....	98
4.1.2.4 Leukemia/lymphoma model.....	98
4.1.3 Summary.....	101
4.2 Epidemiological studies of carcinogenicity in adults.....	107
4.2.1 Occupational exposure.....	108
4.2.1.1 All cancers combined.....	109
4.2.1.2 Leukemia.....	111
4.2.1.3 Brain cancer.....	117
4.2.1.4 Breast cancer.....	119
4.2.1.5 Lung cancer.....	123
4.2.1.6 Other cancers.....	124
4.2.1.7 Central nervous system cancers in the offspring of parents exposed to electromagnetic fields.....	125
4.2.1.8 Meta-analyses of brain cancer and leukemia.....	127
4.2.1.9 Summary.....	129
4.2.2 Residential exposure.....	133
4.2.2.1 All cancers.....	133
4.2.2.2 Leukemia.....	134
4.2.2.3 Breast cancer.....	140
4.2.2.4 Tumors of the central nervous system.....	143
4.2.2.5 Summary.....	144
4.3 Epidemiological studies of carcinogenicity in children.....	167
4.3.1 Effects of power lines.....	167
4.3.2 Effects of appliances.....	178
4.3.3 Meta-analyses of studies of effects of power lines.....	183
4.3.4 Summary.....	184
4.4 Non-cancer health effects in experimental animals.....	209
4.4.1 Immunological effects.....	209
4.4.1.1 Magnetic and electric fields.....	209
4.4.1.2 Magnetic fields.....	210
4.4.1.3 Magnetic fields and 7,12-dimethylbenz[<i>a</i>]anthracene.....	211
4.4.1.4 Summary.....	212
4.4.2 Hematological effects.....	216
4.4.2.1 Magnetic and electric fields.....	216
4.4.2.2 Summary.....	217
4.4.3 Effects on the nervous system.....	217
4.4.3.1 Field detection.....	217
4.4.3.2 Avoidance and aversion.....	218
4.4.3.3 Learning and performance.....	221
4.4.3.4 Neurophysiology.....	224
4.4.3.5 Electrophysiology.....	227
4.4.3.6 Summary.....	229
4.4.4 Reproductive and developmental effects.....	237

4.4.4.1 Birds	237
4.4.4.2 Mice	238
4.4.4.3 Rats	239
4.4.4.4 Hamsters	240
4.4.4.5 Summary	240
4.4.5 Effects on melatonin.....	244
4.4.5.1 Electric fields	244
4.4.5.2 Exposure to magnetic fields for < 1 h.....	245
4.4.5.3 Exposure to magnetic fields for 1–24 h.....	247
4.4.5.4 Exposure to magnetic fields for > 24 h.....	248
4.4.5.5 Exposure to electric and magnetic fields.....	251
4.4.5.6 Summary	251
4.4.6 Bone and tissue repair and adaptation	256
4.4.6.1 Clinical bone healing with pulsed electromagnetic fields.....	256
4.4.6.2 Experimental studies	260
4.4.6.3 Summary	269
4.5 Epidemiological studies of non-cancer health effects in humans.....	272
4.5.1 Occupational exposure.....	272
4.5.1.1 Reproductive effects	272
4.5.1.2 Neurodegenerative diseases	276
4.5.1.3 Suicide and depression	282
4.5.1.4 Cardiovascular disease.....	283
4.5.1.5 Summary	284
4.5.2 Environmental exposure.....	287
4.5.2.1 Pregnancy outcome	287
4.5.2.2 Neurodegenerative diseases and neurobiological disorders.....	292
4.5.2.3 Summary	292
4.6 Laboratory studies of non-cancer health effects in humans.....	301
4.6.1 Sensation and perception	302
4.6.1.1 Field perception	302
4.6.1.2 Visual effects.....	302
4.6.2 Central nervous system.....	303
4.6.2.1 Electroencephalographic spectral analysis.....	303
4.6.2.2 Event-related potential.....	305
4.6.2.3 Sleep electrophysiology.....	306
4.6.2.4 Cognition and performance	308
4.6.3 Cardiovascular system	308
4.6.3.1 Heart rate.....	308
4.6.3.2 Heart-rate variability.....	309
4.6.4 Other effects.....	311
4.6.4.1 Melatonin.....	311
4.6.4.2 Neuroendocrinology.....	313
4.6.4.3 Immune system.....	313
4.6.5 Mood disturbances.....	314
4.6.6 Electromagnetic hypersensitivity.....	314
4.6.7 Summary	316

4.7 <i>In vitro</i> and mechanistic studies.....	326
4.7.1 Genotoxicity and regulation of gene expression.....	326
4.7.1.1 Genotoxicity.....	327
4.7.1.2 Transcription.....	330
4.7.1.3 Translation and protein synthesis.....	332
4.7.1.4 Summary.....	333
4.7.2 Signal transduction and proliferation.....	334
4.7.2.1 Calcium homeostasis and flux.....	335
4.7.2.2 Receptor-mediated signaling pathways.....	337
4.7.2.3 Cell proliferation.....	338
4.7.2.4 Enzyme synthesis and activity.....	340
4.7.2.5 Apoptosis.....	341
4.7.2.6 Summary.....	342
4.7.3 Induction of cytological markers.....	342
4.7.3.1 Embryonic staging.....	343
4.7.3.2 Matrix synthesis and extracellular interactions.....	345
4.7.3.3 Cell surface markers.....	346
4.7.3.4 Matrix interactions: Adhesion, morphology, and motility.....	348
4.7.3.5 Cell–cell communication and gap junctions.....	351
4.7.3.6 Summary.....	352
4.7.4 Summary.....	354
4.8 Biophysics of interactions of ELF EMF with biological systems.....	355
4.8.1 Biologically important interactions at the molecular level.....	358
4.8.1.1 Forces and torques on ions and molecules.....	358
4.8.1.2 Perturbation of chemical reactions.....	359
4.8.1.3 Temporal averaging and time-dependent processes.....	360
4.8.2 Comparison of changes induced by EMF and competing physical processes.....	361
4.8.2.1 Comparison with the geomagnetic field.....	361
4.8.2.2 Comparison with endogenous electric fields.....	361
4.8.2.3 Comparison with thermal noise.....	362
4.8.2.4 Comparison with shot and $1/f$ noise.....	365
4.8.2.5 Magnitude of competing thermal effects.....	366
4.8.3 Proposed physical mechanisms.....	368
4.8.3.1 Effects of electric fields on cell surface structures and cell attachment.....	368
4.8.3.2 Cyclotron resonance and ion parametric resonance.....	371
4.8.3.3 Biological electron transfer.....	375
4.8.3.4 Effects on biogenic magnetite.....	376
4.8.3.5 Magnetochemistry: Effects of magnetic fields on free-radical reactions.....	377
4.8.3.6 Non-linear dynamics and application of stochastic resonance.....	380
4.8.4 Summary.....	382
5 FINAL SUMMARY AND EVALUATION.....	395
5.1 Carcinogenicity in humans.....	396

5.1.1 Evidence from epidemiological studies to support the evaluation.....	396
5.1.2 Evidence from studies of carcinogenicity in experimental animals <i>in vivo</i> to support the evaluation.....	397
5.1.3 Mechanistic and <i>in vitro</i> evidence to support the evaluation	398
5.1.4 Discussion.....	399
5.2 Non-cancer health effects.....	399
5.2.1 Non-cancer adverse health effects.....	399
5.2.2 Other biological effects.....	401
5.3 Overall evaluation.....	402
 6 REFERENCES.....	 403
 7 ABBREVIATIONS	 467
 8 GLOSSARY.....	 471
 APPENDIX A - IARC Monographs Programme on the Evaluation of Carcinogenic Risks To Human - Preamble	 479
 APPENDIX B - Minority Statement on Animal Carcinogenicity.....	 505

Figures

Figure 2.1 Electromagnetic spectrum showing extremely low frequency and other bands.....	55
Figure 2.2 Field-particle interactions: “classical” forces, torques, and energies.....	56
Figure 2.3 Illustration of “cross-product” (equations (a), (C) and (c) in Figure 2.2: The resulting vector $c = a \times b$ is in a direction perpendicular to the plane defined by a and b and its magnitude is equal to the product of their mutually perpendicular components: $c = a \cdot b \sin \phi$).....	57
Figure 4.1 Equivalent circuit for an array of N membrane channels with conductive media on each side of the membrane. Resistance value is associated with each channel (R_G) and with each of the access resistances (R_A and R_B) near the channel mouths. All resistors in the circuit produce voltage noise, and these sources (V_{Gi} , V_{Ai} , and V_{Bi}) are completely independent and uncorrelated. When circuit analysis techniques with the proper methods are used for summing incoherent signals, the net noise voltage across an arbitrary channel (V_1 in this figure) can be calculated. Note that the noise voltage of interest (V_1) is that occurring across the channel, and not across the series combination of the channel and access resistances. The model assumes that any voltage gating mechanism is inside the channel or at the channel mouth. From Gailey (Gailey, 1996).....	385
Figure 4.2 Normalized correlation coefficients for thermal electrical noise occurring across an ion channel as a function of the number of channels in the membrane (Electrical parameters used in this calculation apply to gap-junction channels with a channel resistance of $6.5 \text{ G}\Omega$ and an access resistance of $0.33 \text{ G}\Omega$.) The coherence or correlation between noise signals occurring in different channels decreases by a factor of 10 per decade with increasing number of channels. From Gailey (Gailey, 1996)....	386
Figure 4.3. Improvement in signal-to-(thermal) voltage noise ratio due to lack of correlation between noise signals occurring in different open channels in the membrane (The x axis is the absolute value of the slope of the closing rate constant divided by the slope of the opening rate constant. The solid line was generated from equation 4.15 with equal opening and closing rate constants and assuming no effect of thermal voltage noise on the closing rate constants ($\gamma = 0$, $N_o \rightarrow \infty$)). When the slight correlation between voltage noise in the open channels and the effect of the uncorrelated noise in these channels is included, the dashed line is obtained for a membrane with 50,000 open channels. From Gailey (Gailey, 1996).	387
Figure 4.4. Voltage noise spectra of a frog node of Ranvier at various membrane potentials. From Verveen and DeFelice (Verveen & DeFelice, 1974); reproduced by Barnes (Barnes, 1986).....	388

Figure 4.5. Effect of magnetic fields on radical-pair energy levels (Electron spins in the three sub-levels of the triplet state: T_{+1} spins parallel in the direction of the magnetic field, T_{-1} spins parallel in the direction opposite to the magnetic field, T_0 spins antiparallel but in phase in the field direction.). S, singlet state From Polk (Polk, 1992a).389

Figure 4.6. Maximum change in escape probability and maximum relative change are shown as a function of cage retainment time for an increment of $5 \mu\text{T}$ to an external field of $50 \mu\text{T}$ (The recombination probability for electrons in a relative singlet state is taken as twice the escape probability and the internal field magnitudes and directions are selected from Monte Carlo procedures, as is the direction of the external field. The variation of escape probability with cage time of radicals with fields chosen so as to maximize the escape at a cage time of 10 ns, is also shown.) From Adair (Adair, 1997).390

Tables

Table 2.1	Field meter characteristics.....	58
Table 2.2	Magnetic field exposure metrics used in epidemiological studies	59
Table 2.3	Standard occupational classification codes and job categories of "electrical jobs".....	60
Table 2.4	Electrical occupations derived from job titles with TWA magnetic field exposures.....	61
Table 2.5	Occupational exposure measurements in occupational studies.....	73
Table 2.6	Distribution of wire code categories of control subjects' homes in seven studies in the USA	75
Table 2.7	Measured magnetic fields and Wertheimer-Leeper wire codes in six studies in the USA	76
Table 2.8	Comparison of the percentage of homes in wire code categories > 0.2 or 0.3 μ T in four studies in the USA.....	77
Table 2.9	Estimated median magnetic fields in the 1000 homes survey	36
Table 2.10	Average magnetic flux densities in schools in Canada.....	45
Table 2.11	Magnetic fields associated with use of appliances.....	47
Table 3.1	Typical average electric fields in bone marrow in numerical dosimetric studies of uniform conditions of exposure to electric or magnetic fields at 60 Hz.....	80
Table 3.2	Calculated average induced electric fields in selected tissues in a human adult from a 1.0 μ T, 60 Hz magnetic field orientated from shoulders and assumed tissue conductivities.....	81
Table 4.1	Results of long term chronic bioassays in rodents exposed to EMF	103
Table 4.2	Assays of co-initiation and of promotion of: mammary cancer.....	104
Table 4.3	Incidences of mammary gland lesions in female rats exposed to 10 mg DMBA plus sham exposure or exposure to magnetic fields.....	94
Table 4.4	Studies of promotion and co-promotion of skin cancer	105
Table 4.5	Studies of promotion and co-promotion of liver cancer.....	106
Table 4.6	Studies of promotion of: Lymphoma/leukemia.....	106
Table 4.7	Lymphoma incidence in mice treated with ionizing radiation and EMF.....	99
Table 4.8	Leukemia/lymphoma in transgenic mice exposed to 60 Hz magnetic fields.....	101

Table 4.9 Minimal exposure assessment required for a study to be included in this review	109
Table 4.10 Epidemiological studies of exposure to EMF and cancer at all sites.....	146
Table 4.11 Epidemiological studies of leukemia with full-shift measurements of magnetic fields.....	147
Table 4.12 Epidemiological studies of brain cancer with full-shift measurements of magnetic fields.....	151
Table 4.13 Cohort studies of breast cancer and occupational exposure to EMF.....	154
Table 4.14 Case-control studies of male breast cancer and occupational exposure to EMF.....	155
Table 4.15 Case-control studies of female breast cancer and occupational studies of EMF.....	157
Table 4.16 Epidemiological studies of lung cancer with full-shift measurements of magnetic fields.....	158
Table 4.17 Central nervous system tumors in offspring of EMF-exposed parents	159
Table 4.18 Design of studies of leukemia and residential exposure to EMF	161
Table 4.19 Results of studies of leukemia and residential exposure to EMF	164
Table 4.20 Summary of epidemiological studies on childhood cancers.....	190
Table 4.21 Childhood leukemia.....	196
Table 4.22 Results for childhood nervous system tumors.....	200
Table 4.23 Results for childhood lymphoma.....	202
Table 4.24 Summary of appliance studies	203
Table 4.25 Summary of meta-analysis results	205
Table 4.26 Summary of NIEHS meta-analysis	207
Table 4.27 Summary of immunological studies of exposure to EMF in experimental animals	213
Table 4.28 Perception in experimental animals exposed to EMF.....	230
Table 4.29 Summary of experiments assessing aversion in experimental animals fields.....	231
Table 4.30 Learning and performance in experimental animals exposed to EMF	232
Table 4.31 Neurophysiological effects of EMF in experimental animals	234
Table 4.32 Electrophysiological effects of EMF in experimental animals.....	236
Table 4.33 Studies on EMF exposures and reproductive and developmental effects of EMF in experimental animals and birds.....	241

Table 4.34 Studies of the effect of exposure to EMF on melatonin in experimental animals.....	253
Table 4.35 Minimal exposure assessment required for a study to be included in this review.....	272
Table 4.36 Adverse pregnancy outcomes and maternal exposure to EMF.....	293
Table 4.37 Alzheimer disease and dementia in association with exposure to EMF.....	295
Table 4.38 Amyotrophic lateral sclerosis in association with exposure to EMF.....	297
Table 4.39 Suicide and depression in association with exposure to EMF.....	299
Table 4.40 Mortality from cardiovascular disease in relation to exposure to magnetic fields (Savitz <i>et al.</i> , 1998c).....	300
Table 4.41 Effects on exposure to EMF on measures of electrical activity in human brain.....	318
Table 4.42 Laboratory studies of the effects of magnetic fields on electroencephalographic measures of human sleep.....	320
Table 4.43 EMF effects of exposure to EMF on human cognition and performance.....	321
Table 4.44 Effects of exposure to EMF on heart rate and heart rate variability in human volunteers.....	323
Table 4.45 Effects of exposure to EMF on melatonin and its metabolite in humans.....	324
Table 4.46 Maximum numbers of turnovers of some enzymes.....	391
Table 4.47 Cells showing Ca ⁺⁺ oscillations.....	391
Table 4.48 Average endogenous fields due to heart activity induced field (Hz).....	391
Table 4.49 Experimental papers reporting resonance depending on the static magnetic fields (B _{DC}).....	392
Table 8.1 Units.....	477

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1 Introduction

Electric power is used all over the world. In the United States, the generation, transmission, and use of electric energy is associated with the production of weak electric and magnetic fields (EMF) which oscillate 60 times per second (power-line frequency). These fields are a fact of daily life: they are emitted by power lines, transformers, service wires, and electrical panels as well as by home appliances (such as electric blankets, waterbeds, clocks, shavers, and televisions). Electricity has been used, to great advantage, for 100 years without society being aware of any adverse health effect, other than thermal injury and electrocution.

Thus, when Wertheimer and Leeper reported in 1979 that children living near power lines had an increased risk for developing cancer, the concern was immediate, and a controversial area of research was born. Yet, despite a multitude of studies, there remains considerable debate over what, if any, health effects result from exposure to EMF. There is still no clear answer to the question, “Can exposure to electric and magnetic fields resulting from the production, distribution, and use of electricity promote cancer or initiate other health problems?”

Faced with growing concern on the part of the public about whether EMF might be adverse to human health, Congress mandated the Electric and Magnetic Fields Research and Public Information Dissemination (*EMFRAPID*) Program in the 1992 Energy Policy Act, Public Law 102-104. The National Institute of Environmental Health Sciences (NIEHS) and the Department of Energy (DOE) were given the responsibility for directing and managing the program. This five-year effort, jointly funded by Federal and matching private funds, was designed to improve our understanding of the potential adverse health effects of exposure to extremely low frequency (ELF) EMF, especially those produced by the generation, transmission, and use of electricity. The *EMFRAPID* Program sought to explain any links between EMF exposures and human health and any special conditions under which cause-effect relationships might occur. The 1992 Energy Policy Act requires a report from the NIEHS Director outlining the possible human health risks upon completion of the Program.

As part of its strategy for preparation of the report, the NIEHS developed a novel program that brought together diverse areas of science. The program involved large numbers of research scientists with diverse expertise both within and outside the EMF research field. With the aid of the National EMF Advisory Committee and the EMF Interagency Committee, the NIEHS used its existing peer-review grants process, worked with the DOE to characterize and improve methods for measuring exposure, and conducted a two-year study of carcinogenicity in experimental animals.

As the program entered its last two years, the NIEHS enacted a two-tiered process for collecting and evaluating information for the Director's report: Science Review Symposia

were held in which open public debate was encouraged with regard to key research findings on EMF; and a rigorous, multi-disciplinary, scientific assessment of available data on the health effects of EMF was conducted by a Working Group. This publication represents the output of the Working Group. The process was publicly open, scholarly, objective, and sufficiently flexible to accommodate the changing face of EMF research and public health concerns.

In the first step of the process, with the aid of their advisory committees and scientists in the field, the NIEHS opened the review on the interaction of ELF EMF with biological systems by holding the first Science Review Symposium in Durham, NC, in March 1997. The participants addressed specific questions concerning the mechanisms governing the interactions of ELF EMF with biological systems *in vitro* and using biophysical theories. The participants included engineers, molecular biologists, toxicologists, physiologists, epidemiologists, mathematicians, and physicists, some specialized in EMF and others from different fields. The report of the discussions has been published (Portier & Wolfe, 1997). Two further symposia were held, one on the epidemiology of exposure to ELF EMF in San Antonio, Texas, in January 1998 (Portier & Wolfe, 1998a), and the other on *in-vivo*/clinical investigations in Phoenix, Arizona, in April 1998 (Portier & Wolfe, 1998b). Through this series of three symposia, the NIEHS identified the key aspects of science that should be used in making any decision about health effects.

In the second step of the process, a Working Group was selected carefully after screening by the NIEHS and discussions with its two standing external advisory boards. The members of the Group represented a wide range of scientific disciplines, with and without a particular interest in EMF. During a nine-day working session in Brooklyn Park, Minnesota, they conducted a careful, thorough scientific review of all of the evidence related to health effects associated with exposure to ELF EMF. Certain members of the Group developed drafts in advance of the meeting to be used as the basis for discussion on specific aspects of research on ELF EMF. At the meeting, subgroups read, modified, and rewrote the drafts to reflect the consensus of the Group.

The attached document is the report of the Working Group on the health effects of exposure to ELF EMF. The evaluations of carcinogenicity were reached following the guidelines used in the International Agency for Research on Cancer (IARC) *Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, with minor modifications (see footnotes, Appendix A). Evaluations of other health end-points followed the same criteria, with minor exceptions relating to final evaluations (see footnotes, Appendix A).

2 Occurrence and Measurement of Extremely Low Frequency Electromagnetic Fields

2.1 What are electromagnetic fields?

Wherever electricity is generated, transmitted, or used, electric and magnetic fields (EMF) are created, due to the presence and motion of electric charges. Generally, these fields are time-varying vector quantities characterized by a number of parameters, including their frequency, phase, direction, and magnitude. A simple analogy provides some insight into the complexity of summarizing an exposure variable.

Consider the motion of an airplane in flight. A time-varying vector describes the velocity (km/h) of the passengers as the plane travels between two cities. At a particular time, the magnitude of the velocity vector gives the passengers' speed without regard to the heading. The three directional components (x, y, z) of the velocity vector at some time will give the speed with respect to its position in space, described by a position vector in altitude, longitude, and latitude coordinates. Over time, a variety of measures could be chosen to summarize the passengers' time-varying velocity vector. For example, the average vector magnitude would describe their average speed, or the average vertical position would give their average altitude. We could even choose some measure of change in the vector components with time to describe features such as the rate of descent or acceleration. All of these summary measures are equally valid in a physical sense but describe qualitatively different aspects of the passengers' motion that may not be equally important in relation to a biological response.

The challenge for exposure assessment is to choose a summary measure that is physically meaningful and biologically relevant. To illustrate this point, the average speed of the passengers may be useful for deciding how long their trip will take but is essentially useless for predicting whether the passengers will become airsick; however, another summary measure, describing velocity fluctuations up and down, would probably be a very good predictor of possible air sickness during a flight. A different summary measure, involving the directional components of the motion, would be needed to predict another biological response such as jet lag. Thus, the choice of summary measure depends on both the physical characteristic to be described and the biological response of interest.

An electromagnetic field is composed of two components, the electric and the magnetic fields. The electric field is created by the presence of an electric charge. It describes the magnitude and direction of the force it exerts on a positive electric charge. The magnitude of the electric field depends on the difference in potential between charge-carrying bodies, including conductors, regardless of the amount of current that is flowing in them. In contrast, a magnetic field is created by the motion of electric charges. Typically, this motion is represented by a flow of charge in the form of an electric current, which gives

the number of charges per second passing through the conductor. The magnetic field acts only on other electric charges in motion. Thus, a magnetic field is created by an electric current and describes the magnitude and direction of the force exerted on a nearby current (moving charges). The magnitude of the magnetic field is proportional to the current flow in a conductor, regardless of the voltage present.

The discussion in this document focuses primarily on magnetic fields but will include electric fields when possible because of their inherently close association with electric power systems. Voltage and current determine the magnitude of the electric and the magnetic fields at a location, respectively, with the source geometry and distance from the source to the measurement location. The strength of an electric field is usually measured in volts per meter (V/m) or sometimes in kilovolts per meter (1 kV/m = 1000 V/m). Magnetic fields can be designated by either magnetic flux density (B) or magnetic field strength (H); both are proportional to the magnitude of the current. B is measured in the centimeter-gram-second unit, the gauss (G), or the unit of the Systeme Internationale (SI), the tesla (T); $1 \text{ mG} = 1 \times 10^{-3} \text{ G} = 0.1 \text{ } \mu\text{T}$. H is measured in SI units of amperes/meter (A/m). B and H are related through the equation: $B = \mu_0 H$, where $\mu_0 = 1.26 \times 10^{-6}$ henry/m is the magnetic permeability of a vacuum. To a close approximation, μ_0 remains the same for air and body tissues, and only one of the variables, B or H, need be measured. In practice, B is the usual measured quantity, and, for the purpose of this document, ‘magnetic field’ refers to the magnetic flux density in microtesla (μT ; $1 \text{ } \mu\text{T} = 1 \times 10^{-6} \text{ T}$). Unless otherwise stated, all voltage, current, and magnetic flux values are rms (root mean square), as defined in equation 2.4.

EMF can be arranged in an orderly fashion in an electromagnetic spectrum, according to their frequency (f) or wavelength (λ), where $\lambda = c/f$ and c is the velocity of light. The electromagnetic spectrum spans an enormous range of frequencies (Figure 2.1), more than 15 orders of magnitude. This document focuses principally on EMF resulting from the use and distribution of electric power, allowing a great deal of simplification as these fields vary rather slowly over time. The frequency of EMF depends on the power-line source; in North America, power systems operate at a frequency of 60 cycles per second, or 60 hertz (Hz). Generally, these power-line fields fall in the extremely low frequency (ELF) region of the electromagnetic spectrum, which is defined by frequencies from 3 to 3000 Hz (Poole & Ozonoff, 1996). The alternating current flowing in the electric power system has dominant sinusoidal voltage and current waveforms; however, although 60 Hz is the predominant fundamental frequency, humans are exposed to a mixture of frequencies, and much higher frequencies can arise. For example, switching events can generate abrupt spikes in voltage and current waveforms, leading to high frequency ‘transients’, which can extend into radio frequencies above several megahertz (1 MHz = 10^6 Hz). Nonlinear characteristics in electrical devices can generate harmonics at integer multiples of the fundamental frequency extending up to several kilohertz (1 kHz = 10^3 Hz). EMF frequencies from some electronic equipment, like televisions and visual display terminals (VDT), can routinely extend up to 50 kHz.

Most devices that have electric wires, e.g. electric motors, electric equipment such as electric power lines, residential appliances, and industrial equipment, are potential sources of EMF. Residential exposures are dominated by ELF sources but also include exposure to very low frequencies, 3–30-kHz radio frequencies, and microwave sources.

The Earth also produces EMF. Unlike the fields from power lines and other alternating current sources, the Earth’s fields are largely ‘static’, that is they do not change over time. In contrast, EMF from power lines and other alternating current sources have a periodic component. The Earth’s magnetic field has a magnitude of about 50 μT over most of the USA and is oriented toward magnetic North; the vertical field component accounts for about two-thirds of the total vector magnitude. Devices that operate on direct current (DC) also produce static magnetic fields, and some occupational environments, such as aluminum smelting, can have extremely strong static fields.

For the most part, researchers have focused on ELF magnetic fields resulting from power lines, appliances, and occupational exposures. In the broader context of human exposures and epidemiological studies, it should be remembered that typical exposures to EMF occur over a wide range of frequencies and in conjunction with static fields.

ELF electric fields at relatively high intensities can have acute biological effects. Nerve and muscle stimulation results in an immediate behavioral response in humans and other vertebrates (Malmivuo & Plonsey, 1995; Reilly, 1992). Extremely strong electric fields can permanently or transiently damage cell membranes (Weaver & Chizmadzhev, 1996) and produce burn injuries (Tropea & Lee, 1992). Stimulation of peripheral nerves at power frequencies in humans generally requires electric current densities in muscle tissue in the order of 1.0 A/m^2 , which corresponds roughly inside tissues with an electric conductivity of $\sigma \approx 1 \text{ S/m}$ to internal electric fields on the order of 1.0 V/m . Production of such currents inside living tissue at 60 Hz requires either direct, electrically conductive contact with a source of electric power or the presence of an electric field in the surrounding air in the order of several 100 kV/m . Without conductive contact, the electric field outside body tissues (E_{OUT}) must be much larger than the field inside (E_{INS}). This requirement is a consequence of the physical laws of conservation of electric charge and continuity of electric displacement. In the case of steady-state sinusoidal electric fields of frequency f at a plane boundary between ‘semi-infinite’ media, the ratio of the external electric field over the internal field is described by the relation (Polk, 1986):

$$\frac{E_{OUT}}{E_{INS}} \approx \frac{\sigma}{\omega\epsilon} \quad \text{Eq. 2.1}$$

where $\omega = 2\pi f$, ϵ is the dielectric permittivity of air and σ is the conductivity of tissue $\approx 1 \text{ S/m}$. Since for dry air $\epsilon \approx 8.84 \times 10^{-12} \text{ F/m}$, the ratio given by equation 2.1, which describes the attenuation of an external electric field relative to the apparent field inside the body, is roughly 100 million. Distortion of the field in air by the presence of a

‘conducting’ body, air moisture, contact with an electrically conducting earth, and variation of σ within the body, can reduce this ratio somewhat, but it will never be much less than 10 million. Details of current and field distributions that take into account body orientation and in homogeneity have been given, for example, by Kaune (Kaune & Forsythe, 1985) and Dawson (Dawson *et al.*, 1996).

Typical 60 Hz electric fields in homes rarely exceed 100 V/m (Barnes *et al.*, 1989) and are not more than 10 kV/m near ground level directly underneath a very high-voltage (~ 500 kV) transmission line. It is clear that the only persons who will experience internal electric fields in the order of even 10^{-3} V/m due to an external electric field are utility workers in the immediate vicinity of high-voltage wires.

Time-varying magnetic fields induce electric fields into any material, according to Faraday’s law:

$$\oint \mathbf{E} \cdot d\mathbf{l} = -\iint \frac{\partial \mathbf{B}}{\partial t} \cdot d\mathbf{s} \quad \text{Eq. 2.2}$$

The term on the left-hand side of the equation indicates the electric field integrated over a closed boundary; the term on the right-hand side is the integral of the rate of change of the magnetic flux density, \mathbf{B} , perpendicular to and integrated over the area enclosed by the contour designated on the left-hand side. The integral $\iint \mathbf{B} \cdot d\mathbf{s}$ is also called the magnetic flux ϕ . For a reasonably long, cylindrical body of radius r , eq. 2.2 leads to (Polk, 1986):

$$E = \pi f B r \quad \text{Eq. 2.3}$$

where B is the magnetic flux in tesla and r is in meters, which is frequently used to estimate the average electric field induced by a time-varying magnetic field. Since the left-hand side of equation 2.2 gives only the induced electric field summed over a closed contour, equation 2.3 applies only to an electrically homogeneous medium; however, in electrically inhomogeneous tissue, this induced field can vary locally, giving rise to much larger or smaller values than the average (Polk, 1992c).

The magnetic permeability (μ) of living tissue (with very few, localized exceptions) is practically equal to that of free space. Consequently, the magnetic flux density inside the body is nearly equal to that outside. Equation 2.3 then indicates that a 60 Hz field of 100 μT oriented along the head-to-feet axis of a human, with an average radius of 15 cm, will induce near the periphery of the body an average electric field of 2.8×10^{-3} V/m. In comparison, the average electric field near the rim of a petri dish, with a radius of 3 cm, induced by a vertical 60 Hz, 100- μT magnetic field will be about 0.56×10^{-3} V/m.

These magnetically induced internal electric fields are very much larger than those due to a 100-V/m external electric field in air. A 100-V/m electric field represents the upper limit of those found in typical homes; however, induced electric fields are still much smaller than internal electric fields associated with nerve and muscle stimulation. The average electric field induced by a 0.3- μ T 60 Hz field near the surface of a human with a 15-cm radius is only 8.5×10^{-6} V/m. Thus, typical magnetic fields encountered in epidemiological studies of residences induce internal currents and electric fields that are roughly one million times smaller than the currents required to produce acute nerve and muscle stimulation.

The basic laws derived from ‘classical’ physics, which can operate either directly or indirectly and at either the macroscopic or the microscopic (molecular) level in field–biosystems interactions, are summarized in Figures 2.2 and 2.3; quantum mechanical considerations are discussed in Section 4.7.5. Forces and torques are given for both electric fields and magnetic flux densities. Individual electric charges, electric dipoles, and magnetic dipoles or magnetic moments are considered. These equations indicate that stationary or moving individual electric charges will undergo translatory motion in the direction of an applied electric field. In comparison, only charges that are already moving at some velocity, v , will be subjected to a magnetic or ‘Lorentz’ force in a magnetic flux density, B , that is perpendicular to both v and B (as indicated by the cross-product). This perpendicular force on electric charges in a magnetic field leads to a circular motion and the ‘cyclotron resonance’ phenomenon (Liboff, 1985), which will appear only when the probability of collisions with stationary or randomly moving particles is extremely small (Durney *et al.*, 1988). Translatory motion of electric dipoles, ‘dielectrophoresis’ (Pohl, 1978), and of magnetic moments requires very large spatial field gradients (Barnes, 1986). The appearance of torques, producing rotation, requires either the pre-existence of dipole moments or their generation by an applied field. This includes phenomena at the atomic level, where the nuclear magnetic moment and nuclear angular momentum are responsible for nuclear magnetic resonance at frequencies determined by an applied DC magnetic field.

Various biophysical mechanisms have been proposed to account for the effects of EMF (see section 4.8). Some mechanisms predict a strong (or weak) dependence on the frequency content, magnitude, or spatial direction of the fields. Some mechanisms proposed for the interaction of magnetic field with tissues suggest a response from both the time-varying and static-field components or specify a unique combination of the static and time-varying field vectors for a particular target molecule. Also, we cannot ignore the possible role of the state of the biological system, for example awake or sleeping, which could make the timing of exposure important. A great variety of possible exposure factors could be considered, none of which can be excluded *a priori*, and several different mechanisms have been postulated. Assumptions must thus be made when measuring EMF and constructing a few simple summary measures of exposure for the purposes of health assessment.

2.2 Measurements, unit conventions, and sources

In the power distribution system, the line voltage or current is usually designated by the rms value. To compute the rms value, the instantaneous values are squared and averaged and the square root is taken. Mathematically, the rms magnetic flux density is described by:

$$B_{rms} = \sqrt{\frac{1}{T} \int_{t=0}^{t=T} B(t)^2 dt} \quad \text{Eq. 2.4}$$

where $B(t)$ is the instantaneous magnetic flux density and T is the time for an integral over a number of periods of the fundamental frequency.

For a pure sinusoidal waveform, the rms value is related to the instantaneous peak value by a factor of $\sqrt{2}$, i.e. $B_{peak} = \sqrt{2} B_{rms}$. Similar formulas apply for computing the rms voltage. The rms value is always positive and can be related to the average power in watts (energy per unit time), where watts are defined by the instantaneous product of voltage and current delivered to a load. Note that ultimately it is the integral of power with time (i.e. watt-hours or kilowatt-hours) that represents the amount of energy delivered by a utility to a customer.

The measurements of EMF used in most studies are records of the magnitude of the field; they do not retain information on the directional orientation in space or changes in direction over time. This is accomplished by measuring the rms value of three orthogonal spatial components (x , y , and z), and then combining these three values to find the magnitude of the rms. This value, sometimes referred to as the rms resultant, is computed as:

$$B_{res} = \sqrt{B_x^2 + B_y^2 + B_z^2} \quad \text{Eq. 2.5}$$

where B_x , B_y , and B_z are the orthogonal magnetic flux density spatial components. Throughout this document, the quantity B_{res} is referred to as the magnitude of the magnetic field or vector. As noted above, the magnitude does not depend on the direction of the field vector in space. Therefore, B_{res} provides an isotropic measure that does not depend on the orientation of the coordinate system for the measuring device. This is a convenient property for personal exposure meters, in which the spatial orientation constantly changes as the subject moves about.

In many studies, instruments have been used to measure or estimate the time-weighted average (TWA) magnitude of the magnetic field. The TWA is computed from the equation:

$$B_{TWA} = \frac{1}{T} \int_0^T B(t) dt \quad \text{Eq. 2.6}$$

where T is the averaging time.

Note that for a series of measurements uniformly spaced over time, the TWA reduces to the simple average (mean) of the values over T , the time interval. The TWA is by far the commonest exposure metric. It represents a measure of field magnitude, averaged over time. These definitions have been given in terms of magnetic field components, but similar quantities can be derived for electric fields.

The electric power system in North America is arranged in a series of building blocks or segments, with power lines connecting generating stations via a network of transmission lines, intermediate substations, and switching points to the local distribution lines, and ultimately to utility customers. By design, the voltage in a given portion of the system remains nearly constant; large transmission lines typically operate at > 35 kV, and primary distribution lines operate at about 4–35 kV. These higher voltages on the transmission lines are stepped down at local substations by transformers to produce the voltages for the primary distribution lines. The primary distribution lines are further reduced by transformers at other points to a correspondingly lower voltage and higher current for residential or commercial use. Typically, residential service operates at 120 and 240 V. Roughly speaking, the power delivery in each segment of the electric system is the product of the voltage and current load. So power is delivered by creating high voltage at moderate current in the transmission segments and transforming this into high current at moderate voltage for residential distribution. An important consequence of this distribution system is that transmission lines are usually larger sources of electric fields, because of the high line voltage. In most cases, transmission lines carry larger load currents than primary distribution lines but are located farther away from residences; however, in some cases transmission lines carry load currents similar to those of primary distribution lines. Thus, overall, commercial and residential power distribution systems can be a more significant source of magnetic fields than transmission lines but are usually not a very significant source of large electric fields.

Although the voltage in a given segment of the power system remains nearly constant, the current in each portion is highly variable over time, depending on the changing demand for electric power. As a result, in the absence of other changes (such as introducing shielding materials) at locations near power lines, electric fields remain fairly constant, while magnetic fields generally vary significantly over time. Interestingly, residential measurements of magnetic fields show appreciable morning and evening peaks (Dovan *et al.*, 1993) and a seasonal component which varies by geographic region and closely follows the electrical use patterns of urban residents. Consequently, the timing of measurements during a day or season can lead to systematic bias in estimates of 24-h or annual average exposures (Bracken *et al.*, 1993).

Calculations of EMF frequently involve a spatial arrangement of one or more charge or current elements, known as multipoles (Lorrain & Corson, 1970). A monopole consists of a single positive or negative electric point charge; a small displacement of this point charge and replacement of the original charge element by a charge of equal magnitude but opposite sign creates an electric dipole. A magnetic dipole represents the basic element that describes the magnetic field from a current loop. A small displacement of a dipole and replacement of the original by a dipole of equal magnitude and opposite sign creates a quadrupole. This concept can be extended indefinitely to describe the spatial extent of fields in terms of a general multipole expansion of order 2^n , where n is the number of poles. The magnetic field produced at a distance R by a multipole of order n can be described by the equation:

$$B_n = \mu \frac{Mf(\phi)}{R^{n+1}} \quad \text{Eq. 2.7}$$

with field in μT , distance in meters, and multipole in Am^n , where M is the multipole vector term describing the source current. At a given frequency, the magnitude and direction of M are a function of the source current magnitude and geometry, ϕ is the angle between the direction of M and R , and $f(\phi)$ designates a function of ϕ . Both M and B can be elliptically polarized, that is the vectors rotate in space, describing an ellipse over every cycle of the power frequency. As the distance R increases, the field produced by higher-order multipoles becomes less important. At most practical distances for exposure assessment, significant fields are produced only by terms associated with monopoles and dipoles, with order $n = 1$ or 2 for power lines and up to order $n = 3$ for appliances, with which people are nearly in contact when exposed. Magnetic monopoles do not actually exist but are a useful approximation near one pole of a large dipole.

A consequence of this dependence on geometry is that the magnitude of the magnetic field decreases fairly rapidly with movement away from an isolated source; the magnitude falls at least inversely with distance and often with the square of distance or more. A worker standing next to a magnetic field source such as a small motor might experience a field magnitude of $100 \mu\text{T}$, but by moving a few feet away the magnitude may fall to background levels of $< 0.1 \mu\text{T}$. Naturally, the decrease in field strength with distance depends on the magnetic field source, and the pattern is different for a small motor and for a power line. A small motor or computer monitor is essentially a point source, in that the fields originate from a small defined area. In contrast, a power line is a line source which may decrease in strength much more slowly with distance and contribute exposure over a much larger area. Field strength at the source is only one consideration in assessing the contribution of a source to exposure to magnetic field; equally important is the individual's proximity to the source and the amount of time spent near it. Together, these factors determine the relative contribution of a source to the individual's total exposure to magnetic fields.

2.3 Exposure assessment

2.3.1 Instrumentation

Exposure assessment may be broadly defined as the task of estimating, for an individual or group of individuals, the magnitude, frequency of occurrence, and length of time an agent is present and available to the target receptor. Exposure in this sense refers to the joint presence of some biologically active agent with a person in space and time (Sussman, 1995). Exposure is distinct from dose in that it usually refers to the external measure of the agent, whereas dose usually refers to the amount reaching an internal target organ or tissue.

Exposure to EMF is assessed for many purposes, including compliance with recommended standards or regulatory limits, to evaluate the prevalence of EMF in some environment, or for use in epidemiological studies of possible health effects. The underlying purpose of the monitoring often affects the kind of information gathered, the choice of instrumentation, and the quality of the survey.

Data collected for a specific purpose may not be useful in another context. For example, data collected at a workplace in a non-random fashion or specifically to identify a worst-case exposure scenario for compliance with a standard may not provide any meaningful information on typical exposures in those jobs. The study design also must allow a sufficient sample size to achieve the desired level of precision. Another consideration is the use of assessment procedures that have been used in previous studies in order to obtain comparable results. If other data are available from the literature and consistent collection methods are used, it may be possible to combine data on exposure from several sources so as to draw broader conclusions.

As noted earlier, describing EMF with a summary measure involves many assumptions. All instruments selectively measure certain aspects of field, usually ignoring others. Consequently, no single instrument or study captures all aspects of potential human exposure to EMF. Without guidance from studies of the biomechanisms of EMF, the instrument makers made the following implicit assumptions (Heroux, 1991); (Bracken *et al.*, 1993) :

- Magnetic fields are a higher priority for research than electric fields. Most monitors measure the magnetic field well, but only a few have a built-in electric field sensor.
- The important frequencies are those of electric power (50–60 Hz) and harmonics up to about 500 Hz generated by common electrical appliances and industrial

equipment. The low-frequency response should be limited to approximately 35 Hz in order to filter out signals due to movement in the geomagnetic field.

- Exposure is best summarized by the rms magnitude of the ELF magnetic field vector averaged over several cycles.
- As temporal variation in the magnitude of the magnetic field may be important, many instruments can log data.
- The location of a measurement on the body is of secondary importance

In general, exposure to magnetic fields can be estimated with a personal exposure meter, with a fixed location monitor, or by taking spot measurements. In some studies, fixed location monitoring or spot measurements are made at multiple locations in order to capture spatial variability. More recent studies have emphasized personal measurements of exposure to magnetic fields by the use of data-logging meters, but some researchers contend that spot measurements can be used to classify such exposure as well as personal measurements in some residential situations (Delpizzo *et al.*, 1991); (Dovan *et al.*, 1993).

Personal exposure monitoring was made possible by the availability of reliable compact instruments, notably the AMEX-3D, EMDEX-C, EMDEX II, EMDEX Lite, and Positron meters. All of these meters measure the rms magnitude of the magnetic field, thus sacrificing most of the information about the field's frequency content, spatial orientation, and polarization. Magnetic fields are easier to measure for personal exposure than electric fields because they are not perturbed by the body and other conductive objects; however, some meters, like the Positron and the EMDEX-C, include both electric and magnetic field sensors and provide some indication of both components. Table 2.1 summarizes the characteristics of various common exposure meters.

The EMDEX II (Electric and Magnetic Digital Exposure meter), like many other data-logging meters, measures the near 60 Hz rms directional components of the magnetic field, has some ability to distinguish higher-frequency harmonics, and can be used to monitor electric fields when fitted with a sensor. The EMDEX II covers a frequency range of about 40–800 Hz. Sahl *et al.* argued that these frequencies probably contain information about the biologically relevant characteristics of EMF, but biological support for that assertion is limited (Sahl *et al.*, 1994). The simplest meter, the AMEX-3D (Average Magnetic Exposure), measures only the average magnetic field (i.e. the TWA) over time (Kaune *et al.*, 1992). All of the personal exposure meters except the AMEX-3D provide data logging to capture temporal variation in exposures. Data loggers store measurements at regular intervals, ranging from 1 s to 1 min. Investigators may explore various exposure metrics in addition to the TWA, such as the geometric mean (GM) and the fraction of measurements that exceed a threshold. In addition to personal exposure meters, many hand-held survey meters are available for taking single spot readings of magnetic fields. A

comparison of many magnetic field meters showed that most are reasonably accurate when properly calibrated (Misakian *et al.*, 1991; Olsen *et al.*, 1991).

EMF monitors typically have electronic filters to restrict measurement to bandwidths in the ELF range. Most instruments have inductive coil sensors which cannot measure static magnetic fields and which can produce a low-frequency signal (around 3–30 Hz), created by motion through static field gradients, which is usually filtered out. Higher frequencies, above 1 kHz in the very low-frequency band, from induction heaters, VDT, and other sources are also filtered out. Some exceptions exist: the portable MultiWave system has flux gate sensors and captures both static magnetic fields and alternating fields up to about 3 kHz; the Positron meter includes a controversial high-frequency ‘transient EMF’ sensor which detects radio-frequency electric field signals around 5–20 MHz (Deadman *et al.*, 1988); (Heroux, 1991).

In studies in which measurement of personal exposure to magnetic fields is part of the exposure assessment, hip-worn exposure meters are by far the most commonly used. As some investigators have shown that exposure to magnetic fields varies with elevation, it may be desirable to design monitors that could take measurements near potential target organs (when known). Fortunately, monitors on the waist are close to the reproductive organs and the pelvis, the largest reservoir of bone marrow and the presumed origin of leukemic cells.

The efficacy of hip-worn and chest-worn exposure meters for estimating exposure of the whole body and head was examined in detail by DelPizzo (DelPizzo, 1993). The participants wore six exposure meters at a time, positioned at various locations on the body. Over a 2-h period, they engaged in one of the following activities: office work (without a VDT), work on a VDT, mechanical work (excluding welding), and electronics work. While DelPizzo found that hip-worn exposure meters consistently underestimated whole-body average and head exposure, the measurements were highly correlated ($R = 0.91$ for whole body average, $R = 0.83$ for head exposure). Chest-worn exposure meters provided better estimates of whole-body and head exposure than those worn on the hip.

2.3.2 Exposure metrics

Assessment of exposure to EMF has a number of challenging features. First, this exposure is not perceptible by humans at typical nonoccupational intensities, so that it is difficult to assess past exposure from questionnaires or other elicitation tools. Second, the sources of EMF are ubiquitous in modern urban life, and the contribution of many sources is only starting to be recognized. For example, currents flowing in the electrical grounding systems of buildings or on water pipes can be an important source of magnetic fields (Lanera *et al.*, 1997). It is thus difficult to predict circumstances that might lead to particularly high exposures or to identify situations in which little or no exposure will occur. Third, EMF are highly variable in space and time and can fluctuate systematically

with electric power use (Bracken *et al.*, 1993). Thus, measurements can be subject to large random variation, and a carefully designed sampling plan may be needed to avoid poor precision or systematic bias in the sample estimates. Fourth, there is no generally accepted biophysical mechanism for the biological effects of EMF and no established biomarkers of exposure or response. It is therefore very difficult to determine which features should be measured.

In exposure assessment, a way must be found to summarize the characteristics of exposure across time, within groups of individuals, and between many exposure environments. A variety of exposure metrics has been developed to capture the various physical aspects of fields and to provide a summary measure of exposure characteristics that can be aggregated across individual measurements.

A complete description of EMF is possible only with vector mathematics to describe the magnitude and direction in space of the fields over time. A large variety of summary variables can be used to describe a time-varying EMF vector. These variables, called exposure metrics, are intended to capture some particular aspect of the field; however, at this time there is great uncertainty about which exposure metrics (if any) are related to biological responses, and studies have been based mainly on the TWA magnetic field. Some studies also have measured the magnitude of the electric field, and others have explored exposure metrics related to the TWA, such as the geometric mean or percent time exposed to $> 0.2\text{-}\mu\text{T}$ threshold, but not in great detail. Consequently, the problem of defining and measuring a biologically relevant exposure to EMF is complex and largely unresolved.

Valberg summarized many of the features of exposure to magnetic fields that can be considered in defining exposure metrics (Valberg *et al.*, 1995). He identified some 18 field attributes related to exposure in laboratory experiments (see below), but the list is also applicable to human exposure assessment. The attributes fall into four major categories: (1) characteristics of exposure intensity and timing, (2) frequency domain characteristics, (3) spatial characteristics, and (4) combined EMF exposure characteristics. The first category describes the magnitude and history of exposure, which is most often the focus of studies of exposure to EMF. The second category describes the frequency domain aspects of exposure, such as harmonic content, intermittence, and switching transients, which have been poorly characterized in most cases. The third category describes the characteristics of the vector's spatial orientation, such as field polarization (periodic rotation of the vector) and the spatial uniformity of the fields. The fourth category describes the characteristics arising from combined vector fields, such as the joint occurrence or orientation of alternating and static fields or the joint occurrence of electric and magnetic fields. These four categories represent a hierarchy of increasing complexity in exposure assessment, and increasing levels of mechanistic detail are needed in order to specify an appropriate summary exposure metric.

Despite the uncertainty about biologically meaningful metrics, assessment of exposure to EMF has considerably advanced understanding of the sources and conditions that contribute to EMF in daily life. A variety of factors have been hypothesized to contribute to possible harmful effects of magnetic fields: TWA exposure, percent of time exceeding a certain threshold, frequency harmonics, intermittent exposures, highly variable and constant exposures, and peak exposures are just a few possible metrics considered. To some extent, most time-dependent exposure metrics are correlated with the TWA field magnitude, which is universally measured. Various EMF exposure metrics have been compared in at least two studies, and many of the alternatives were found to be highly correlated with the TWA magnitude of the magnetic field (Armstrong *et al.*, 1990); (Savitz *et al.*, 1994). The high degree of intercorrelation among exposure metrics argues that studies in which TWA field magnitude is used as the primary exposure metric would probably produce similar results, even with another metric of field magnitude; however, these two studies examined only a limited range of exposure metrics that are closely related to the characteristics of exposure magnitude and timing (category 1 above). These exposure metrics can be expected to be well correlated with the TWA field magnitude. No studies have broadly addressed exposure metrics spanning all four of the above categories.

Some examples indicate that exposure metrics for other categories outlined by Valberg may be only weakly correlated and inadequately assessed by relying on the TWA field magnitude. For example, the magnitude of the electric field appears to be largely uncorrelated with the magnitude of the magnetic field in the studies of Armstrong *et al.* (Armstrong *et al.*, 1990) and Savitz *et al.* (Savitz *et al.*, 1994), which represent comparisons involving combined EMF exposure characteristics (category 4). Breysse *et al.* (Breysse *et al.*, 1994b) studied various measures of temporal variability, including first-lag autocorrelation, and found that these exposure metrics ranked the exposures of telephone workers quite differently than the TWA, suggesting a low degree of correlation.

Table 2.2 lists a variety of candidate metrics for exposure to magnetic fields which have been used in epidemiological studies. The Table summarizes the characteristics of each metric in terms of its relation to five attributes of the measured magnetic field: magnitude, frequency content, time variability, spatial characteristics, and relationship to the geomagnetic field. The measures of variation include metrics of both short-term and overall variation, where short-term variation describes some measure of change in field magnitude between two or more successive samples recorded in the data logger. The variation measures are usually dependent on the sampling rate selected for the data logger: higher sampling rates usually show higher overall variation.

A number of epidemiological studies (see Section 4, and Section 2.3.4) have addressed the issue of adverse health effects and exposure to ELF magnetic fields and have used a variety of methods to evaluate power-frequency magnetic fields in residential environments. The primary exposure metric measured has been the average magnitude of the magnetic field. Other surrogate measures of exposure, such as wiring codes and job titles, have also been used. Assessments of past exposure to magnetic fields have focused primarily on the residential environment and on specialized occupations, such as electrical

utility workers; however, these jobs are relatively rare in the general population, and far more people are employed in other services, business, or industry, where there may also may be high exposures (NIOSH, 1996).

2.3.3 Exposure environments

Assessment of exposure to EMF has tended to focus not just on the individual but also on the environment in which the exposure takes place. This approach is useful for two reasons: first, from the standpoint of defining homogeneous exposure groups it helps to identify common sources and attributes of exposure or appropriate surrogates; second, studies focused on just one environment can derive greater detail for a particular study population.

Four main groupings of exposure environments can be drawn from work on the assessment of exposure to EMF: studies of residential, occupational, school, and transport environments. Together, these environments describe a large cross-section of the US population. Occupational environments have been extensively studied in the context of specific industries and worker populations, particularly the electric utility industry where high exposure to EMF was anticipated. Residential studies have addressed the exposures to children and adults, usually as part of population-based or case-control epidemiological investigations in selected cities. A nationwide survey of residences has been completed that provides a broad overview of sources of EMF in homes. Exposure has also been assessed in schools and transport, but the literature is less extensive.

Most of these studies have a cross-sectional design. In evaluating them, it must be recognized that the results reflect defined study populations over a particular time. Extrapolating the results of one study to other groups or other periods necessarily involves assumptions about the trends over time and how representative the results are for other populations. Various surrogates and measurement techniques may be used, such as job titles, spot readings, personal exposure measurements, and stationary monitoring. These techniques may not always produce comparable estimates of exposure and may have dissimilar errors or bias. Finally, the underlying purpose of the studies may differ: some are designed to characterize the exposures of particular individuals and others to identify and characterize sources, appliances, or unique machinery in an industrial setting. Many studies in the occupational environment are designed to characterize particular jobs or work activities that may be used as surrogates of exposure, such as the exposures of utility lineman or electrical power-line repair maintenance workers.

2.3.4 Exposure assessment for epidemiological studies

Direct measurements of relevant exposure for studies of health effects are often difficult or impossible to obtain, particularly for chronic diseases. Sometimes, the exposure of interest occurred years earlier, the actual circumstances of exposure cannot be recreated, access and cooperation of subjects cannot be obtained, or insufficient details are available. For this and a variety of other reasons, it is frequently necessary to use surrogates instead of direct measures. Exposure surrogates are individual or group attributes that can be used to arrive indirectly at a ranking of the true exposure or to assign a numerical estimate of the true exposure to an agent. Two primary surrogates have been widely used in research on EMF: job titles in occupational studies and wiring configuration coding (wire codes) in residential studies. These two surrogates and the validity of the methods are discussed in detail below. It should be noted that a direct measure of EMF may be considered an exposure surrogate if the measured quantity does not capture the biologically meaningful signal.

The concept of homogeneous exposure within groups is the underlying basis for exposure assessment in most epidemiological studies. Ideally, when homogeneous exposure groups exist, all members within the group have an essentially comparable exposure, and all variation in exposure occurs between groups. Although this ideal situation never occurs, it can be approximated. The exposure can be characterized by partitioning the total exposure variation in an analysis of variance (ANOVA) model. The goal of the exposure assessment is to identify a method of grouping individuals in which a large fraction of the total variation is between the groups and a small fraction remains within the groups. Much effort has been devoted over the past 10 years to methods for identifying exposure groupings and applying this concept to exposure surveys (Rappaport *et al.*, 1993).

A frequent problem in epidemiological exposure assessment is defining the characteristics that can be used to define exposure group membership. A variety of historical exposure estimates have been used, such as field readings at some point in time (spot measurements), survey measurements in a residence or workplace, and personal monitoring, but more often other factors, such as work, school, or residential environment, duties performed at a work site, job title, or occupational history, are used as grouping factors. These factors become useful exposure surrogates to the extent that they provide reliable, meaningful partitioning of the exposure variation in the study population.

If measurements have large errors, the surrogates are not specific, or the data are otherwise unreliable, the exposure of study subjects to EMF may be misclassified. Misclassification is often essentially random, leading to switching of individuals between exposure groups. Misclassification may also have a systematic effect that affects certain groups more than others. The effects of random exposure misclassification are usually to decrease the precision of an epidemiological study, making it more difficult to observe an association with disease. When there are multiple exposure groupings, random

misclassification can lead to spurious associations in the results (Flegal *et al.*, 1986). The usual effect of systematic misclassification is to bias the risk estimates, possibly creating a spurious association or masking a real one.

2.4 Occupational exposure

2.4.1 General occupational environments

A variety of methods for exposure assessment have been devised and applied to epidemiological studies of the effects of EMF in occupational settings. The methods range from rather crude job-classification methods, to sophisticated job–exposure matrix (JEM) modeling based on personal exposure measurements and reconstruction of past exposure. The methods have their potential strengths and weaknesses and at best allow only an estimate of the true exposure of the study population. In the following, except where indicated, the assumed exposure metric is the TWA rms field or a closely related measure of ‘average’ field magnitude.

The main features of the exposure assessment methods used in epidemiological studies can be summarized by three terms: sensitivity, specificity, and potential bias (Lilienfeld & Stolley, 1994). The first two characteristics usually affect individual exposure estimates relative to a group classification, while the last affects group estimates. Sensitivity is the ability of the method to classify correctly an individual who is truly exposed. Specificity refers to the method’s ability to classify accurately an individual who is truly not exposed. Bias is the potential for shifting or skewing of exposure estimates away from the true values. Consequently, a biased assessment method may either systematically overestimate or underestimate desired exposure features for groups of individuals in the study population. Bias can be introduced in many ways but most often stems from fundamental limitations of the study design or from limited access to a portion of the study population. Bias can also be introduced by flaws in the sampling strategy used in the exposure assessment, particularly when random sampling or systematic sampling (stratified or cluster sampling) plans are not used.

Considerable emphasis has been placed on the use of personal monitoring for studies of occupational exposure to EMF. Personal monitoring relies on an exposure meter, which is carried on a subject’s body to capture spatial and temporal variation in exposure as a series of measurements over time. The individual is the sampling unit, which has the advantage that both within-subject and between-subject exposure variation can be characterized and homogeneous exposure groups can be formed. In some cases, spot measurements may provide a reasonable alternative to personal measurements. In retrospective studies, it is impossible to measure the exposure of the same worker for whom occupational information was gathered; subjects may be untraceable, dead, or inaccessible for reasons of confidentiality or may be in a different exposure circumstance.

In such situations, it may be necessary to rely on contemporary measurements of personal exposure from a different, surrogate worker. Contemporary measurements are based on the premise that work practices and sources have remained relatively constant over time. If the spot measurements can capture relevant differences in exposures between jobs, then use of surrogate workers is not necessarily any more meaningful than spot measurements in a work area.

An occupational or work history is a body of data obtained for a study subject, which contains information on the jobs that the subject held throughout his or her working life. Such information is often obtained through questionnaire interviews or databases such as company records. Work histories usually contain information on self-reported job and industry title, company name, a brief job description, how long each job was held, and hours worked per week. In addition, medical records may be obtained from health maintenance organizations, doctors' offices, and disease registries. Death certificates have also been used to obtain information on occupations (Lin *et al.*, 1985).

Job and industry titles are commonly used as surrogates for exposure to EMF and other types of exposure in epidemiological studies. As investigators often have no prior direct measurements of the subjects' past exposures, an entire occupational history must be re-created for each study subject and used to infer past exposure. Usually, researchers cannot obtain individual measurements of exposure for all subjects in a study; consequently, researchers have developed various ways of estimating the exposure of groups of individuals, by re-creating their occupational history and quantifying the related workplace exposures.

Many coding schemes are available, including the Standard Industrial Classification, Standard Occupational Classification (Table 2.3), US census codes, *The Dictionary of Occupational Titles*, and international occupational codes. Although these codes provide standardized classification methods for jobs or industries, most of these systems were derived for economic or statistical recording purposes and not for the purpose of exposure groupings. Consequently, the coding may not efficiently aggregate similar exposures or even logically classify workers who perform similar tasks and have similar exposures. The Standard Occupational Classification coding system has been widely used in the USA for epidemiological studies. This coding provides a hierarchy of classification that at least tends to keep similar jobs in neighboring groups. This feature is useful when aggregating data from many studies or for clustering jobs held over a working lifetime.

A JEM is a convenient way of organizing data that link job titles or an occupational history to exposure. In a JEM, occupational classification is shown along one axis. Job titles, industry categories, or a combination of these factors are included on this axis. The exposure agent appears across the other axis. Where the rows and columns intersect in the body of the matrix, a level of exposure is displayed. A degree of confidence is often added to the level of exposure, or a percentage of the population exposed may be incorporated. Early versions of JEMs can be traced back to the 1940s, but the first modern JEM was reported in 1980 (Hoar *et al.*, 1980). Although use of JEMs in occupational epidemiology

is relatively recent, it has gained wide acceptance in case-control studies (Smith, 1987). The main advantage is the possibility of collapsing many job titles into a smaller number of homogeneous exposure groups. Combining workers into homogeneous groups allows analysis and comparison of data exposure between groups, so that differences in job-exposure and dose-response relationships can be explored. A JEM also can help to economize future research by combining data from many sources; JEMs are often used in hypothesis-generating studies to re-analyze existing data.

Exposure level can be represented in several different ways in a JEM. The most basic JEM simply indicates the presence or absence of a particular exposure for a particular job title. If more information is available, exposure may be ranked, for instance as high, medium, or low. Numerical data from actual measurements is the most desirable source for creating a JEM. In this case, each cell in the JEM ideally contains a group mean value for the exposure metric and some measure of within-group variability.

Although early developments focused on exposure to chemicals, detailed data on personal exposure make it possible to create a JEM for EMF. Today, JEMs incorporating measurements are probably the best approach for assessing exposure to EMF in occupational studies. JEMs allow merging of quantitative measurements with information on job title, industry, and work site to arrive at a grouped estimates of exposure; however, the availability of historically accurate information on exposure to EMF remains a challenge. In general, it is easier to assess past exposures agents such as solvents, because exposure to them is much more memorable to workers or supervisors, and some groups can be identified *a priori* as having little or no exposure. This is not true for EMF, since virtually everyone is exposed to some degree, and typical exposures are not memorable. In addition, there are usually many more potential sources of EMF than chemicals in a workplace (Savitz, 1993).

An alternative to measuring exposure for a JEM is asking a panel of experts to assign exposure. Such experts should have background knowledge of the tasks in a job, sources of EMF, and specific exposure situations (Loomis *et al.*, 1994a). Job and industry titles may be insufficient to classify the exposures of workers in the absence of specific information on actual work sites. Expert judgment can incorporate this kind of site-specific information, resulting in a better exposure assessment for a particular occupation when information is obtained from a work history or from questionnaires (Post *et al.*, 1991); (Kromhout, 1992). Often, an expert panel is made up of current or former company employees, such as plant workers, supervisors, and industrial hygienists or medical staff.

JEMs used in epidemiological studies of EMF are often specific to a certain industry or location, such as electric power utilities, and may focus solely on occupational exposures. The rationale for ignoring residential exposures in occupational studies is the assumption that occupational exposures dominate the total daily or annual exposure to such an extent that other sources are unimportant. This assumption has several potential flaws. First, it presumes that the magnitude of the field is the appropriate measure of disease risk.

Second, it assumes that all exposures are additive in time. Third, it assumes that residential sources are much less intense than occupational sources. Fourth, it assumes that the timing of exposure and circadian effects (for example, exposure during sleep, which is not typical on the job) play no role in defining a biologically meaningful exposure. To some extent, all of these assumptions are questionable for EMF, but the last two in particular are not supported by recent studies of EMF. TWA measures of residential exposure can be at least equal to those received in many jobs, and residential appliances can contribute intense (but usually brief) exposure.

Job and industry title can be used as surrogates for exposure to EMF because they allow assumptions to be made about the workers' duties. Certain tasks can be associated with high or low exposure to EMF. For instance, a worker employed as a welder is likely to be exposed to high levels; in contrast, an agricultural worker picking fruit will probably have little exposure to EMF.

Retrospective exposure assessment from job titles can present problems. Workers with the same job title or workers in the same industry today may not have the same exposures as workers had 20 or 30 years ago, and some job titles that were common in the past may have been rendered obsolete by changing technology. For example, 'keypunch operator' was a common job in the computer industry but has essentially disappeared. Another example is secretarial and administrative work: 30–40 years ago most such workers probably sat at a desk with a telephone and a manual typewriter. Today, it is common for secretaries to have computers, fax machines, and photocopiers within arm's reach of their desks. The addition of these appliances may greatly increase average daily exposure to EMF.

The classifications 'electrical jobs' and 'non-electrical jobs' were developed by Milham to dichotomize workers into exposed and unexposed groups (Milham, 1985). This classification found wide use in early mortality and morbidity studies of EMF. Although this grouping probably leads to considerable misclassification and does not allow derivation of quantitative exposure–response relationships, it makes few assumptions about the nature of exposure to EMF. A three-level classification indicating a degree of exposure to EMF, by background, intermittent, and continuous exposure, was used by Guénel *et al.* (Guénel *et al.*, 1993).

Measurements of exposure to magnetic field have been collected in a number of occupational studies. Table 2.4 shows the exposures to EMF assigned to different job titles in the occupational epidemiological studies reviewed in this document. The occupations in which exposure to EMF is assumed to be above 'background' levels are listed in order of the arithmetic mean of the TWA magnetic field measured. These exposures have been summarized in a JEM (Yost *et al.*, 1997). When the standard deviations are greater than the arithmetic mean, the distribution is skewed, and the arithmetic mean is not necessarily the best statistic for the central tendency (although many investigators report nothing better). To give perspective, the Table includes magnetic fields measured in some common occupations not considered to involve

exposure to EMF and also includes percentiles from a distribution of TWA exposures measured in a population-based study of male workers (Floderus *et al.*, 1996).

Magnetic fields experienced in a variety of categories of jobs, homes, and offices were assessed by Bowman *et al.* (Bowman *et al.*, 1988) (see Table 2.5). They found significant increase in exposure to EMF in electrical jobs overall. At the work sites examined, spot measurements were taken as close to the worker as possible in the direction of the most likely field sources. In the residences, spot measurements were taken in the center of the living room, bedroom, kitchen, and backyard, under conditions of both low and normal power. The magnetic fields observed at work sites ranged from 0.003 μT (microelectronics assembler) to 10 μT (electrician in industrial power supply). Only a few measurements were taken in the office environment: one secretary using a VDT had a geometric mean exposure of 0.31 μT . Three secretaries who did not use VDTs had a geometric mean exposure of 0.11 μT . In the 18 residences measured, a geometric mean exposure of 0.06 μT was found.

Using personal exposure meters, Deadman *et al.* (Deadman *et al.*, 1988) assessed the occupational and residential exposure of a group of electrical utility workers and a comparison background group over one week. The study cohort consisted of 20 workers from six electric utility occupations and 16 workers from two office buildings. Exposures at work and away from work were determined for the two groups. The geometric mean exposure was 1.7 μT for the exposed group and 0.16 μT for the background group at work and 0.31 μT for the exposed and 0.19 μT for the background group away from work. The authors proposed that the difference was due to misclassification of some work as non-work. The background group had slightly higher exposure to magnetic fields away from work than at work (0.19 vs. 0.16 μT). This difference was presumed to be due to the greater use of hand-held and other electrical appliances at home.

In a study of exposures to magnetic fields in the electric utility work environment (Sahl *et al.*, 1994), exposure to magnetic fields was obtained for 770 work days for the following occupational categories: office staff, meter readers, mechanics, groundmen, lineman, splicers, laborers, plant operators, welders, technicians, machinists, substation operators, and electricians. The fraction of exposures exceeding a 0.5 μT summary measure was used to classify occupations into three main groups. The high-exposure group included electricians and substation operators with mean exposures of 2.1 and 1.8 μT , respectively; the low-exposure group included office staff, meter readers, and groundmen; and the remaining craft occupations made up the medium-exposure group. The mean exposure for three classifications of office workers ($n = 73$ workdays) was 0.1, 0.18, and 0.23 μT .

Barroetavena *et al.* (Barroetavena *et al.*, 1994) compared electric and magnetic fields measured at 132 locations in three pulp and paper mills. The median magnetic field

strengths in the three facilities were 0.12, 0.33, and 0.15 μT , respectively, which were statistically significantly different ($p = 0.006$), on the basis of the overall electrical consumption at each facility. Differences in measured magnetic fields were also observed in offices at the facilities, with median measurements of 0.05 μT in two offices in one facility, 0.18 μT in three offices in another facility, and 0.26 μT in five offices in the third.

In Denmark, Skotte (Skotte, 1994) studied the 24-h exposure of electric utility workers, office workers, industrial workers, and people living near high power lines to power-frequency electromagnetic fields. A total of 396 measurements were gathered from 301 subjects, 55 of whom were office workers outside the utility companies. The geometric mean exposure observed for office workers was 0.09 μT (geometric standard deviation [GSD] 1.8). In normal residences, defined as those not near high-voltage transmission lines, the geometric mean exposure of all study participants was 0.05 μT (GSD, 2.1).

Breyse *et al.* (Breyse *et al.*, 1994b) measured ELF magnetic fields in office environments by taking spot and personal measurements of magnetic field in a large payroll department. Personal exposure was collected for 15 female employees with either an EMDEX C or EMDEX II exposure meter. The spot measurements revealed exposure to 0.13–2.7 μT for work with office equipment such as VDTs and photocopiers. The highest measured flux density was attributed to an electrical utility duct. The TWA personal work exposures were 0.1–0.65 μT (mean, $0.32 \pm 0.15 \mu\text{T}$).

Burch *et al.* (Burch *et al.*, 1998) compared exposure to magnetic fields and light with urinary melatonin metabolites in 194 utility workers in northern Colorado, USA. This study is unique because it related exposure to magnetic fields to a short-term change in a human biomarker. Magnetic field and light readings were collected from personal exposure meters for full 24-h periods over five consecutive days. Post-shift and overnight urine samples were used to follow melatonin metabolite excretion. A variety of exposure metrics was used, including a measure of rate of change to describe temporal changes in the field readings and a standardized rate of change metric to measure temporal stability. The standardized metric closely predicted decreased melatonin excretion for both work and night exposures, the values being 0.64 ± 0.04 at work and 0.5 ± 0.04 during sleep for distribution workers and 0.73 ± 0.03 at work and 0.58 ± 0.04 during sleep for office and administrative workers. The TWA exposures over the same intervals showed no association with melatonin, unless combined with the standardized rate of change metric. This result suggests that it may be important to characterize the temporal characteristics of exposure to magnetic fields.

The EMDEX project, conducted by Bracken *et al.* (Bracken *et al.*, 1995b), was one of the first to document personal exposure for a broad group of utility workers. The exposure of volunteers were collected from utility employees in 13 job classifications at 59 sites in four countries over one year. Uniform sampling procedures and data collection protocols

were used at all sites. The volunteers kept diaries of the work and non-work environments they occupied while wearing an exposure meter. Approximately 50 000 h of exposure to magnetic fields taken at 10-s intervals were obtained, about 70% of which were from work environments. Exposure and time spent in environments were analyzed by primary work environment, by occupied environment, and by job classification. The utility-specific job classifications were typically associated with higher exposures; the job classifications with the highest (median workday mean) exposure were substation operators (0.7 μT) and electricians (0.5 μT). Total variance also tended to be largest for utility-specific job classifications, while the contributions of between-worker and within-worker variation to total variance were about the same. Estimates of time-integrated exposure indicated that in utility-specific job classifications approximately one-half of the total exposure was received on the job. The distributions of non-work exposure were comparable for workers in all job categories, with a median non-workday mean of about 0.09 μT .

Savitz *et al.* (Savitz & Loomis, 1995) studied exposure to magnetic fields in relation to mortality from leukemia and brain cancer among a cohort of 138 905 electric utility workers at five companies in the USA. An extensive personal sampling protocol was used to develop a JEM for exposure reconstruction. Randomly selected workers within occupational categories wore a time-integrating magnetic-field meter (AMEX-3D) so that daily exposure could be estimated for job categories. The mean TWA exposures ranged from 0.12 to 1.27 μT for the various categories. Exposure was estimated by linking individual work histories to a JEM based on 2842 work-shift magnetic field measurements. The JEM was optimized to partition variance into between-day (the largest contributor), within occupational categories, and between occupational categories. Kromhout *et al.* (Kromhout & Loomis, 1997) examined the effectiveness of six alternative grouping strategies for assessing cumulative exposure to magnetic fields in this study population. The quantitative relationship between cumulative exposure to magnetic fields and mortality from brain cancer was sensitive to the choice of grouping scheme, the optimized grouping scheme indicating a stronger relationship than standard grouping based only on job titles.

Thériault *et al.* (Thériault *et al.*, 1994) conducted a large study of occupational exposure to magnetic fields in relation to cancer risks among three cohorts of electric utility workers in Ontario and Quebec, Canada, and France. A JEM was constructed after monitoring of contemporary occupations to link exposure to 50–60 Hz EMF to the occupational histories of workers at three electric utilities: Electricité de France–Gaz de France, 170 000 men; Ontario Hydro, 31 543 men; and Hydro-Québec, 21, 749 men. Each participant's cumulative exposure to magnetic fields was estimated from measurements of the current personal exposure of 2066 workers who performed tasks similar to those of workers in the cohorts. Past exposure was estimated from knowledge of current loading, work practices, and usage. The median cumulative exposure to magnetic fields was 3.1 μT -years, and the 90th percentile was 15.7 μT -years.

Baris and Armstrong (Baris *et al.*, 1996b) conducted a substudy to investigate how closely the exposures to magnetic fields based on the last job held compared with exposures based on the workers' entire employment history within the company. The correlations between exposure indices based on the last job and on all jobs varied between 0.75 and 0.78. The mean exposure of all workers was slightly lower when only the last job was considered; however, the last job was particularly useful for identifying the most highly exposed people: the 90th percentile cut-point for the last job had a sensitivity = 0.69, a specificity = 0.97, and a concordance = 0.66 in comparison with all jobs held. These results indicate that use only of the last job to classify exposures results in a greater loss of information than a complete history. Although not all workers starting in highly exposed jobs stayed in them, those who ended their working life in highly exposed jobs had been in these jobs for an extended period. [This finding may be limited to work within the same company.]

Floderus *et al.* (Floderus *et al.*, 1996) conducted a large population-based study of occupational exposure to EMF (50 Hz) in relation to adult leukemia in Sweden. The exposure assessment was based on a JEM derived from extensive measurements of personal exposure in 1015 workplaces. The JEM derived from these data covered 100 of the commonest occupations in Sweden, with a minimum of four measurements for each occupation. The median workday mean was 0.17 μT , and the 95th percentile was 0.66 μT . Median workday means for occupations with low exposure were 0.04 μT for earth-mover operators and 0.05 μT for concrete workers; the corresponding value for electrical and electronics engineers and technicians and welders was 0.19 μT . Overall, the workday mean in the population was 0.28 μT with a standard deviation of 0.62. This data set is perhaps the most extensive to date for exposure of the general population to EMF.

2.4.2 Visual display terminal operators

Some studies have investigated VDTs as a source of exposure to EMF, particularly in connection with adverse reproductive outcomes. VDTs are relatively unique EMF sources in that they produce a broad range of ELF frequencies and VLF harmonics ranging from about 50 Hz up to 50 kHz. VDT sources are often directional and have complicated time-varying vector properties. Measuring these sources requires careful attention to instrumentation if the desired field parameters are to be captured. Many studies of VDT operators have relied on surrogate exposure measures such as time spent in front of a VDT, distance to the VDT, and job titles. Sometimes, spot measures of field magnitude over a limited portion of the ELF band at a fixed distance in front of the VDT are used to estimate exposure. Haes and Fitzgerald (Haes & Fitzgerald, 1995) obtained measurements of VLF magnetic fields from 140 VDTs and electric field measurements from 40 devices over a three-year period. They compared measurements 50 cm from the centerline of the screen with readings taken 30 cm above the seat, at the approximate location of the reproductive organs of a seated female user. The results demonstrate little correlation between the two locations.

The validity of various exposure surrogates for describing exposure to EMF in office VDT users was examined by Abdollahzadeh *et al.* (Abdollahzadeh *et al.*, 1996). They compared 8-h TWA personal exposures to 30–1000 Hz magnetic fields at waist level with a variety of surrogates including: measurements of magnetic fields at 40–1000 Hz at a fixed distance from the VDTs; reported hours of VDT use; and reported distance between the VDT and the subject's waist. The results showed a weak correlation between the 8-h TWA exposure of a VDT user and the magnetic field measured 46 cm from the VDT ($R = 0.52$, $n = 67$, $p < 0.001$). They found no association between self-reported hours of VDT use or self-reported distance between waist and VDT and the average magnetic field. Moreover, individuals' average exposure to magnetic fields did not seem to be affected by other variables such as the position of the VDT on the desk, hours of desk use, and the VDT type (color vs. monochrome).

Nair and Zhang (Nair & Zhang, 1995) also examined a variety of exposure metrics for VDTs by a method based on effects function, to determine the extent to which VDTs can be distinguished from other common sources. They found that that VDT exposure may be of consequence if exposure depends on certain types of time variation of the field. Their work demonstrates that the choice of an exposure–response relationship (i.e. the effects function) can determine if a source will make a small or large contribution to the total exposure.

A study by Lindbohm *et al.* (Lindbohm *et al.*, 1992) of exposure to VDTs in connection with spontaneous abortions incorporated both measurements and exposure surrogates. They assessed the type of VDT used and the duration of use by questionnaires and employer information. ELF and VLF magnetic field measurements on a representative sample of VDT units in a laboratory provided the exposure information. A relatively high threshold of 0.4 μT (ELF) was used for VDT readings to define the low-exposure group; the high-exposure group was defined as receiving $> 0.9 \mu\text{T}$. This grouping scheme made it likely that VDTs would be a strong contributor to exposures, although validation could not be made with personal exposure readings. Electric fields were measured with an active dipole antenna which had a frequency response extending up to 10 Mhz (see Table 2.1). The electric fields 30 cm from the screen were in the range 1.8–22 V/m.

These studies point out the difficulties of conducting a study of VDT operators due to the many possible sources of exposure and the problems in defining an exposure metric that captures the unique characteristics of VDTs.

2.5 Residential exposure

The exposure assessment method known as wiring configurations or 'wire coding' developed by Wertheimer and Leeper (Wertheimer & Leeper, 1979) in a study of childhood leukemia deserves special mention because of its place in the literature on EMF. Wire coding was developed in Denver, Colorado, USA, to provide a surrogate

measure of exposure to EMF, with a relatively simple scheme for ranking possible exposures by assigning residences into wiring configuration categories. The original classification had only two categories, but this was expanded later to five categories: underground wiring, very low current configuration, ordinary low current configuration, ordinary high current configuration, and very high current configuration (VHCC) homes (Wertheimer & Leeper, 1982). The classification scheme is based on the identifying characteristics of the power lines visible from outside a home and the distance from the home to the wires. Therefore, it does not require access to the home or instruments, and it can be used to assess exposure in current and previous residences, thus largely avoiding participation bias.

Wire coding is also a historically stable metric because the type of power distribution lines outside a house do not in general change much over the years. This method is often used in retrospective studies, in which historical stability is important; however, other types of error such as misclassification of wires may be introduced. Wire coding may also introduce confounding or bias that has not been fully understood. Researchers have continued to measure residential exposures with methods such as wire coding, despite the limitations of this method and the modest association with measurements of magnetic fields taken in residences. Wire coding does not provide an estimate of exposure to electric fields within homes (Savitz, 1993).

Table 2.6 shows the distribution of wire codes from seven studies conducted in the USA over the past 15 years. The prevalence of homes with VHCC varies markedly across the studies, from 3% in Denver to 12% in Los Angeles. As some studies excluded underground wiring in homes, the proportions in the remaining categories are somewhat inflated. Table 2.7 shows measured magnetic fields with wire code categories in six studies conducted in the USA since 1982. Measures of central tendency were selected from those available in the studies. Considerable variation can be seen in the measures in each category and particularly in the highest VHCC wire code category, probably reflecting the varying ability of wire codes to capture higher exposures. Table 2.8 shows the percentage of homes in various wire code categories with measured values above a 0.2 or 0.3 μT threshold and indicates that the usefulness of wire codes for identifying high field values in homes varies widely. The proportions in categories in studies from which underground homes were excluded should be interpreted with caution since they are inflated relative to the others.

2.5.1 Direct measurements

One of the earliest residential studies in which direct magnetic field measurements were used in addition to wiring configurations was the study of childhood cancer conducted in Denver, Colorado, by Savitz *et al.* (Savitz *et al.*, 1988). The authors relied on spot measurements of the field magnitude taken inside the residence to assess potential exposure to EMF. Although the study showed an association between wire codes and

magnetic fields, it found no association between wire codes and electric fields (see Table 2.7).

DelPizzo *et al.* (Delpizzo *et al.*, 1991) tested the usefulness of spot measurements for classifying residential levels of magnetic fields. Spot measurements were compared with data collected from stationary 24-h monitors. Homes with mean 24-h magnetic fields $> 0.075 \mu\text{T}$ were classified as exposed, and those with mean levels $< 0.075 \mu\text{T}$ were classified as unexposed. They found that a single spot measurement had at least an 80% chance of classifying a house in agreement with the classification based on the 24-h mean magnetic field and concluded that a small number of readings collected manually over several points within a home can serve to characterize the magnetic field as well as stationary monitoring. DelPizzo and Salzberg (Delpizzo & Salzberg, 1992) found that averaging four or five spot measurement readings over time instead of using a single point in time measurements resulted in a dramatic improvement in the observed-to-true ratio for classifying residential fields; however, these studies were limited because the stationary 24-h measurements in the homes were used as the measure of 'true' exposure. The authors did not measure personal exposures and could not assess the effects of personal activity and use of appliances on exposure classification.

Spot measurements were the basis of a standardized protocol for measuring magnetic fields in homes for a large study of reproductive toxicity conducted in northern California (Yost *et al.*, 1992). A pilot study, which involved taking 252 spot measurements in 24 San Francisco Bay Area homes, was conducted to identify an appropriate sampling strategy. Measurements were taken in multiple locations (center, front right, front left, back right, and back left) in the kitchen, living room, and bedroom of each home, under both low-power (all electrical devices turned off/unplugged) and normal-power conditions. They found that the center normal-power spot measurement was representative of those in other locations. In addition, 79% of the variation in home spot measurements was due to differences between homes ($p < 0.00001$). The differences between rooms were also significant ($p < 0.01$). In this protocol spot measurements were taken at the front door and in the center of the kitchen, living room, and bedroom under normal-power conditions. Under that protocol, no more than 45% (and probably considerably less) of the variance would result from within homes. The authors pointed out that London *et al.* (London *et al.*, 1991), using a similar spot measurement protocol, reported that 19% of the variance was within homes.

In an earlier study, Silva *et al.* (Silva *et al.*, 1989) reported the spatial distributions of the vertical magnetic field in five types of room found in residences: living rooms, dining rooms, bedrooms, kitchens, and bathrooms. Scatter plots of the vertical field component in the various rooms showed correlation coefficients between center-of-room measurements and elsewhere within the same room that ranged from 0.64 to near 0.8. Although measurements were performed in 81 residences, they were limited because only a single field component was recorded.

The Electric Power Research Institute (EPRI) conducted a survey of 996 residences to determine the levels and sources of residential power-frequency magnetic fields (Zaffanella, 1993). The survey, often called the 'EPRI 1000 homes study', involved a random two-stage cluster sampling plan to achieve a statistically representative sample of EPRI utility customers nationwide. This unique survey, although not designed to describe individual exposures, provides a snapshot of residential fields and the results are probably reasonably representative of residential conditions. An extensive measurement protocol was used, including spot measurements inside the rooms, field recordings in the home, Wertheimer-Leeper wiring codes, measurements of field profiles from wiring outside the home, measurements of household appliances, and measurement of fields from currents in the electrical grounding system. The overall average spot magnitude of the magnetic field inside the surveyed residences was 0.09 μT . The median value for the average spot magnetic field reading was 0.06 μT and exceeded 0.29 μT in 5% of all measured residences. The survey results were corrected by reference to the sample base population representative of national residences. About 28% (95% CI = 22–34) of the homes nationwide exceeded an average interior magnetic field magnitude of 0.1 μT , about 3.3% (95% CI = 1.7–5%) exceeded 0.25 μT , and 0.3% (95% CI = 0.1–0.6) of residences exceeded 0.5 μT .

The 1000 homes study included extensive engineering investigations to identify possible determinants of residential magnetic fields. In most residences, currents in outside power lines and currents flowing in the electrical grounding system were the dominant contributors. Power lines contributed most to the background average magnitude of the magnetic field distributed over the entire residence over the course of a day. Thus, power lines were identified as a significant source of the background fields in the home environment. Currents flowing in the electrical grounding system, in contrast, produced larger variations in magnetic fields over space and time. In some cases, specific features of the electrical system in the residence could be linked to higher magnetic fields: grounding of electrical sub-panels contributed in 4.6% of residences, multiple three-way switches in 5.2% of homes, electric ceiling heat in 2% of homes, and old-style wiring (knob and tube wiring) in 7% of homes. Other more general characteristics of the homes were also associated with higher fields. For example, fields were typically higher in older residences, homes with grounding to a metallic water line, and in duplex or apartment residences. Factors found to be unrelated to interior magnetic fields were household electric energy consumption, construction materials, presence of electric heating (other than radiant ceiling heat), and the presence of children in the home.

One goal of the survey was to evaluate various measurement methods to reliably classify residences with regard to interior magnetic fields. Previous studies had involved a variety of protocols, such as 24-h recordings and spot measurements taken in several rooms, to measure magnetic fields. One comparison of considerable interest concerns the usefulness of spot magnetic field measurements to correctly identify high-field residences. The protocol of the 1000 homes survey was similar to the California protocol described above, with spot measurements taken at the center of several rooms in the home. In the 1000 homes survey, 24-h measurements were also made of both power-line fields and

grounding-system fields and they were combined to estimate median fields in the residences. The results are shown in Table 2.9. Remarkably, the median spot readings obtained with the two methods agree quite well. This shows that spot measurements could be used as a first approximation for characterizing magnetic fields in homes.

Table 2.9. Estimated median magnetic fields in the 1000 homes survey

% of homes in which values were exceeded	60 Hz magnetic field spot measurements (μT) ^a					24-h combined field from power-line and ground system (median) ^b
	Kitchen	Bedrooms	Highest	All rooms		
				Average	Median	
50	0.07	0.05	0.11	0.06	0.05	0.05
25	0.12	0.1	0.21	0.11	0.1	0.10
15	0.24	0.2	0.38	0.21	0.17	0.18
5	0.35	0.29	0.56	0.3	0.26	0.26
1	0.64	0.77	1.22	0.66	0.58	0.55

^a Data from 992 residences

^b Data from 986 residences

^c Room with highest spot reading

Kavet *et al.* (Kavet *et al.*, 1992) assessed the exposure of adults in Maine who lived either near or far from overhead transmission lines. The assessment included 24-h personal exposure measurements, spot measurements in three rooms of every residence, and a 24-h fixed location bedroom measurement. They found greater home and total exposure for subjects residing near highly loaded transmission lines than for subjects living far away from power lines. Both the room spot measurements and 24-h fixed-site bedroom measurement were correlated with home exposure ($R = 0.70$ and 0.68 , respectively). Similarly, in another residential study, Kaune *et al.* (Kaune *et al.*, 1987) found that spot and 24-h magnetic field measurements were associated, with a correlation coefficient of 0.5 .

Kaune *et al.* (Kaune *et al.*, 1994) also studied 29 children four months to eight years of age to determine whether area (spot and/or 24-h) measurements of power-frequency magnetic fields in residences and schools could be used to predict measured 24-h personal exposures. The average 24-h personal exposure observed was $0.1 \mu\text{T}$ (geometric mean). Greater variation between subjects was found for home exposure than for school exposure. The TWA spot measurements in the home were highly correlated with residential personal exposure ($R = 0.9$). On the basis of these findings, they established a protocol for measuring residential exposures to magnetic fields. This protocol, like the California protocol developed by Yost *et al.* (Yost *et al.*, 1992) calls for the following measurements: spot measurements inside the home (center of the subject's bedroom, kitchen, and one other room occupied most frequently by the subject), spot

measurements taken immediately outside the front door, and a 24-h fixed measurement in the subject's bedroom.

The repeatability of assessments of residential magnetic fields and wiring codes was examined by Dovan *et al.* (Dovan *et al.*, 1993) in a study widely known as the 'back to Denver' study. The purpose of the study was to evaluate the long-term stability of wire codes and residential spot magnetic field readings in classifying residential magnetic fields. Wiring code and magnetic field measurements obtained in Colorado homes in 1985 as part of the Savitz study were compared with measurements taken more than five years later. The wire code measurements were in agreement for 73 of 81 homes (90%), and the correlation between spot magnetic field measurements taken in 56 homes in 1985 and measurements taken in 1990 was $R = 0.7$. A diurnal trend was observed when the average home spot measurements were compared over 24 h, the highest magnetic fields being observed in the late afternoon or early evening and the lowest in the early morning.

London *et al.* (London *et al.*, 1991) investigated the relationship between childhood leukemia and measurements of EMF in homes or exposure assessed by surrogates such as wiring configurations and self-reported use of appliances in Los Angeles County, California. They recorded detailed measurements of the magnetic field in the child's bedroom over more than 24 h (164 cases and 144 controls), spot measurements of EMF (140 cases and 109 controls), and wiring configurations. The 24-h average magnetic field recorded for the controls was reported as $0.12 \pm 0.16 \mu\text{T}$ and the 90th percentile was $0.19 \pm 0.3 \mu\text{T}$. The average electric field in the bedrooms of controls was reported as $8 \pm 12 \text{ V/m}$. A gradient in the average magnetic field readings was observed for increasing wiring configuration categories: homes with underground wiring, $0.05 \mu\text{T}$, and VHCC homes, $0.12 \mu\text{T}$. The measurements were similar to those reported by Savitz in Denver, but the prevalence of VHCC homes was higher (11% of control homes in Los Angeles and 3.1% in Denver).

The correlation between magnetic fields and exposure over time was also examined by Kaune and Zaffanella (Kaune & Zaffanella, 1994). Their exposure assessment incorporated spot measurements, stationary 24-h measurements in two locations, and personal exposure measurements for 35 children living in western Massachusetts and northern California. Measurements were taken in the spring of 1990 and again in the winter of 1990–1991. They found a poor correlation between personal exposure measured at the two times ($R = 0.1$) but fair correlations between spot measurements repeated twice ($R = 0.7$) and between stationary 24-h measurements repeated twice ($R = 0.8$).

Kleinerman *et al.* (Kleinerman *et al.*, 1997) reported on assessment of exposure to magnetic fields for a nine-state residential study of childhood leukemia. Residential magnetic fields were measured in 1354 current and former homes of cases and controls in the study. The TWA magnitude of the magnetic field weighted by the length of time the subject lived in each home was the main exposure metric. The TWA for subjects was estimated by a weighted average of the 24-h bedroom reading with spot readings taken in

other rooms. They found that 24-h bedroom measurements adequately characterized the residential exposure of children and that measurements in other rooms contribute only slightly. The mean value for the TWA magnetic field in the homes was 0.11 μT , with a standard deviation of 0.11. All of the spot readings were highly correlated with the 24-h bedroom average; the rank correlations ranged from 0.83 in the bedroom to 0.66 for kitchen locations. Front-door spot measurements provided useful information when interior measurements were missing. The rank correlation of the front-door spot reading in comparison with the 24-h reading in the child's bedroom was 0.72; this improved to 0.79 when compared with the estimated TWA for the whole residence. [This study indicates that contemporary spot measurements or front-door readings are reasonably reliable predictors of other contemporary measures of residential magnetic field magnitude.]

Friedman *et al.* (Friedman *et al.*, 1996) provided the basis for the residential magnetic field survey methods reported by Kleinerman. They compared 24-h stationary measurements in a bedroom with personal exposure measurements for 64 children aged 2–14 years during a typical weekday. The information recorded in activity diaries indicated that the children spent more than 40% of the 24 h in their bedrooms and 68% of their time at home. For children under nine, the levels of exposure at home were highly correlated with total personal exposure ($R = 0.94$); the correlation was lower in older children ($R = 0.59$). The 24-h bedroom measures correlated well with personal exposure at home ($R = 0.76$) for all of the children combined. [These results indicate that 24-h bedroom measurement is a good predictor of both residential and total personal exposure, particularly for younger children.]

Zaffanella *et al.* (Zaffanella & Kalton, 1998) made a US nationwide random-sample survey of 1000 individuals to provide a more comprehensive picture of exposure to magnetic fields. This study is the first serious effort to evaluate a cross-section of exposure to magnetic fields in the general population. Although somewhat limited by the response rates and potential participation bias, the study provides valuable insight into total exposure to magnetic fields. The preliminary results of this survey were released at a symposium on engineering research into magnetic fields organized by the DOE. The subjects for the survey were recruited by telephone, and those who agreed to participate were mailed a packet with instructions, a time-activity diary, and a personal exposure meter that recorded the magnetic field resultant at a 0.5-s sampling rate. The following conclusions were drawn from the interim analysis of 853 individuals:

- The distribution of 24-h TWA exposure in the population is approximately log-normal with a geometric mean of 0.09 μT (95% CI, 0.085–0.096) and a geometric standard deviation of 2.2 (95% CI, 2.1–2.3).
- Approximately 15% (95% CI, 12–18%) of the population was estimated to have 24-h TWA exposure exceeding 0.2 μT , about 2.4% (95% CI, 1.5–3.9%) to have exposures exceeding 0.5 μT , and about 0.4% to have exposures exceeding 1.0 μT . The

last value indicates that about 1 million people in the USA have an average 24-h exposure greater than 1.0 μT .

- Some variation in 24-h exposures was found by age: the geometric mean exposure for working-age people was about 0.1 μT , and that for retirement-age people was 0.08 μT . The geometric mean exposure for school-age children was about 0.08 μT , and that for pre-school children, 0.06 μT .
- About 0.5% of the population have an estimated maximum (peak) exposure to magnetic fields of 100 μT .

2.5.2 Calculated historical fields

Feychting and Ahlbom (Feychting & Ahlbom, 1993) conducted a study of leukemia in children living near high-voltage transmission lines in Sweden. An important feature of this study was that a computer model was used to calculate magnetic fields from the transmission lines in homes around the time of diagnosis, rather than relying on contemporary measurements. Those calculations of the magnetic fields from the transmission lines that took into account distance from the home, the power-line geometry, and the current load on the line are reliable for transmission lines because of the technical characteristics of those lines and the availability of the necessary data. Information about historical current loads on the power lines was used to calculate the magnetic fields for the year closest to the time to diagnosis. The model was evaluated by comparing calculations based on contemporary transmission line currents with contemporary spot measurements of the magnetic field. The calculated fields showed good agreement with spot measurements in single-dwelling homes. For example, in the highest measurement category ($> 0.2 \mu\text{T}$), only 15% of the calculations underestimated the contemporary measurements. The calculated values showed poorer agreement with measurements in apartments; for example, in the highest measurement category ($> 0.2 \mu\text{T}$), 47% of the calculations underestimated the contemporary measurements. The overall discrepancies between calculations and spot measurements for single homes and apartments were 11% and 32%, respectively. [While information on historical load currents permitted estimations of past exposure to magnetic fields in this study, the calculated values did not capture contributions to the field from local sources. Also, the calculated values can only be as good as the quality of the load current data.] The historical currents were known to within 100 A increments, and the average historical load current was 300 A (Kaune *et al.*, 1998). [The effect of the above factors on the amount of exposure misclassification cannot be estimated from the available information.]

The Swedish study of transmission-line fields represented an important advance over previous studies that were based on distribution-line wiring configurations in that it provides a method for estimating historical fields. The calculations are based on established laws of physics and on available physical and operational data rather than on

empirical classifications, as for the Denver wiring codes. The calculation method can not be reliably applied to distribution lines because of fundamental differences in the design and operation of the lines and the lack of historical data on load for distribution lines. Consequently, only the magnetic field contribution of the transmission lines can be reliably evaluated. Feychting *et al.* (Feychting & Ahlbom, 1993) applied the magnetic field calculation method to distribution lines near an unreported number of residences where the distribution line was judged to be a potentially important source of exposure to magnetic fields. [The questionable validity of the calculated field levels near distribution lines may have contributed to some of the inconsistency between contemporary measurements and contemporary calculations discussed above.]

Feychting and Ahlbom (Feychting & Ahlbom, 1994) conducted a study of adult cancers in relation to calculated historical fields. The exposure assessment method was virtually identical to that used by the same authors in their study of childhood cancer (Feychting & Ahlbom, 1993), except that one of the dose metrics calculated was cumulative exposure during the 15 years before diagnosis.

Li *et al.* (Li *et al.*, 1997) conducted a study of adult cancers in relation to calculated historical fields in Taiwan. They considered in some detail the locations of transmission lines (five voltage categories, from 69 to 345 kV) and homes, with distance readings derived from maps. The stated distance resolution was ± 10 m. The exposure fields were calculated from formulas based on the Biot-Savart law, accounting for line height, phasing, and other factors. No adjustment was made for local distribution lines or local sources, although for apartments the assumed building height was raised to 15 m. The historical average annual load currents, distances from homes to conductors, height of conductors, current phase, and geographic resistivity were provided by the Department of Transmission and Substation Project. Data on the resolution and accuracy of the line current used for historical measurements were not provided. The model calculations were validated by comparing contemporary calculations and measurements, with mixed results: with fields partitioned into three categories < 0.1 , $0.1\text{--}0.2$, and > 0.2 μT , the comparisons showed a concordance of 0.64 between the two exposure estimates. Measurements and calculations for the category > 0.2 μT , with cut-points 0.5 and 1 μT had a concordance of 0.82. The model calculations appeared to have the best predictive value for the highest exposure categories. [The discrepancy between calculations and measurements may be due in part to a contribution of local magnetic field sources to the field, but no indication was provided that the discrepancy is due to the presence of measured fields that were too high or too low. The ± 10 -m precision of distance could have had a significant impact on calculations for residences within 20 m of the power lines but would contribute less error for points further away from the transmission line.]

Valjus *et al.* (Valjus *et al.*, 1995) conducted a detailed analysis of historical field modeling calculations for a study of cancer in Finland. They examined the uncertainty in model calculated fields from transmission lines with considerable thoroughness. For example, the error distributions of power-line and building locations, hourly measurement records of load currents, tower dimensions, variations in conductor height, phase of currents, non-

parallel lines, and unbalanced currents were considered in a Monte Carlo analysis. The estimated precision of historical load data was examined by comparison of the estimate to currents calculated from power measurements. The estimate and the calculated value were highly correlated ($R^2 \sim 0.85$). The resolution reported for distance was ± 10 m. [Despite the completeness of the analysis, it is remarkable that no measurements of the magnetic field were performed as part of a verification process for the calculations.]

Olsen *et al.* (Olsen *et al.*, 1993) calculated magnetic fields to estimate human exposure from power lines and substations for a study of cancer in Denmark. The input parameters for the calculation include distance of the dwelling from source, type of line, dates of construction and reconstruction, average current for year, and ordering phases. [The problems with this study include: only estimates of historical load currents were available, which were provided by experts experienced in the planning and operation of the Danish transmission system; there was no experimental verification of the calculations; and the geometry of substations is much more complicated than that of transmission lines, entailing greater uncertainties. The use of experts is probably not a serious flaw, since they probably had information on historical annual currents from planning surveys.]

In a follow-up analysis of their study of childhood leukemia, Feychting *et al.* (Feychting *et al.*, 1996) investigated the importance of short-term variability in the time interval of measurement and other factors in residential exposure assessment. They evaluated the validity of contemporary spot measurements and the relative importance of distance from power transmission lines, and, when estimating past exposure to magnetic fields, calculated them with a computer model. Spot measurements were taken 5–31 years after diagnosis, with a median of 16 years. Their study showed that distance was not a simple surrogate for exposure, as first suggested. The relative risks for measurements at the time of the study (contemporary annual average fields, spot calculations, and spot measurements) were all close to or below unity. Neutra and DelPizzo (Neutra & DelPizzo, 1996) noted that spot readings appeared to have poor sensitivity, specificity, and predictive value, even though historical fields were reasonably well correlated with contemporary spot readings ($R = 0.7$).

[Together, these studies suggest that it is important to account for the historical relationship between exposure and disease outcomes. Contemporary spot or daily readings may introduce enough random and systematic error to obscure or enhance a possible association with disease risk.]

Zaffanella *et al.* (Zaffanella *et al.*, 1997) studied the use of computer modeling to estimate residential exposures, which could be useful for assessing exposure when access to residences is not possible or when planning a residential development. They used the RESICALC computer program to model magnetic fields due to currents on arbitrary configurations of electric transmission lines, primary and secondary distribution lines, and ground-return currents in neighborhoods based on residential loads and impedance.

Experiments conducted at the Magnetic Field Research Facility in Lenox, Massachusetts, simulated a residential electric distribution system. The results showed that the program could accurately model magnetic fields from both supply and ground currents. In some cases, the estimated fields were sensitive to impedance values assigned to the ground network. [Computer modeling for distribution lines requires intensive effort for input data collection, such as careful mapping of power lines, residential coordinates, acquiring load, and grounding data. These input values are critical if the model is to give valid estimates of exposure; however, because these input data are not routinely available and would require special instrumentation to be installed by the electric utility, widespread use of this computer model would be difficult.]

Bowman *et al.* (Bowman *et al.*, 1997) studied magnetic fields in residences using a physically based multipole model. The model parameters were determined by nonlinear regression techniques in order to fit the 24-h magnitude of the magnetic field recorded in a child's bedroom. The predictions were better correlated with the bedroom readings ($R = 0.4$) than with Wertheimer-Leeper wire codes ($R = 0.27$). [Since this model has not been tested in other locations, its generalizability is unknown.]

2.5.3 Wire codes as an exposure surrogate

Kheifets *et al.* (Kheifets *et al.*, 1997c) examined data on wire codes and spot magnetic field measurements from seven studies to determine the distribution of wire code categories among residences in different parts of the country. The percentage of homes falling within the VHCC category varied markedly among the data sets, but all fell within the range observed between controls in the study of Savitz (~ 3%) and in the study of London (~ 12%). Of the five studies with intermediate values, all showed less than ~ 8% homes with VHCC, except for the control homes in the study of Preston-Martin (11%) which was conducted in the same city as that of London. The number of homes in the two lowest categories was markedly smaller in Los Angeles (London *et al.*, 1994; Preston-Martin *et al.*, 1996b) than in the areas with predominantly lower-category homes. The authors also examined the distribution of spot-measured magnetic fields within each of the wire code categories in four of the data sets. All showed a monotonic trend for increasing median field with increasing wire code in the ordinary low current configuration, ordinary high current configuration, and VHCC categories, but the 10–90 percentile ranges in each category overlapped widely. The range of fields measured in each wire code category were similar in the data from the 1000 homes study and the EMDEX residential data sets (measured at numerous locations throughout the country) to that in the Savitz data set but markedly larger (spanning higher values) than that in the London data set. [These findings suggest that the relationship between wire codes and spot magnetic fields are in general similar throughout the country to that observed by Savitz in Denver but markedly different in the Los Angeles area.]

Kheifets *et al.* (Kheifets *et al.*, 1997c) also reviewed the historical stability of spot measurements and concluded that they are sufficiently stable over a period of five years

to make them suitable for estimating past exposure. In another data set, they examined the usefulness of various surrogates (wire codes, stationary measurements, spot measurements, and personal exposure measurements) for estimating personal exposure measured approximately four months earlier. Contemporary two-day personal exposure measurements were the best indicator of personal exposure, and wire codes were the poorest. The percent variability in exposure explained by the surrogate was 15% for wire codes, 46% for 24-h recordings, 54% for spot readings, and 66% for personal exposures. Contemporary spot and 24-h stationary measurements were similarly effective for estimating past exposure and intermediate between contemporary personal exposure and wire codes in effectiveness. The authors concluded that the potential for exposure misclassification when using wire codes is similar to or greater than that for contemporaneously measured magnetic fields.

Tarone *et al.* (Tarone *et al.*, 1998) examined the relationship between wire code category and 24-h magnetic field measurements on a state-by-state basis over a nine-state study area. There were insufficient data from Wisconsin for its inclusion in the analysis. More mean measured fields were in the VHCC category than in other categories in six states; two states in which there was no strong trend for increasing fields with wire code (Michigan and Minnesota) were among those with the fewest VHCC homes (four and three homes, respectively). Thus, the aberrant relationship between high wire code and field is probably a result of random variation due to small numbers. [This conclusion is supported by the observation that in the other state with few VHCC homes, the highest mean field was found in those homes.]

Tarone *et al.* (Tarone *et al.*, 1998) also looked at the distribution of homes with different wire codes, the distribution of mean and median fields within wire codes, and the percentage of homes with exposure > 0.2 and $0.3 \mu\text{T}$ within a wire code category. While wire codes did not differentiate among measured values, as in the study of Savitz, they were more effective than in the London study. The effectiveness of using wire codes was comparable to or better than that for measured data in other areas examined by Kheifets *et al.* (Kheifets *et al.*, 1997c). Tarone *et al.* (Tarone *et al.*, 1998) also looked at the reliability of wire coding in a subgroup of homes where replicate wire coding was done for quality control. Inconsistent determinations were reported for 15 of the 187 homes examined (8%). Of the discrepancies, seven involved distance and only two of the inconsistencies involved VHCC homes.

2.6 Exposure in transport

Wenzl (Wenzl, 1997) studied exposure to ELF magnetic fields among rail maintenance workers near Philadelphia, Pennsylvania. The workers were exposed to 25 Hz magnetic fields from electrified rail lines in addition to 60 Hz fields from other sources. Because of the mix of frequencies expected, spot readings of the magnetic fields were taken with a Multiwave system and fast Fourier transform to analyze for the frequency components. Personal exposure monitoring was also conducted. [The instrument response was limited

to frequencies in the range 40–1000 Hz, which would not include exposure to 25 Hz.] Current flowing in the overhead catenary lines was the primary source of magnetic fields when a train was near the maintenance work site. The peak magnetic fields were 3.4–19 μT near a transformer, while the medians at five other locations were 0.7–4 μT . TWA personal exposures were estimated by combining spot measurements at occupied locations with estimates of the amount of time spent at each location; the values were 0.3–1.8 μT , depending on the location and how frequently trains passed the work site. Comparisons between the spot measurements in the 40–1000 Hz frequency range and the personal exposure readings showed reasonably good agreement. [Further characterization of personal exposures in this environment may be justified, since workers and passengers on trains may be more highly exposed and for longer times.]

Electrified mass transit systems are found in many US cities. A US Department of Transportation study (USDT, 1993) of electrified transport systems showed that the average ELF magnetic fields in passenger coaches of trains ranged from approximately 0.5 μT in diesel-powered trains to 13.4 μT in electric-powered trains operating between Washington DC and New York. The maximum fields were found to be approximately five times larger than the average fields. Magnetic fields within the passenger coaches of mass transit systems (subways, trolleys, light rail transit systems) were highly dependent on the vehicle propulsion control system. The average magnetic fields in the passenger coaches of most trolleys and subways were 0.3–0.9 μT , but one system was found to have an average field of 17.8 μT . The principal frequency of the magnetic fields in most transport systems was other than 60 Hz, and, for many systems, the principal field components were at frequencies less than 50 Hz. Consequently, personal exposure measurements with existing exposure monitors do not accurately assess exposure to ELF magnetic fields. The electric fields were small within the coaches of all transport systems tested. Electric fields from external power supply circuits did not significantly penetrate the metallic passenger compartments. The magnitude of EMF in the drivers' compartments of the transport vehicles examined was generally comparable to or lower than the average fields within the passenger coaches.

2.7 Exposure in schools

Exposure to EMF in schools has recently received more attention because of concern raised in studies indicating associations between childhood cancer and EMF in residences. Children can spend a substantial amount of time in school, and this environment accounts for most of their daily activity away from residences. Like residences, school buildings may be located near electrical utility lines that can contribute to indoor EMF. Unlike residences, however, schools may also have extensive electrical bus networks, large transformers, and other EMF-generating equipment inside the buildings, similar to large office complexes and industrial settings.

Sun *et al.* (Sun *et al.*, 1995) conducted a survey of EMF in 79 schools in Canada for the Carlton Board of Education. They found that the typical magnitude of the magnetic field

in classrooms was lower than those in many occupational settings, with a mean of 0.08 μT (Table 2.10). They also attempted to identify possible sources of EMF, such as external wiring and building attributes that contribute to EMF in classrooms. Two-story buildings produced higher fields (geometric mean, 0.08 μT) than did one-story structures (geometric mean, 0.056 μT). Wiring in the floors of classrooms was the most frequently identified local source, while electric typewriters and computers were also common. Outside wiring was a contributing source, but transmission lines were not common enough to be identified as a contributing factor. [Overall, the levels reported in the study were similar to those in many residential and office environments.]

Table 2.10. Average magnetic flux densities in schools in Canada

Type of school	No. of schools	Mean (μT)	GM	GSD	% > 0.2 μT^a	95% CI for GM
Elementary	57	0.085 ^b	0.065 ^b	2.0	8.1	0.054–0.078
Intermediate	7	0.072	0.061	1.9	8.3	0.037–0.099
Secondary	15	0.084	0.072	1.8	7.3	0.054–0.096
All	79	0.082 ^b	0.066	1.9	7.8	0.057–0.077

GM, geometric mean; GSD, geometric mean standard deviation

^a Percent of all readings greater than 0.2 μT

^b Summary value calculated from data in the text

The California Public Health Foundation is performing a statewide measurement survey of EMF in California schools in order to determine the range of EMF in California public schools. Measurements are to be made in a random sampling of about 90 public schools to identify and characterize the sources of the magnetic fields and to evaluate possible mitigation techniques. The measurements will include a survey of classrooms and outdoor activity areas, identification and characterization of magnetic field sources, 24-h field recordings, wire code classification, and identification of nearby outdoor electrical facilities. Preliminary results from the pilot study were presented at the 1996 DOE EMF Contractors Review Meeting in San Antonio, Texas (Neutra *et al.*, 1996). Six schools were involved in the pilot study, and 163 classrooms were measured. Approximately 4% of the classrooms measured in the study were found to have average magnetic field magnitudes > 0.2 μT ; the median value for these classrooms was about 0.08 μT . The commonest overall source of the magnetic fields was ground currents flowing on water pipes or electrical conduits, although for classrooms with fields > 0.2 μT outside distribution lines and ground currents contributed about equally to the number of sources observed.

2.8 Exposure from appliances

To date, there have been no extensive studies of the relationship between use of appliances and personal exposures to EMF. The sampling strategies must be refined in order to assess the contributions of appliances to total exposure to EMF. Fields in the vicinity of appliances have been quantified in most studies.

Gauger (Gauger, 1985) studied the magnetic fields from appliances as a function of distance. The levels near hand-held hair-dryers were 0.3–2 μT at 10 cm. Vacuum cleaners, microwave ovens, and small hand-held appliances were identified as projecting the highest fields and/or projecting the furthest distance; 95% of the maximum observed magnetic fields from appliances were $< 0.1 \mu\text{T}$ at a distance of 1.5 m.

Mader and Peralta (Mader & Peralta, 1992) demonstrated that the magnitude of magnetic fields drops off at a rate inversely proportional to distance cubed. They presented a method for assessing magnetic fields and a model for predicting the exposure of body extremities. Like Gauger, they found that proximity to the appliance was an important factor. They concluded that appliances do not contribute significantly to whole-body exposure although they may be a dominant source of exposure of the extremities.

Florig and Hoburg (Florig & Hoburg, 1990) modeled and measured magnetic fields from electric blankets. They estimated that the volume-average whole-body exposure for adults was 1.9–2.2 μT ; the corresponding values for an eight-year-old child were 2.6–2.7 μT . The magnetic field estimated at the mid-sagittal line 10 cm above the bed was approximately 1 μT . Wilson *et al.* (Wilson *et al.*, 1996) reported the results of a validation study of a protocol for measuring magnetic fields from electric blankets in homes. The average field over seven spots 10 cm above the bed was $0.45 \pm 0.05 \mu\text{T}$. The values obtained by Wilson *et al.* are within a factor of 2 of those reported by Florig and Hoburg. DelPizzo (Delpizzo, 1990) proposed a model for exposure to electric blankets, mattress pads, and other appliances. He suggested that cumulative exposure to magnetic fields of $> 400 \mu\text{T-h}$ per year would be necessary to add significant exposure over background levels.

In the EPRI 1000 homes study, Zaffanella (Zaffanella, 1993) examined a variety of household sources. Appliances were found to produce the highest magnetic fields near the source, but the fields typically decreased rapidly with distance. For example, 13 electric can openers had a median magnetic field magnitude of about 20 μT at 20 cm from the source, but this fell to 0.3 μT at a distance of 117 cm; microwave ovens had a median power-frequency magnetic field magnitude at 25 cm of 3.7 μT , which fell to 1 μT at 56 cm. The results for some other appliances in the survey are included in Table 2.11.

Table 2.11. Magnetic fields associated with use of appliances

Appliance	Distance = 25 cm			Distance = 56 cm		
	95th percentile	5th percentile	Median	95th percentile	5th percentile	Median
Non-ceiling fan	9.2	0.03	0.3	1.6		0.04
Can opener	32.5	1.2	21.0	3.2	0.2	2.4
Clock-radio (digital)	0.3	0.1	0.1	0.1	0.01	0.02
Clock-radio (analog)	2.5	0.3	1.5	0.4	0.1	0.2
Ceiling fan	1.6	0.03	0.3	0.3	< 0.01	0.1
Electric range	1.9	0.2	0.9	0.3	0.04	0.2
Microwave oven	6.7	1.7	3.7	1.7	0.5	1.0
Color TV	1.2	0.4	0.7	0.3	0.1	0.2
Refrigerator	0.5	0.2	0.3	0.3	0.1	0.1

2.9 Laboratory exposure systems

The operating constraints of systems designed for laboratory experiments of exposure characterization are very different from those of observational exposure measurements. In the laboratory setting, the operational goal is to provide a precise, known, consistent condition of exposure to EMF with as much control over environmental factors as possible. In recent years, laboratory systems both *in vitro* and *in vivo* have grown in sophistication and complexity.

The prototype of a laboratory apparatus for exposure to magnetic fields is a Helmholtz coil, consisting of a pair of circular coils aligned along their open center axis and separated by a distance of one radius. A pair of conductive parallel plates forming an air capacitor is frequently used for exposure to electric fields. Both of these devices produce a reasonably uniform magnetic or electric field around the geometric centerline; the magnitude of the field depends on the physical dimensions, number of turns in the coil, and current (or voltage) applied to the system. In the case of magnetic fields, calibration requires careful attention to construction details and precise control of the current flow in the coils. The uniform region in the center of a Helmholtz coil is rather small, and for large-scale experiments more complex coil designs may have advantages. Kirschvink (Kirschvink, 1992b) described several superior designs with three, four, or five coils which provide highly uniform fields over a large volume. Other exposure systems include solenoids (Merritt *et al.*, 1983; Mullins *et al.*, 1993) or a current sheet to produce uniform magnetic fields.

A common goal in EMF experimentation is to provide a matched control condition that is identical to the exposure in every way except for the desired field exposure. To attain this, a sham exposure is usually set up with an identical apparatus but some modification of the current flow pathway. One method is simply to interrupt the current flow of the Helmholtz pair or the voltage to the parallel plates. This method has the disadvantage that any heat produced by the energized coil is not reproduced in the sham condition. This is not of material concern if the coils are constructed with sufficiently large wire to produce

negligible heating. A superior system consists of bifilar windings around the coils, with a parallel pair of insulated wires (Kirschvink, 1992b). In normal operation, parallel currents in the windings yield an external magnetic field. In the sham ('bucked') condition, currents flow in anti-parallel directions, so that the magnetic fields generated by each strand cancel and yield virtually no external magnetic field. The double-wrapped sham produces the same ohmic heating and largely controls for temperature effects. Differences in vibration between the sham and exposed conditions may still occur, but these are usually controlled by careful isolation of the experimental subjects and solid construction of the coils. Identical and interchangeable sham and exposure systems facilitate the conduct of truly double-blind experimental protocols, because the same apparatus can be used for both experimental and control groups, with a simple switch to change the operating conditions.

Another problem encountered in laboratory systems is that stray fields produced by the exposure apparatus or other equipment can contribute to background exposure in the sham controls. Stuchly *et al.* (Stuchly *et al.*, 1991) devised a system consisting of a quadrupole-coil configuration with four square-wound Merritt coils to minimize stray magnetic fields from the exposure system. The system provides a uniform field within a volume occupied by 16 animal cages and produces a mean flux density of 2 mT which varies by < 10% over the cages. The flux density decreases to < 0.1 μ T at 2 m from the coils.

Sometimes, incubators, heaters, motors, and other laboratory equipment can produce large stray fields. To limit these fields, magnetic shielding boxes made of highly permeable materials such as mu-metal may be used. These boxes can reduce stray fields by more than 30-fold and also reduce DC fields. [The biological significance of removing the geomagnetic fields has not been thoroughly studied.] When used inside incubators, shield boxes can degrade temperature control, degrade gas exchange in the culture system, and degrade the field uniformity from theoretical calculated values. Coupling of the magnetic field to the shield box can produce significant mechanical forces, leading to greater vibration in the system.

Some experiments require exposure to combinations of AC and DC fields or control of the magnetic field vector (such as circular polarization) (Shigemitsu *et al.*, 1993). To achieve this, the exposure apparatus is made up of multiple coil windings or sets of orthogonal coils arranged to produce the desired vector components. Careful alignment of the coils and phasing of the currents is needed to produce the desired results (Doynov *et al.*, 1998). [DC magnetic fields are often not controlled in large exposure systems and can vary substantially.]

Another important aspect of laboratory system design is the control of external environmental factors, such as changes in temperature and humidity, light intensity, lighting spectrum, and noise or air-flow distribution inside the animal housing due to air-conditioning equipment. These environmental factors can provide subtle cues to animals or humans and may also alter cell culture conditions. These concerns have led to experimental designs in which assignment between sham and experimental conditions is

randomized or counterbalanced. Sometimes it is desirable to randomize cage assignments and periodically rotate cage positions to account for such environmental factors. Light exposure and timing must be controlled especially in experiments involving circadian changes in hormones or behavior. Light intensity, timing, and duration are frequently controlled, but the spectral distribution of the light is often overlooked (Prato *et al.*, 1997).

Careful measurement, spatial mapping, and periodic checking of exposure conditions in the laboratory are necessary for engineering documentation and quality control. Usually, a complete set of engineering measurements is collected before the experiments begin. This includes mapping of field uniformity and measurements of possible frequency harmonics in magnetic field readings. It is also important to characterize any switching transients or other anomalies arising from infrequent operating conditions that may occur during an experiment, such as the effect of opening an incubator door. In the past, there has been strong emphasis on reducing switching events that produce a high rate of change in the magnetic field.

In *in vitro* experiments with EMF, cultures are routinely exposed to a uniform external magnetic flux density. Initially, many researchers did not measure or estimate the resulting induced electric field strength or current density in the sample medium. The magnitude and spatial distribution of the induced electric field are highly dependent on the sample geometry and the relative orientation of the culture medium with respect to the magnetic field (Misakian, 1997; Misakian & Kaune, 1990). Bassen *et al.* (Bassen *et al.*, 1992) studied the electric fields induced in several of the most frequently used laboratory culture dishes and flasks under various exposure conditions. They developed a set of simple, quantitative tables to predict the induced electric fields and currents which were based on measurements and calculations of the electric field distributions in the aqueous sample volume subjected to a uniform, sinusoidal magnetic field of known strength and frequency. The electric field and current density can also be calculated numerically from relatively simple but flexible spreadsheet models (Hart, 1996).

These studies highlight the need for careful engineering design and evaluation of laboratory exposure systems, since all laboratory systems have potential strong points and weaknesses and involve engineering compromises. Researchers should understand these design elements in order to use the exposure apparatus to the best advantage. Close collaboration between engineers and laboratory scientists is necessary, and can result in clever adaptations of exposure systems to focus on a desired experimental test. Several funding agencies have made external site reviews for quality control.

2.10 Summary

Assessment of exposure to electromagnetic fields (EMF) is the subject of an extensive literature, much of it relating to exposure to power-frequency magnetic fields. In many of

the epidemiological studies of adults, personal exposure measurements were used to evaluate magnetic fields in the workplace or in residences on the basis of the time-weighted average (TWA) magnitude. Relatively few studies have addressed electric field exposures or investigated alternative metrics for exposure to magnetic fields, such as vector polarization, high frequency transients, and frequency harmonics.

Personal exposure has been estimated in the residential setting in order to study children's exposure. Kleinerman (Kleinerman *et al.*, 1997) estimated the exposure of 1633 children < 14 years of age and found that their daily mean exposure was about $0.11 \pm 0.11 \mu\text{T}$. These values are not based on direct personal monitoring but do attempt to account for total exposure.

Studies of occupational exposure have focused on electrical and utility workers; only recently have data become available on the exposure of the general population. Studies in the general population indicate that the median of the daily mean occupational exposure for adults is about $0.17 \mu\text{T}$. Zaffanella *et al.* (Zaffanella & Kalton, 1998) estimated that the distribution of 24-h TWA exposure in the general US population was log-normal, with a geometric mean of $0.09 \mu\text{T}$ and a geometric standard deviation of 2.2. Thus, about 15% of the population have 24-h exposures exceeding $0.2 \mu\text{T}$, about 2.4% are exposed to $> 0.5 \mu\text{T}$, and 0.5% to $> 1 \mu\text{T}$.

When they are practical, direct personal measurements of magnetic fields are generally the preferable method of exposure assessment. Direct measurements provide a quantitative estimate of exposure to a clearly defined field. Even direct measurements, however, may not allay substantial uncertainty about classification of the exposure, as factors such as seasonal variation, changes in work tasks, intermittent use of appliances or tools, changing current loads, and variable proximity to wiring can contribute to large day-to-day variation in measurements. The time of data collection during a day or a season can lead to systematic bias in estimates of daily or annual average exposure. Personal exposure monitors can also be intrusive, so that people may alter their usual activities because they are wearing the meter. Because of the wide variation in exposure to magnetic fields, very many measurements must be made in order to obtain reasonably precise estimates of exposure. It should also be noted that the TWA fails to reflect a large number of potentially relevant exposure parameters, such as time above thresholds, intermittency, and transients.

Many studies of EMF have been based on measurements at one point in time (spot measurements), stationary monitoring over time, or area measurements involving mapping of the spatial characteristics of fields. While offering a quantitative estimate of fields, such measures also lead to substantial uncertainty about exposure classification. These types of measurements have several disadvantages, including the fact that they ignore personal activity patterns such as mobility and use of tools or appliances; they do not reflect past exposure; and they exclude possible parameters of exposure such as specific frequency content, polarization, and static magnetic fields. These types of measure do, however, have the advantage of simplicity and can provide reasonable estimates of human exposure

when mobility is restricted to a particular room or residence. With additional equipment, stationary monitoring can be used to capture a wider range of EMF characteristics, providing a greater variety of potential exposure metrics. Contemporary spot measurements are useful for checking the validity and appropriateness of calculations for magnetic fields from power lines in some situations.

The value of contemporary spot measurements as surrogates for past exposure remains uncertain. The limited data indicate that spot measurements are reasonably well correlated ($R \approx 0.7$) with similar measurements over several years. Dovan (Dovan *et al.*, 1993) found that contemporary spot measurements taken within wire code categories remained correlated with home average readings collected five years earlier ($R \approx 0.7$ for low power). Dovan purposely oversampled high-field very high frequency and case homes from the data set of Savitz *et al.* (Savitz *et al.*, 1988), so this may overstate the predictive value of spot measurements somewhat. The relationship between spot measurements and personal exposure is less clear. Kaune and Zaffanella (Kaune & Zaffanella, 1994) found essentially no correlation over time for the personal exposure of children in residences; Koontz (Koontz *et al.*, 1992), in a study of children's exposure, found a significant correlation over a few days but not across seasons. In residences, the combination of 24-h bedroom measurements with spot measurements in several other rooms appears to be a good method for determining the contemporary TWA household exposures of children. The correlation improves as the age of the child decreases.

Assessment of exposure to EMF for studies of human health effects is difficult because direct measurements often cannot be obtained, particularly for studies of chronic diseases, as the exposure of interest may have occurred years previously, and the actual circumstances of exposure cannot be recreated. In such studies, therefore, all assessments of exposure, including direct measurements, are surrogates for the exposure of interest. The surrogates most widely used are contemporary measurements, job titles, proximity to electrical equipment, calculated historical fields, and wiring configuration coding (wire codes).

Occupational histories are often incomplete and lack sufficient detail on actual work activities for past exposures to be reconstructed. As exposures to EMF are not memorable, questionnaires are of limited value. Contemporary measurements of similar workplaces may account for all sources but may be poor surrogates for past exposures. Classification of exposure on the basis of 'electrical jobs' provides a crude but useful tool for studies of EMF. The wide variation in EMF intensity results in considerable overlap and misclassification. This classification scheme, however, includes few assumptions about the exposure metric used.

An alternative method is use of a job-exposure matrix (JEM) to obtain quantitative estimates of exposure to electric or magnetic fields. In modern occupational studies, the JEM appears to provide the most flexible, stable tool for reconstructing exposure. A JEM can be constructed for almost any desired exposure if measurements are available, although it still relies fundamentally on occupational titles to classify exposure. The

absence of complete data on exposures in a wide variety of occupations remains a limitation in studies of occupational exposure.

Many different surrogates for exposure have been used in studies of residential exposure, including wire coding, spot measurements, 24-h bedroom measurements, personal monitoring, and calculations based on physical models. All of these techniques have some limitations, and all of them result in misclassification of exposure. Measurements have the advantage that they capture all sources of exposure. Yet, as noted above, contemporary measurements may be poor predictors of past exposures. Estimates based on wiring configurations or model calculations are of historical value, but these techniques account only for external sources of EMF such as transmission and distribution power lines. These methods also result in misclassification of exposure, perhaps non-randomly, and tend to lead to underestimates of total exposure as many local sources are not taken into account.

The system of wire codes was developed by Wertheimer and Leeper (Wertheimer & Leeper, 1979) to predict residential magnetic fields from the distance and configuration of transmission and distribution lines near residences. The validity of wire codes has been questioned because the different wire code categories for contemporary measured fields overlap widely. Several studies have shown that wire codes can be used consistently to rank homes crudely according to the median magnetic field intensity. Dovan (Dovan *et al.*, 1993) showed that wire codes change little over time, but their usefulness for predicting past exposures remains an open question. The strengths of the wire code method include the following:

- A correlation exists between wire codes and median magnetic fields in residences.
- The codes are probably related to historical magnetic fields since the physical characteristics of power lines usually change little over time.
- Wire codes may indicate high magnetic fields in some cases.
- Wire codes make it possible to estimate fields in residences without subject participation.

The weaknesses of the wire code method include the following:

- The values for contemporary fields are widely dispersed around the median for each category, resulting in overlap among categories.
- The historical stability of wire codes, which are based on the physical characteristics of power lines, may not be a reliable indicator of the stability of magnetic fields.

- The relationship between wire codes and field intensities varies with different wiring practices.
- Exposure to local sources of magnetic fields in residences (i.e. electrical appliances, building wiring, and ground currents) and away from the residence (perhaps important for older occupants) are not captured.

Wire codes also are not a simple surrogate for the TWA magnetic field and may be related in a complex way to various field parameters. Little information is available on the relationship between wire codes and other candidate parameters of exposure such as frequency, polarization, and ‘transients’. Homes with VHCC may have a greater tendency for high-frequency transients. Kheifets *et al.* (Kheifets *et al.*, 1997c) examined several candidate metrics but found no clear relationship with wire codes.

In an alternative method for assessing residential exposure, physics-based calculations are used to estimate past fields. Generally, retrospective residential exposure assessment based on calculations of magnetic fields from nearby transmission lines on the basis of historical load currents should be more accurate than either wire codes or contemporaneous measurements, especially for single-family homes sufficiently close to a transmission line to ensure that the fields originated mainly from that source. In those homes, failure to account for fields from local sources should have less impact because transmission line fields dominate over most local field sources. The calculations for distribution lines are less reliable owing to the presence of ground currents and fluctuating loads; however, this method may be better than wire codes. Calculations for apartments, where local field sources might still dominate, are also uncertain. In some cases, the methods of calculation have been validated against contemporary spot measurements, and this has helped to establish the predictive value of the models in study populations.

Calculations of historical magnetic fields are most applicable when the geometry of the power-line sources is relatively simple, e.g. transmission lines, provided there are adequate data on load currents. Limited resolution in the measurement of distance to the residence can dominate the uncertainty in field estimates near the line. Close proximity to high-voltage transmission lines may also be an indication of substantial exposure to both magnetic and electric fields. The availability of high-quality data on load currents is also critical for this approach to succeed, although in some cases it may be possible to obtain reasonable estimates from informed experts. With the deregulation of utilities in the USA, it may become more difficult to obtain data on load currents because of proprietary interests. The strengths associated with modeling historical fields are the possibilities of estimating:

- TWA magnetic fields in homes that are not accessible;
- TWA past exposures over extended periods;

- short-term variations in fields from power lines (with good data on load current); and
- polarization and other metrics (with good data on load current).

Weaknesses associated with calculations of historical magnetic fields include:

- the inability to capture fields from local sources;
- the inability to capture non-residential exposures;
- difficulty in applying the method to distribution lines; and
- the limited availability of historical load current data.

Good instrumentation for measuring TWA exposures to EMF is available, but the complex field vector still cannot be measured completely with personal exposure meters. Some of the various exposure meters used in studies of EMF are designed for spot measurements or stationary monitoring. The currently available exposure meters have a very limited ability to detect frequency harmonics or transient fields and cannot be used to measure combined AC and DC fields or vector polarization. None of these aspects of exposure to EMF can be adequately assessed with present-day personal monitoring instruments. Consequently, the summary measures of exposure described in existing epidemiological studies involve many assumptions, and the existing exposure measures can be regarded as surrogates for the underlying ideal exposure metric. Thus, the available instrumentation has somewhat limited the ability of researchers to explore alternative magnetic field metrics in human population studies. Even if instrumentation can be improved, however, biologically based exposure metrics should be identified. Assessment of the highly variable, complex, ubiquitous exposures to EMF for studies of health effects thus requires considerable effort.

Figure 2.1 Electromagnetic spectrum showing extremely low frequency and other bands

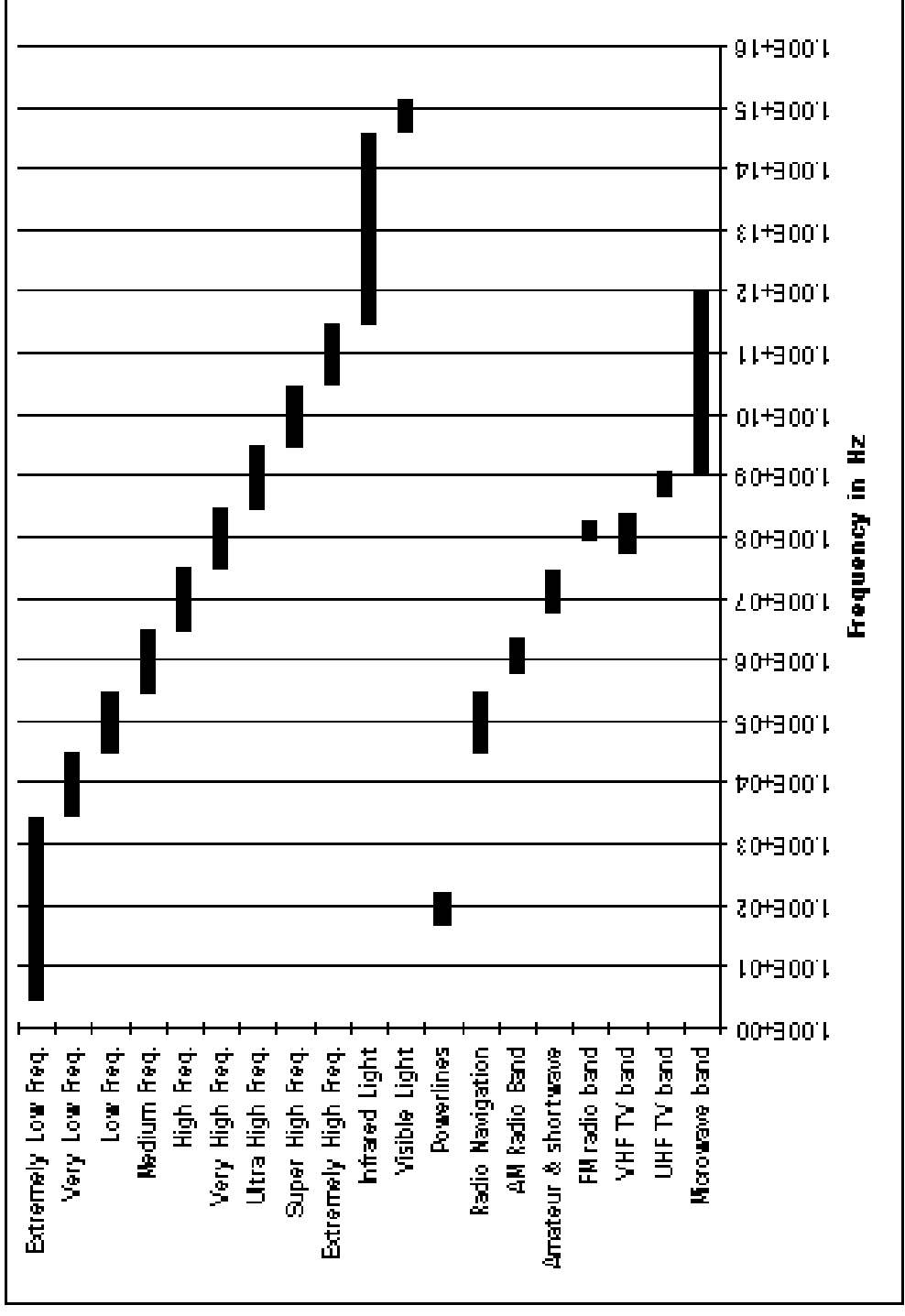


Figure 2.2 Field-particle interactions: “classical” forces, torques, and energies

Electric fields	Magnetic fields
(A) $\mathbf{F} = q\mathbf{E}$	$F = q(\mathbf{v}\times\mathbf{B})$ (a)
(B) $F = p \frac{dE}{dx}$	$F = m \frac{dB}{dx}$ (b)
(C) $\mathbf{T} = \mathbf{p}\times\mathbf{E}$	$\mathbf{T} = \mathbf{m}\times\mathbf{B}$ (c)
(D) $W_e = \frac{1}{2} \epsilon_0 \epsilon_r E^2$	$W_m = \frac{1}{2} \frac{B^2}{\mu_0 \mu_r}$ (d)
(E) $\mathbf{W}_p = \mathbf{p} \cdot \mathbf{E}$	$\mathbf{W}_m = \mathbf{m} \cdot \mathbf{B}$ (e)

For explanation of the “cross-product” in equations (a), (C) and (c), see Figure 2.2. The “dot-product” or scalar product of two vectors a and b (equations. (E) and (e)) is equal to $ab \cos \phi$ where ϕ is the angle between the vectors a and b.

Figure 2.3 Illustration of “cross-product” (equations (a), (C) and (c) in Figure 2.2: The resulting vector $c = a \times b$ is in a direction perpendicular to the plane defined by a and b and its magnitude is equal to the product of their mutually perpendicular components: $c = a \cdot b \sin \phi$).

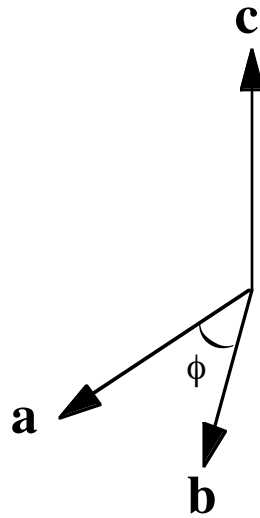


Table 2.1 Field meter characteristics

MeterName	Fields	Sensor	No. of Axes	Frequency Response(Hz) ^a	Maximum Full Scale Range ^a (μT)	Output	Function	Comment	
Amex	B	C	1	-----	12.5	TWA	AVG	P	
Amex-3D	B	C	3	25 Hz -1.2 kHz	15	TWA	AVG	P	
Emdex C	B,E	C,P	3,1	40-400 Hz	2550	D,DL	AVG	P	Built-in E field
Emdex II	B	C	3	40-800 Hz	300	D,DL	RMS	P	Has harmonic capability
Positron	B,E,HF	C,P,F	3,1	50/60 Hz	50	D,DL	PEAK	P	Built-in E field
Monitor Ind.	B	C	1	40 Hz -1 kHz	250	A	RMS	S	
Multiwave	B	C, FG	3	0-10 kHz	500	D,DL	RMS	S	Waveform capture
Power frequency Meter MOD120	B,E	C,P	1	35-600 Hz	3000	A	AVG	S	
STAR	B	C	3	60 Hz	51	D,DL	RMS	S	
MAG 01	B	FG	1	0-10 Hz	200	D	---	S	
IREQ	B	C	3	40 Hz - 1 kHz	100	D,DL	RMS	S	
Heitanen & Jokela, 1990	B,E	D	1,1	25 Hz -10 Mhz	---	---	---	S	
Juutilainen & Saali, 1986b	B	C	1	< 50 Hz -25 kHz	380	A	RMS	S	Oscilloscope output
Sydskraft	B	C	3	50-60 Hz	20	D,DL	AVG	S	

(Bowman *et al.*, 1998; Feychting & Ahlbom, 1993; Heitanen & Jokela, 1990; Juutilainen & Saali, 1986b; Olsen *et al.*, 1991)

E, electric; B, magnetic; HF, high frequency; C, coil; P (function), plate; F, conductive foam; FG, flux gate; D (sensor), active dipole; D (output), digital spot; A, analog spot; DL, data logging; TWA, single readout of TWA; AVG, average; RMS, root-mean-square; P (function), personal monitor; S, survey

^a Frequency response and maximum range refer only to the magnetic field measurement channel

Table 2.2 Magnetic field exposure metrics used in epidemiological studies

Exposure Metric	Abbreviation	Reference	Measures
Arithmetic mean (TWA)	TWA	All	Magnitude
Geometric mean	GM	All	Magnitude
Median (50th percentile)	B ₅₀ Med	All	Magnitude
Peak (maximum) value	B _{peak}	All	Magnitude
99th or Nth upper percentile	B ₉₉	Armstrong	Peak magnitude
Percent of time > threshold	Tn	Armstrong	% magnitude > limit
Percent of time < threshold	Tn	Armstrong	% magnitude < limit
Percent of time in window	Tw	Armstrong	% magnitude > limit1 & < limit2
Total harmonic distortion	THD	Zaffanella 1993, Breyse 1997	Frequency B-field
High frequency electric transients	HFET	Deadman	Frequency, E-Field
Average absolute sequential difference	AASD	Breyse 1994 Zaffanella 1993	Short term variability
First lag autocorrelation		Breyse 1994 Thomas 1996	Short term correlation
Standardized rate of change	RCM	Birch <i>et.al.</i>	Short term correlation
Jaggedness index	Jag	Wenzel	Short term variability
RMS Rate of change	RC	Wilson <i>et.al.</i>	Short term variability
Standard deviation	SD	Armstrong, <i>etc</i>	Time variability
Geometric standard deviation	GSD	Armstrong, <i>etc</i>	Time variability

TWA, time-weighted average; rms, root mean square

Table 2.3 Standard occupational classification codes and job categories of "electrical jobs"

Code	Job category
1633	Electrical and electronic engineers Electrical and electronic technicians Broadcast equipment operators Electronic repair, communications & industrial equipment workers Data processing equipment repairers Household appliance and power tool repairers Telephone line installers and repairers Telephone installers and repairers Miscellaneous electrical and electronic equipment repairers Supervisors, electricians and power installers, and repairers Electricians Electricians apprentices Electric power installers and repairers Power plant operators Motion picture projectionists Electric power wire and cable workers Power station operators
7714	Welders and cutters Television and radio repairman
1636	Computer engineers
1712	Computer systems analysts
3650	Radiological technologists and technicians
3971	Programmers, business
4732	Telephone Operators
4752	Production and planning clerks
6881	Precision inspectors, testers, and graders
7830	Production testers

Table 2.4 Electrical occupations derived from job titles with TWA magnetic field exposures

Occupation	Industry or company	Epidemiological study	Exposure	TWA magnetic field (μT)	
				AM	SD
Engine driver	Railroad	(Floderus <i>et al.</i> , 1994) (Sobel <i>et al.</i> , 1995) (Sobel <i>et al.</i> , 1996)		4.03	NR
Driver of electric vehicle	Railroad	(Guénel <i>et al.</i> , 1993)	Continuous	4.03	NR
Railroad engineer		(Lin <i>et al.</i> , 1985)	A (definite)	4.03	NR
Railroad engine driver		(Tynes <i>et al.</i> , 1992)	Intermediate	4.03	NR
Cable joiner and lineman		(Fear <i>et al.</i> , 1996)		3.61	10.92
Electric power line installers and repairers		(Milham, 1985) (Deapen & Henderson, 1986) (Demers <i>et al.</i> , 1991) (Loomis <i>et al.</i> , 1994b) (Savitz <i>et al.</i> , 1994) (Spitz & Johnson, 1985) (Nasca <i>et al.</i> , 1988) (Wilkins & Wellage, 1996) (Savitz <i>et al.</i> , 1998b)		3.61	10.92
Lineman	Electric company	(Lin <i>et al.</i> , 1985)	A (definite)	3.61	10.92
Power-line worker		(Tynes <i>et al.</i> , 1992)	Heavy EMF	3.61	10.92
Electrician	So. Cal. Edison	(Sahl <i>et al.</i> , 1993)		3.01	NR
Sewing-machine operators	Garment industry	None		3.00	0.28
Dressmakers, seamstresses and tailors		(Sobel <i>et al.</i> , 1995) (Sobel <i>et al.</i> , 1996)		3.00 ^a	0.28
Dressmakers and tailors		(Coogan <i>et al.</i> , 1996)	Low	3.00	0.28
Machinist	So. Cal. Edison	(Sahl <i>et al.</i> , 1993)		2.69	NR
Forestry and logging jobs		NONE		2.48	7.70
Welder		(Lin <i>et al.</i> , 1985)	B (probable)	2.00	4.01

Table 2.4 (continued)

Occupation	Industry or company	Epidemiological study	Exposure	TWA magnetic field (μT)	
				AM	SD
Welders and flame cutters		(Milham, 1985) (Deapen & Henderson, 1986) (Demers <i>et al.</i> , 1991) (Spitz & Johnson, 1985) (Nasca <i>et al.</i> , 1988) (Wilkins & Wellage, 1996) (Rosenbaum <i>et al.</i> , 1994)		2.00	4.01
Welders and flame cutters		(Coogan <i>et al.</i> , 1996)	Medium	2.00	4.01
Welder		(Sobel <i>et al.</i> , 1996) (Sobel <i>et al.</i> , 1995) (Davanipour <i>et al.</i> , 1997)	High	2.00	4.01
Electrical fitter		(Sobel <i>et al.</i> , 1996) (Sobel <i>et al.</i> , 1995) (Fear <i>et al.</i> , 1996)		1.56	1.63
Electrical and electronic production fitter				1.56	1.63
Electrician	Electric power	(Guénel <i>et al.</i> , 1993)	Continuous	1.56	1.63
Electrician	Industry	(Lin <i>et al.</i> , 1985)	A (definite)	1.56	1.63
Electrician	Steel mill	(Davanipour <i>et al.</i> , 1997)	High	1.56	1.63
Electrician	Manufacturer of electrical machinery	(Guénel <i>et al.</i> , 1993)	Continuous	1.56	1.63
Electrician, power supply		(Tynes <i>et al.</i> , 1992)	Heavy EMF	1.56	1.63
Cable splicer	5 US electric utilities	(Savitz & Loomis, 1995)		1.50	3.12
Power station operator		(Milham, 1985) (Deapen & Henderson, 1986) (Tynes <i>et al.</i> , 1992) (Loomis <i>et al.</i> , 1994b) (Savitz <i>et al.</i> , 1994) (Wilkins & Wellage, 1996) (Fear <i>et al.</i> , 1996) (Savitz <i>et al.</i> , 1998a)		1.43	2.24
Power plant operator		(Demers <i>et al.</i> , 1991)	Group 1	1.43	2.24
Worker	Sewing factory	(Sobel <i>et al.</i> ,		1.40	1.47

Table 2.4 (continued)

Occupation	Industry or company	Epidemiological study	Exposure	TWA magnetic field (μT)	
				AM	SD
Relay technician	5 US electric utilities	1996) (Sobel <i>et al.</i> , 1995) (Savitz & Loomis, 1995)		1.34	2.34
Sheet metal worker		(Sobel <i>et al.</i> , 1996) (Sobel <i>et al.</i> , 1995)		1.34	4.19
Technician	Southern California Edison	(Sahl <i>et al.</i> , 1993)		1.32	NR
Electrician	5 US electric utilities	(Savitz & Loomis, 1995)		1.11	2.18
Power plant operator		(Sahl <i>et al.</i> , 1993)		1.08	NR
Lineman	Southern California Edison	(Sahl <i>et al.</i> , 1993)		1.03	NR
Welder	Southern California Edison	(Sahl <i>et al.</i> , 1993)		1.02	NR
Motion picture projectionist		(Milham, 1985) (Deapen & Henderson, 1986) (Loomis <i>et al.</i> , 1994b) (Savitz <i>et al.</i> , 1994) (Sobel <i>et al.</i> , 1996) (Sobel <i>et al.</i> , 1995) (Wilkins & Wellage, 1996) (Savitz <i>et al.</i> , 1998a)		0.80	0.68
Substation operator	5 US electric utilities	(Savitz & Loomis, 1995)		0.80	1.13
Welder	5 US electric utilities	(Savitz & Loomis, 1995)		0.80	1.08
Electric generation plant operator	5 US electric utilities	(Savitz & Loomis, 1995)		0.79	2.34
Mechanic	Southern California Edison	(Sahl <i>et al.</i> , 1993)		0.77	NR
Machinist	5 US electric utilities	(Savitz & Loomis, 1995)		0.72	1.95
95th percentile of males				0.66	
Lineman	5 US electric utilities	(Savitz & Loomis, 1995)		0.65	1.59
Dental hygienist		(Davanipour <i>et al.</i> , 1997)	Medium	0.64	1.65
Conductor	Railroad	(Floderus <i>et al.</i> , 1994)		0.61	NR
Railroad assistants and	Railroad	(Floderus <i>et al.</i> ,		0.59	NR

Table 2.4 (continued)

Occupation	Industry or company	Epidemiological study	Exposure	TWA magnetic field (μT)	
				AM	SD
lineman Railroad track walker		1994) (Tynes <i>et al.</i> , 1992)	Weak EMF	0.59	NR
Tram driver		(Tynes <i>et al.</i> , 1992)	Intermediate	0.57	0.61
Conductors and motormen, urban rail transit		(Milham, 1985) (Deapen & Henderson, 1986);		0.57	0.61
Electrical and electronics assembler		(Coogan <i>et al.</i> , 1996) (Wilkins & Wellage, 1996) (Johnson & Spitz, 1989) (Fear <i>et al.</i> , 1996) (Sobel <i>et al.</i> , 1996) (Sobel <i>et al.</i> , 1995) (Rosenbaum <i>et al.</i> , 1994)		0.57	0.25
Employee	Utilities	(Spitz & Johnson, 1985)	Narrow definition	0.57	1.51
Employee	Utilities	(Nasca <i>et al.</i> , 1988)	Broad definition	0.57	1.51
Electrical and electronic equipment repair		(Loomis <i>et al.</i> , 1994b) (Savitz <i>et al.</i> , 1994) (Savitz <i>et al.</i> , 1998b)		0.51	0.61
Electrical and electronics apparatus mechanics and installers		(Johnson & Spitz, 1989)		0.51	0.61
Electrical equipment repairer		(Coogan <i>et al.</i> , 1996)	Medium	0.51	0.61
Electrical equipment repairman		(Spitz & Johnson, 1985) (Nasca <i>et al.</i> , 1988)	Broad definition	0.51	0.61
Household appliance and power tool repairers		(Wilkins & Wellage, 1996)		0.46	0.52
Household appliance installers and mechanics		(Deapen & Henderson, 1986)		0.46	0.52
Painter	5 U.S. electric utilities	(Savitz & Loomis, 1995)		0.45	0.45
Office machine repairer		(Deapen & Henderson, 1986)		0.44	0.74
Lineman	Telephone company	(Lin <i>et al.</i> , 1985)	A (definite)	0.43	0.05
Telephone technician		(Demers <i>et al.</i> , 1991)	Group 4	0.43	0.10
Mail and message distributing occupations		None		0.43	0.41

Table 2.4 (continued)

Occupation	Industry or company	Epidemiological study	Exposure	TWA magnetic field (μT)	
				AM	SD
Groundskeepers and gardeners		None		0.41	0.90
Boilermaker	5 U.S. electric utilities	(Savitz & Loomis, 1995)		0.41	1.05
Service worker	5 U.S. electric utilities	(Savitz & Loomis, 1995)		0.41	0.69
Serviceman	Electric company	(Lin <i>et al.</i> , 1985)	A (definite)	0.41	0.69
Instrument and control technicians	5 U.S. electric utilities	(Savitz & Loomis, 1995)		0.40	1.12
Rigger	5 U.S. electric utilities	(Savitz & Loomis, 1995)		0.38	0.37
Electrician ^a		(Sobel <i>et al.</i> , 1995) (Sobel <i>et al.</i> , 1996) (Davanipour <i>et al.</i> , 1997)	Medium	0.37	0.32
Electrician		(Demers <i>et al.</i> , 1991)	Group 1	0.37	0.32
Electrician	Electrician; installation	(Guénel <i>et al.</i> , 1993)	Continuous	0.37	0.32
Electrician	Non-industrial	(Lin <i>et al.</i> , 1985)	B (probable)	0.37	0.32
Electrician and apprentice		(Milham, 1985) (Deapen & Henderson, 1986) (Loomis <i>et al.</i> , 1994b) (Savitz <i>et al.</i> , 1994) (Spitz & Johnson, 1985) (Johnson & Spitz, 1989) (Nasca <i>et al.</i> , 1988) (Wilkins & Wellage, 1996) (Fear <i>et al.</i> , 1996) (Rosenbaum <i>et al.</i> , 1994) (Savitz <i>et al.</i> , 1998b)		0.37	0.32
Electrician, installation		(Tynes <i>et al.</i> , 1992)			
Electrician		(Coogan <i>et al.</i> , 1996)	Medium	0.37	0.32
Factory hand and other unskilled worker	Iron and steel works	(Guénel <i>et al.</i> , 1993)	Continuous	0.36	0.43
Factory hand and other unskilled worker	Iron foundries	(Guénel <i>et al.</i> , 1993)	Continuous	0.36	0.43
TV and radio repairman		(Milham, 1985) (Deapen & Henderson, 1986) (Tynes <i>et al.</i> , 1992) (Fear <i>et al.</i> , 1996)		0.36	0.23
TV repairer		(Davanipour <i>et al.</i> , 1997)	Medium	0.36	0.23

Table 2.4 (continued)

Occupation	Industry or company	Epidemiological study	Exposure	TWA magnetic field (μT)	
				AM	SD
Repairman for radio, TV, and electronic appliances		(Lin <i>et al.</i> , 1985)	B (probable)	0.36	0.23
Household appliance and power tool repairer		(Dennis <i>et al.</i> , 1991) (Savitz <i>et al.</i> , 1994)		0.36	0.23
Commercial and industrial electronic equipment repairer		(Demers <i>et al.</i> , 1991) (Wilkins & Wellage, 1996)	Group 2	0.36	0.23
Technical worker	5 U.S. electric utilities	(Savitz & Loomis, 1995)		0.36	0.62
Traffic, shipping, and receiving clerks		NONE		0.36	0.30
Electrical engineering technician		(Milham, 1985) (Deapen & Henderson, 1986) (Loomis <i>et al.</i> , 1994b) (Savitz <i>et al.</i> , 1994) (Wilkins & Wellage, 1996) (Sobel <i>et al.</i> , 1995) (Sobel <i>et al.</i> , 1996) (Savitz <i>et al.</i> , 1998b)		0.35	0.27
Electrical engineering technician		(Coogan <i>et al.</i> , 1996)	High	0.35	0.27
Electrical engineering technician		(Demers <i>et al.</i> , 1991)	Group 4	0.35	0.27
Telecommunication technician	5 U.S. electric utilities	(Savitz & Loomis, 1995)		0.35	0.55
Electrical and electronic engineers		(Milham, 1985) (Deapen & Henderson, 1986) (Loomis <i>et al.</i> , 1994b) (Savitz <i>et al.</i> , 1994) (Johnson & Spitz, 1989) (Wilkins & Wellage, 1996) (Savitz <i>et al.</i> , 1998b)		0.33	0.67
Electrical and electronic engineers		(Coogan <i>et al.</i> , 1996)	High	0.33	0.67
Electrical and electronics engineers		(Demers <i>et al.</i> , 1991)	Group 4	0.33	0.67
Electrical and electronics engineers	Industrial	(Lin <i>et al.</i> , 1985)	A (definite)	0.33	0.67
Electrical and electronic engineers		(Fear <i>et al.</i> , 1996)		0.33	0.67

Table 2.4 (continued)

Occupation	Industry or company	Epidemiological study	Exposure	TWA magnetic field (μT)	
				AM	SD
engineers (professional)					
Electrical engineer (so described)		(Fear <i>et al.</i> , 1996)		0.33	0.67
Other electronic maintenance engineers		(Fear <i>et al.</i> , 1996)		0.33	0.67
Engineer	Electric power	(Guénel <i>et al.</i> , 1993)	Continuous	0.33	0.67
Engineer	Electric company	(Lin <i>et al.</i> , 1985)	A (definite)	0.33	0.67
Engineer	Telephone company	(Lin <i>et al.</i> , 1985)	A (definite)	0.33	0.67
Telecommunications engineer		(Lin <i>et al.</i> , 1985)	A (definite)	0.33	0.67
Maintenance man ^a		(Lin <i>et al.</i> , 1985)	C (possible)	0.32	0.31
AC, heating, and refrigeration repairman		(Deapen & Henderson, 1986)		0.31	0.27
Mechanic, Power plant		(Johnson & Spitz, 1989)		0.30	0.23
Mechanic, utility services		(Johnson & Spitz, 1989)		0.30	0.23
Programmer, systems planner	EDP services	(Guénel <i>et al.</i> , 1993)	Continuous	0.30	0.55
Station master and train dispatcher	Railroad	(Floderus <i>et al.</i> , 1994)		0.30	NR
Electronics wireman		(Fear <i>et al.</i> , 1996)		0.29	0.39
Precision inspectors, testers and related workers		(Coogan <i>et al.</i> , 1996)	Medium	0.29	0.39
Tool and die maker		(Sobel <i>et al.</i> , 1996)		0.28	0.40
		(Sobel <i>et al.</i> , 1995)			
Pipe coverer	5 U.S. electric utilities	(Savitz & Loomis, 1995)		0.28	0.44
Farmer		NONE		0.27	0.54
75th percentile of males				0.27	
Electrical equipment salesman		(Spitz & Johnson, 1985)	Broad definition	0.26	0.14
Electrical goods and appliance salesman		(Johnson & Spitz, 1989)		0.26	0.14
Sales occupations, retail		NONE		0.26	0.14
Computer programmer		(Coogan <i>et al.</i> , 1996)	Medium	0.25	0.28
Computer programmer		(Loomis <i>et al.</i> , 1994b)		0.25	0.28
		(Savitz <i>et al.</i> , 1998b)			
Electrician, other		(Tynes <i>et al.</i> , 1992)	Intermediate	0.25	0.18
Other electrical worker		(Tynes <i>et al.</i> , 1992)	Weak	0.25	0.18
Engineer (nonspecified)	Electric, electronic, aerospace, and tele-communication	(Lin <i>et al.</i> , 1985)	B (probable)	0.25	0.41
Other engineers		(Coogan <i>et al.</i> , 1996)	Medium	0.25	0.41

Table 2.4 (continued)

Occupation	Industry or company	Epidemiological study	Exposure	TWA magnetic field (μT)	
				AM	SD
Repairman	Telecommunications	(Lin <i>et al.</i> , 1985)	B (probable)	0.25	0.03
Craft supervisor	5 U.S. electric utilities	(Savitz & Loomis, 1995)		0.24	0.47
Foreman	Electric company	(Lin <i>et al.</i> , 1985)	A (definite)	0.24	0.47
Supervisors, electricians, and power installers and repairers		(Loomis <i>et al.</i> , 1994b) (Savitz <i>et al.</i> , 1994) (Wilkins & Wellage, 1996) (Savitz <i>et al.</i> , 1998b)		0.24	0.47
Mechanic	5 U.S. electric utilities	(Savitz & Loomis, 1995)		0.23	0.30
Industrial engineer		(Davanipour <i>et al.</i> , 1997)	Medium	0.23	0.23
Food and beverage preparation and service		NONE		0.22	0.13
Carpenter		(Lin <i>et al.</i> , 1985)	C (possible)	0.22	0.14
Carpenter		(Davanipour <i>et al.</i> , 1997) (Sobel <i>et al.</i> , 1996) (Sobel <i>et al.</i> , 1995)	Medium	0.22	0.14
Receptionist		NONE		0.21	0.47
Clothing cutter	Garment industry	(Sobel <i>et al.</i> , 1996) (Sobel <i>et al.</i> , 1995)		0.21	0.25
Heavy equipment operator		(Davanipour <i>et al.</i> , 1997)	Medium	0.21	0.16
Operating engineer		(Coogan <i>et al.</i> , 1996)	Low	0.21	0.16
Woodworking, textile, and shoe machine operators		(Coogan <i>et al.</i> , 1996)	Low	0.21	0.15
Computer system engineer		(Davanipour <i>et al.</i> , 1997)	Medium	0.21	0.41
Computer systems analysts / scientists		(Coogan <i>et al.</i> , 1996)	High	0.21	0.41
Engineering technician		(Coogan <i>et al.</i> , 1996)	Medium	0.20	0.60
Telephone fitter		(Fear <i>et al.</i> , 1996)		0.20	0.13
Telephone line installers and repairers		(Milham, 1985) (Deapen & Henderson, 1986) (Loomis <i>et al.</i> , 1994b) (Savitz <i>et al.</i> , 1994) (Wilkins & Wellage, 1996) (Sobel <i>et al.</i> , 1996) (Sobel <i>et al.</i> ,		0.20	0.13

Table 2.4 (continued)

Occupation	Industry or company	Epidemiological study	Exposure	TWA magnetic field (μT)	
				AM	SD
Telephone line installers and repairers		1995) (Savitz <i>et al.</i> , 1998b) (Demers <i>et al.</i> , 1991)	Group 1	0.20	0.13
Supervisors, sales occupations, insurance, real estate, and business services		NONE		0.20	0.08
Computer equipment operator		(Loomis <i>et al.</i> , 1994b) (Savitz <i>et al.</i> , 1998b)		0.18	0.24
Machine molder	Iron foundries	(Guénel <i>et al.</i> , 1993)	Continuous	0.18	0.09
Printing machine operator		(Coogan <i>et al.</i> , 1996)	Low	0.18	0.09
Serviceman	Telephone company	(Lin <i>et al.</i> , 1985)	A (definite)	0.17	0.02
Lathe worker		(Davanipour <i>et al.</i> , 1997)	Medium	0.17	0.06
Machinist		(Sobel <i>et al.</i> , 1996) (Sobel <i>et al.</i> , 1995)		0.17	0.06
Machinist		(Lin <i>et al.</i> , 1985)	C (possible)	0.17	0.06
Machinists / tool and die makers		(Coogan <i>et al.</i> , 1996)	Medium	0.17	0.06
Toolmaker		(Lin <i>et al.</i> , 1985)		0.17	0.06
Janitors and cleaners		None		0.17	0.09
50th percentile of males				0.17	
Telephone installer		(Tynes <i>et al.</i> , 1992)	Weak	0.16	0.09
Telephone installers and repairers		(Deapen & Henderson, 1986) (Wilkins & Wellage, 1996) (Savitz <i>et al.</i> , 1994) (Rosenbaum <i>et al.</i> , 1994)		0.16	0.09
Authors and technical writers		(Coogan <i>et al.</i> , 1996)	Low	0.15	0.17
Data processing equipment repairer		(Wilkins & Wellage, 1996)		0.15	0.64
EDP equipment repairer		(Coogan <i>et al.</i> , 1996)	High	0.15	0.64
Assembler		(Sobel <i>et al.</i> , 1996) (Sobel <i>et al.</i> , 1995)		0.15	0.02
Assembler	Household appliances	(Deapen & Henderson, 1986)		0.15	0.02
Assembler	Radio, TV and communications equipment	(Deapen & Henderson, 1986)		0.15	0.02

Table 2.4 (continued)

Occupation	Industry or company	Epidemiological study	Exposure	TWA magnetic field (μT)	
				AM	SD
Assembler	Electrical machinery and supplies (NEC)	(Deapen & Henderson, 1986)		0.15	0.02
Assembler		(Deapen & Henderson, 1986)		0.15	0.02
Chemist	Electrical equipment (not specified)	(Davanipour <i>et al.</i> , 1997)	Medium	0.15	0.06
Coil winder		(Fear <i>et al.</i> , 1996)		0.15	0.02
Data processing		(Deapen & Henderson, 1986)		0.15	0.64
machine repairman		(Savitz <i>et al.</i> , 1994)			
Highway patrolman		(Lin <i>et al.</i> , 1985)	B (probable)	0.15	0.09
Mechanics, computers and business machines		(Johnson & Spitz, 1989)		0.15	0.64
General office occupations		NONE		0.15	0.18
Teacher		NONE		0.15	0.09
Accountant		(Davanipour <i>et al.</i> , 1997)	Medium	0.14	0.10
Accountant		(Coogan <i>et al.</i> , 1996)	Low	0.14	0.10
Billing, posting and calculating machine operators		(Coogan <i>et al.</i> , 1996)	Medium	0.14	0.13
Dispatcher		(Lin <i>et al.</i> , 1985)	B (probable) Group 3	0.14	0.23
Dispatcher		(Demers <i>et al.</i> , 1991)		0.14	0.23
Air traffic controller		(Demers <i>et al.</i> , 1991)	Group 3	0.14	0.23
		(Loomis <i>et al.</i> , 1994b)			
		(Savitz <i>et al.</i> , 1998b)			
Broadcast equipment operator		(Demers <i>et al.</i> , 1991)	Group 3	0.14	0.23
		(Loomis <i>et al.</i> , 1994b)			
		(Savitz <i>et al.</i> , 1994)			
		(Wilkins & Wellage, 1996)			
Radio/telegraph operator		(Savitz <i>et al.</i> , 1998b)	RF	0.14	0.23
		(Tynes <i>et al.</i> , 1992)			
Radio and TV performer		(Rosenbaum <i>et al.</i> , 1994)		0.14	0.23
		(Johnson & Spitz, 1989)			
Radio announcer		(Demers <i>et al.</i> , 1991)	Group 3	0.14	0.23
Telegraph operator		(Milham, 1985)		0.14	0.23
		(Rosenbaum <i>et al.</i> , 1994)			
Telegrapher		(Demers <i>et al.</i> , 1991)	Group 3	0.14	0.23

Table 2.4 (continued)

Occupation	Industry or company	Epidemiological study	Exposure	TWA magnetic field (μT)	
				AM	SD
Communications equipment operator		1991) (Coogan <i>et al.</i> , 1996)	Medium	0.14	0.23
Other communications operators		(Loomis <i>et al.</i> , 1994b) (Savitz & Loomis, 1995)		0.14	0.23
Electrical and electronic equipment repair (miscellaneous)		(Demers <i>et al.</i> , 1991) (Wilkins & Wellage, 1996)	Group 2	0.14	0.19
Stock handlers and baggers		None		0.14	0.08
Medical technologist		(Davanipour <i>et al.</i> , 1997)	Medium	0.13	0.19
Foreman	Telephone company	(Lin <i>et al.</i> , 1985)	A (definite)	0.13	0.15
Chief communications operator		(Loomis <i>et al.</i> , 1994b) (Savitz <i>et al.</i> , 1998b)		0.13	0.15
25th percentile of males				0.12	
Brickmason		None		0.11	0.05
Shop assistant	Dairy products and bread	(Guénel <i>et al.</i> , 1993)	Continuous	0.11	0.02
Telephone operator		(Loomis <i>et al.</i> , 1994b) (Savitz <i>et al.</i> , 1998b)		0.10	0.01
Programmer, systems planner	Insurance	(Guénel <i>et al.</i> , 1993)	Continuous	0.10	0.10
Statisticians and scientists		(Coogan <i>et al.</i> , 1996)	Medium	0.10	0.05
Social worker		None		0.09	0.02
Employee	Aluminum industry	(Milham, 1985)		NR	NR
Military communications worker		(Demers <i>et al.</i> , 1991)	Group 3	NR	NR
Air Force pilot		(Davanipour <i>et al.</i> , 1997)	Medium / high	NR	NR
Blue-collar jobs (non-service)	Aluminum and non-ferrous metal production, smelting and refining	(Rosenbaum <i>et al.</i> , 1994)		NR	NR
Data entry keyers		(Loomis <i>et al.</i> , 1994b) (Sobel <i>et al.</i> , 1995) (Sobel <i>et al.</i> , 1996) (Savitz <i>et al.</i> , 1998b)		NR	NR
EDP and card punch operators		(Guénel <i>et al.</i> , 1993)	Continuous	NR	NR
Electrical and electronics workers		(Spitz & Johnson, 1985)	Narrow definition	NR	NR
Electronics workers		(Nasca <i>et al.</i> ,	Narrow	NR	NR

Table 2.4 (continued)

Occupation	Industry or company	Epidemiological study	Exposure	TWA magnetic field (μT)	
				AM	SD
Fork-lift operators		1988) (Wilkins & Wellage, 1996)	definition	NR	NR
Heat-treating, equipment, furnace, kiln, and oven operators		(Coogan <i>et al.</i> , 1996)	Low	NR	NR
Radar operator		(Davanipour <i>et al.</i> , 1997)	High	NR	NR
Radio operators		(Johnson & Spitz, 1989)		NR	NR

NR, not reported

^aNumbers in italics are approximate

Table 2.5 Occupational exposure measurements in occupational studies

Source	Class	Measurement Method	Field	Metric	Notes
(Bowman <i>et al.</i> , 1988)	Non-office electrical work sites	Spot measurement as close to worker as possible, in direction of most likely field source	0.07 μ T (microelectronics assemblers); 10 μ T (electricians)	Geometric mean	
	Offices	Spot measurement as close to worker as possible, in direction of most likely field source	0.31 μ T (one secretary with VDT); 0.11 μ T (3 secretaries w/o VDT)	Geometric mean	
	Residences (18)	Spot measurements at several sites; both low & high power conditions	0.06 μ T	Geometric mean	
(Deadman <i>et al.</i> , 1988)	20 workers from 6 electric utilities	Exposure measured over 7-day period for both work and non-work using personal dosimeters	1.7 μ T at work, 0.31 μ T for non-work	Geometric mean	Possible misclassification of some work time as non-work
	16 workers from 2 office buildings	Exposure measured over 7-day period for both work and non-work using personal dosimeters	0.16 μ T for work, 0.19 μ T for non-work	Geometric mean	
(Sahl <i>et al.</i> , 1994)	Electricians & substation operators	Exposure obtained for 770 workdays	2.1 μ T (electricians); 1.8 (subs. ops.); these were high exposure group	Mean	Occupations studied were classified into 3 groups using fraction of exposures with summary measure > 0.5 μ T
	Officestaff, meter readers, & groundmen	73 workdays of data for 3 classifications of office workers	0.1, 0.18, 0.23 μ T for three classifications of office workers	Mean	
(Barroetavena <i>et al.</i> , 1994)	3 pulp and paper mills (facilities A, B, and C0)	Measurements made at total of 132 locations, and in offices	Facility A - 0.12 μ T Facility B - 0.33 μ T	Median	Difference in non-office levels attributed tot al electric consumption
(Skotte, 1994)	Power frequency MF in elect. util., office, & industrial workers, & in people living near high power lines	301 subjects, total of 396 24-hr measurements; 55 subjects were office workers not from utility companies	0.09 μ T (1.8) office workers; 0.05 μ T (2.1) residences not near high voltage lines	Geometric mean (geometric standard deviation)	

Table 2.5 (continued)

Source	Class	Measurement Method	Field	Metric	Notes
(Breysse <i>et al.</i> , 1994a)	ELF MF in large payroll department.	Spot measurements Personal data for 15 female employees	0.13 to 2.7 μ T for office equipment 0.32 \pm 0.15 μ T, with range of 0.1-0.65 μ T	Range Mean of personal TWAs, range of personal TWAs	
(Burch <i>et al.</i> , 1998)	194 utility workers	MF & light measured by personal dosimeters 24 h/d for 5 consecutive days; melatonin metabolite excretion measured in urine samples	Distribution workers -- 0.64 \pm 0.04 at work, 0.5 \pm 0.04 during sleep; Office and administrative workers -- 0.73 \pm 0.03 at work, 0.58 \pm 0.04 during sleep	RCMS	Standardized rate of change metric (RCMS) for MF was predictor of decreased melatonin excretion
(Bracken <i>et al.</i> , 1995b)	Utility workers in 13 job classes at 59 sites in 4 countries	50,000 hrs of MF data taken at 10s intervals by dosimeter; 70% were from work environments	Substation operators 0.7 mT; electricians 0.5 μ T All work categories, while not working 0.09 μ T	Median workday mean Median non-workday mean TWA	These two groups had highest exposure by this metric. Utility-specific job classifications had about 1/2 of time-integrated exposure on the job. No measurements given in Section 2.3
(Savitz & Loomis, 1995)	138 905 electric utility workers at 5 US companies		Means in exposure categories 0.12 to 1.27 μ T		
(Thériault <i>et al.</i> , 1994)	3 cohorts of electric utility workers in Ontario, Quebec, and France	JEM constructed from current occupations and linked to occupational histories	3.1 μ T-years (median) 15.7 μ T-years (90th percentile)	Cumulative exposure	90th percentile cut-point for last job was good predictor of 90th percentile cut-point for total job history
(Floderus <i>et al.</i> , 1996)	Swedish workers	At least 4 personal exposure measurements/occupation for 100 common occupations at 1015 workplaces; used to form JEM	0.04 μ T (earth mover operators); 0.05 μ T (concrete workers); 0.19 μ T (electrical and electronics engineers and technicians and welders); 0.28 μ T (overall); 0.17 μ T (median of occupations)	Workday mean	

Table 2.6 Distribution of wire code categories of control subjects' homes in seven studies in the USA

Study location (reference)	Homes in indicated category (%)				
	UG	VLCC	OLCC	OHCC	VHCC
Denver area (Wertheimer & Leeper, 1982)	None	13 ^a	56	25	6
Denver area (Savitz <i>et al.</i> , 1988)	34	7	39	17	3
Seattle area (Severson <i>et al.</i> , 1988)	None	45 ^a	33	16	6
Los Angeles area (London <i>et al.</i> , 1991)	5	13	37	33	12
Los Angeles area (Preston- Martin <i>et al.</i> , 1996b)	7	13 ^b	28 ^b	42	10
Seattle area (Gurney <i>et al.</i> , 1996)	40	26	13	15	7
Nine states in USA (Linnet <i>et al.</i> , 1997)	18 ^c	26 ^c	28	22	6

UG, underground wiring; VLCC, very low current configuration; OLCC, ordinary low current configuration; OHCC, ordinary high current configuration; VHCC, very high current configuration

^a Designated as "end pole" in this study

^b Authors reported only the combined percentage of homes in the VLCC and OLCC as 41%. That number is divided between the two categories in accordance with the ratio of all study subjects in those two categories.

^c Authors reported only the combined percentage of homes in the UG and VLCC categories as 44%. That number is divided between the two categories in accordance with the ratio of all study subjects in those two categories.

Table 2.7 Measured magnetic fields and Wertheimer-Leeper wire codes in six studies in the USA

Study location (reference)	Magnetic field (μT)				
	UG	VLCC	OLCC	OHCC	VHCC
(Wertheimer & Leeper, 1982) Median of spot measurements next to home at point near line	excluded	< 0.05	< 0.05	0.12	0.25
(Savitz <i>et al.</i> , 1988) Low power spot measurement in home: Mean	0.049	0.053	0.071	0.12	0.21
Median	0.030	0.030	0.051	0.09	0.22
(Severson <i>et al.</i> , 1988) Median of a small subsample	excluded	.032	.048	.11	.17
(London <i>et al.</i> , 1991) Geometric mean of low power spot measurements	.017	0.017	0.022	.0029	0.060
Geometric mean of 24-h medians	0.045	0.042	0.058	0.066	0.11
(Preston-Martin <i>et al.</i> , 1996b) Mean of 24-h mean in bedroom	0.078	0.076	0.10	0.12	0.18
ibid., Mean of 24-h median in bedroom	0.047	0.057	0.043	0.060	0.11
(Tarone <i>et al.</i> , 1998) Mean of 24-h means	0.064	0.077	0.12	0.14	0.21
Median of 24-h means	0.046	0.049	0.075	0.098	0.13

UG, underground wiring; VLCC, very low current configuration; OLCC, ordinary low current configuration; OHCC, ordinary high current configuration; VHCC, very high current configuration

Table 2.8 Comparison of the percentage of homes in wire code categories > 0.2 or 0.3 μT in four studies in the USA

Study Location (reference)	Wire code category (%)				
	UG	VLCC	OLCC	OHCC	VHCC
(Wertheimer & Leeper, 1982) Outdoor spot measurements > 0.3 μT	excluded	0	1	10	29
(Savitz <i>et al.</i> , 1988) Spot measurement > 0.2 μT	3	0	6	21	60
(Severson <i>et al.</i> , 1988) 24-h mean > 0.2 μT out of a small subsample	excluded	0	6	11	50
(Tarone <i>et al.</i> , 1998) 24-h mean > 0.2 μT	3	6	15	20	40
24-h mean > 0.3 μT	0	3	6	10	23

UG, underground wiring; VLCC, very low current configuration; OLCC, ordinary low current configuration; OHCC, ordinary high current configuration; VHCC, very high current configuration

3 Internal Dosimetry

In chemical toxicology, the delivered dose of a xenobiotic is the concentration of the substance at the cell or tissue of interest. When the toxicant is a chemical, the dose can be measured using analytical devices. With EMF, current knowledge indicates that the combination of the geomagnetic field, AC magnetic fields, and electric fields and currents induced on or in the body may affect biological processes. Because the exact mechanisms by which these potential effects are produced have not been identified, however, it is impossible to clearly define which aspects of EMF constitute the dose. In studies of EMF, description of the relationships between external EMF and the EMF and currents induced in the body is called 'dosimetry'. The dosimetry of EMF can be estimated using the standard analytical techniques of electromagnetics, although the significance of parameters other than intensity must be considered. First, as EMF can be applied separately at low frequencies (< 100 kHz), specifying whether the applied field is electric or magnetic is essential. Second, because EMF are vectors, it is essential to specify not only magnitudes but also field directions with respect to the individual object (axial or transverse). For electric fields, the shape of the exposed object greatly affects the induced currents, and for magnetic fields the cross-sectional dimensions of the individual are critical. In addition, for both electric and magnetic fields it must be known whether the exposed object was electrically insulated or electrically grounded.

The wave shape or frequency content of the applied signal also influences delivered dose significantly. If the signal is purely sinusoidal and is applied continuously, only the frequency and the duration of exposure need to be specified; however, if pulsed fields are used, then specification of wave shape, the rise time, decay time, duration of individual pulses, and pulse repetition rate is essential. In general, the wave shapes of applied magnetic and induced electric pulses are radically different.

Finally, a description of exposure to EMF should include measured values of background fields, since these fields vary widely between laboratories. These include the geomagnetic field, which is essentially static.

3.1 Electric field dosimetry for human exposure

Equation 2.1 in section 2 provides a rough approximation of the electric fields inside and outside an individual subjected to an external electric field. An electric field that is initially uniform becomes distorted in the immediate vicinity of a person. Whether the individual is electrically grounded or is standing on an insulating platform also will significantly affect the field distribution (Table 3.1). Finally, for human exposure, the interest is usually not in the average electric field within the body but rather in the field and current density distribution within parts of the body. The inhomogeneity of electric properties (e.g. bone vs. muscle conductivity) and variations in the cross-section of the limbs and

trunk determine the exact current density distribution. Extensive model calculations and measurements have been made on ‘phantoms’ (saline body models) (Dawson *et al.*, 1997; Kaune & Forsythe, 1985). Thus, the maximum current densities in a human standing on electrically conducting ground in a 10-kV/m, 60 Hz electric field are 0.03 A/m² in the leg and 0.004 A/m² in the neck.

Table 3.1. Typical average electric fields in bone marrow in numerical dosimetric studies of uniform conditions of exposure to electric or magnetic fields at 60 Hz

Vertical electric field (1 kV/m)	Organ-averaged electric field (mV/m)
Grounded man	3.0
Insulated 14.4 mm above ground	1.8
Free space	1.0

From Dawson *et al.* (1997)

Values are given for the tissues with the highest organ-averaged electric fields for each exposure condition

Differences in shape, body size, and body orientation result in substantial differences in induced electric field intensity with equal exposure to external electric fields. Thus, rats in a cage must be exposed to a 30-kV/m, vertical, 60 Hz electric field in order to obtain roughly the same current densities within the rat body as inside a human standing upright in a 10-kV/m, 60 Hz field (Kaune & Phillips, 1980).

3.2 Low-frequency magnetic field dosimetry

3.2.1 Magnetic fields induced in the body by external magnetic fields

The ELF magnetic flux density, $B(t)$, inside living tissues is approximately equal to the external field. This relationship is a consequence of two conditions. First, the magnetic permeability of tissue and cells is approximately equal to that of free space. Second, the relatively low electric conductivity (at most on the order of 1 S/m) of living matter, in comparison with that of metallic structures ($\approx 10^7$ S/m), guarantees that the magnitude of the secondary magnetic field produced by the induced eddy currents is negligible (Polk, 1990). Therefore, the applied magnetic field can be measured externally without need to correct for the presence of an individual in the field.

3.2.2 Magnetic fields induced in the body by external magnetic fields

A time-varying magnetic field vector B also creates an electric field E according to Faraday’s law, such that

$$\oint E dl = - \iint \frac{\partial B}{\partial t} ds \quad \text{Eq. 3.1}$$

where dl is a vector element of length and ds is a vector element of area.

When a magnetic flux density B is applied parallel to the axis of an infinitely long, electrically homogeneous, circular, cylindrical body, equation 3.1 reduces to

$$E_{\phi} = \pi f B r \quad \text{Eq. 3.2}$$

where E_{ϕ} is the circumferentially directed electric field, f is frequency, and r is the radial distance from the center of the cylinder. This last relation is frequently employed in estimating induced electric fields in animal bodies and cell cultures but will give only approximate results because biological tissue is neither cylindrical nor electrically homogeneous. Table 3.2 nevertheless shows that a 60 Hz, 1 μ T magnetic flux density B , orientated from the front to the back of an individual will induce an electric field on the order of 100 μ V/m near the periphery of the body. Detailed calculations are necessary to estimate induced field intensities in organ systems (Dawson *et al.*, 1997).

Table 3.2. Calculated average induced electric fields in selected tissues in a human adult from a 1.0 μ T, 60 Hz magnetic field orientated from shoulders and assumed tissue conductivities

Organ	Tissue conductivity σ (S/m)	Induced electric field (μ V/m)
Brain	0.1–0.17	11–12
Cerebrospinal fluid	1.5–2.0	2.8–5
Lungs	0.07–0.09	21–28
Kidney	0.27	14–24
Prostate	0.11–0.4	17–22

From Dawson *et al.* (1997)

Depending on the biological interaction mechanism, either the internal magnetic field or the induced electric field is the appropriate applied dose.

3.3 Scaling between different organisms, assuming that an observed effect is due to induced electric fields

Equations 3.1 and 3.2 indicate that the magnetic flux density B would have to be varied in inverse proportion to the radius r (in a plane perpendicular to the direction of B) if the same induced electric field is to be obtained in different preparations or organisms. Thus, assuming that a particular physiological system is similar in mice and humans, a 10 μ T, horizontal, 60 Hz magnetic field in a mouse of 2.5-cm diameter and a 1 μ T, vertical 60 Hz magnetic field in a human of 25-cm mean body diameter would produce similar effects.

Because the electric properties of biological substances can change substantially over a scale of nanometers (for example when a membrane is present), predictions of the electric field at every point in a tissue are therefore accurate on a micro-scale only when regions of tissues are correctly represented.

Electric fields inside the human or animal body induced by time-varying ELF magnetic fields will not necessarily produce the same biological effects as internal electric fields due to externally applied magnetic fields. Scaling between different organisms or from in-vitro to in-vivo conditions will differ widely for external electric and magnetic fields, even if the magnetic field exerts its physiological effect only through induced electric fields or current densities. In the absence of detailed numerical micro-scale models, equation 3.2 must be used for first-order scaling.

3.4 Considerations for *in vitro* dosimetry

Several experiments (Blackman *et al.*, 1994; Liboff *et al.*, 1987) have shown that certain biological effects depend on synergism between static and time-varying magnetic fields, suggesting that both magnitude and relative field direction are important. Inside a steel-frame building or a laboratory incubator, the ‘static’ magnetic field may differ substantially in both magnitude and direction from the field in free space and may also vary from point to point. Specifying the characteristics of the background field at the exposure location is therefore essential when biological effects of weak (microtesla) magnetic fields are investigated. Similar considerations are not needed for electric fields because they are substantially lower in saline than in air.

3.4.1 Electric field dosimetry

Culture media generally have an electric conductivity on the order of 1 S/m, similar to that of fluid-saturated living tissue. A material is considered to be an electric conductor, as opposed to an insulator or dielectric, if the ratio of conduction current density, σE , to displacement current density, $\epsilon(\partial E/\partial t)$, is much greater than 1, where σ is the electric conductivity, E is the electric field, and ϵ is the dielectric permittivity. For a field that varies sinusoidally in time at a frequency of $\omega/2\pi$, this relationship is:

$$\frac{\sigma}{\omega\epsilon} \gg 1 \quad \text{Eq. 3.3}$$

The dielectric permittivity is given by $\epsilon = \epsilon_1 \epsilon_0$, where ϵ_0 is the permittivity of free space, which is equal to 8.84×10^{-12} F/m, and ϵ_1 is the relative dielectric constant. Below 100 Hz, the ϵ_1 of living tissue can be as large as 10^6 ; nevertheless, equation 3.3 still gives a

value of 180 at 100 Hz with $\sigma = 1 \text{ S/m}$ and $\epsilon_r = 10^6$. Thus, at ELF, culture media can be considered to be electrically conducting fluids. Electric fields are therefore most easily introduced into cell cultures by contact and by measuring the series current, I . If the electrodes are large enough and their shape is relatively simple, or if the field is calculated at a point in the field at a distance that is relatively far in comparison with the electrode size, then the electric current density, J , is given by I/A , where A is the cross-sectional area of rectangular electrodes or of rectangular vessels. The electric field can then be calculated from $J = \sigma E$ if the conductivity is measured.

All such calculations are based on the assumption that the culture medium of cells and tissues is electrically homogeneous. This approximation is reasonable for freely floating cells at relatively low density. If cells are plated at the bottom of a culture vessel and become confluent, or nearly so, the culture fluid and cell system must be considered a two-layer medium, in which the bottom (cell) layer may have vastly different (and at ELF usually lower) electric conductivity than the fluid. Current density and field evaluation then require more complex calculations.

Electrodes must be introduced cautiously into biological fluids in order to avoid chemical reactions at the electrode surfaces and consequent contamination of the fluid. The most successful method is use of agar bridges. Another method for introducing an electric field into a culture medium is capacitive coupling (Polk, 1995).

3.4.2 Magnetic field dosimetry

A key question in exposure to magnetic fields is the magnitude of the induced electric field. Here, the orientation of a culture dish or any other object within the magnetic field will have major consequences because only the component of the magnetic field that is perpendicular to a surface contributes to the induced electric field in the plane of that surface; different orientations of the magnetic field to the culture dish result in significantly different induced electric field magnitudes and distributions. In the immediate vicinity of a high-voltage transmission line, the electric field induced in a human by the electric field of the line will generally be larger than the electric field induced by the line's magnetic field. Conversely, inside a home or even near a secondary distribution line, the electric field induced inside the body will usually be due to the external time-varying magnetic field (King, 1998; King & Wu, 1995).

3.5 Summary

The occurrence of static and dynamic EMF in the environment will result in the induction of magnetic and electric fields in the body. Because of the low permeability of living tissues, both static and dynamic magnetic fields within the body will be similar to the

magnetic fields outside the body. Conversely, the induction of electric fields in the body due to either time-varying electric or magnetic fields requires careful numerical calculations which incorporate size, shape, and organ conductivity. Peak induced electric fields in the human body due to exposure to a 60 Hz, 1 μ T magnetic field can exceed 0.1 mV/m. Similar computational techniques can be used to determine induced fields in laboratory experiments.

4 Biological Data Relating to the Toxicity of Extremely Low-frequency Electromagnetic Fields

4.1 Carcinogenicity in animals

Although the interaction of an agent with humans is of prime importance and concern, many areas of biological investigation are more efficiently and appropriately conducted with animal species. Studies in laboratory animals provide an integrated system in which experimental variables can be controlled, specific hypotheses can be explored, and exposure can be precisely assessed. Given the uncertainty and the relatively low power of epidemiological studies of EMF to ascertain the relationship between exposure and possible adverse health effects, studies in experimental animals are especially important in evaluating whether there is an association with cancer. These studies have, however, limitations for risk assessment. In several instances, identification of cancer-inducing agents in animals preceded their identification in humans.

Studies of a possible association between exposure to EMF and cancer are challenged by unidentified intensity and/or frequency parameters that can result in reproducible biological responses and dosimetric differences between animals and humans. The effects of EMF have usually been studied at intensities of exposure that are much higher than environmental levels, in order to determine if effects occur. Another approach, not yet used to any great extent, is to focus on exposure parameters at levels commonly experienced by humans. Several designs and animal models have been used in laboratory studies of cancer. The choice of model depends largely on the hypothesis for a particular underlying mechanism. Few carcinogenic agents exert their full effect after a single, brief exposure, and most agents act only after an extended exposure. During that time, exposure to other possibly confounding agents must be kept to a minimum. The long-term bioassay is designed to address this issue. In this design, the animals are observed for most of their lifetime, and the number, type, and time of appearance of tumors are the critical end-points. This type of study should include several doses and a relatively large number of animals, particularly if the natural incidence of the tumor type is low. As might be surmised, studies of complete carcinogenicity are expensive, due to both the length of time and the number of animals involved. One potential problem in such studies is the inadequacy of present knowledge about what aspects of the EMF signal are biologically active.

A consideration in using animal models to investigate the effects of EMF on cancer development is the appropriateness of the model itself in relation to human disease. For example, the rat mammary carcinoma model has been thought to be reasonably relevant in many ways for investigating human breast cancer (Russo *et al.*, 1990), as many of the factors that promote tumors in the animal model also increase breast cancer risk in humans. Nevertheless, other aspects of the rodent model may not be directly relevant to

human disease. Another commonly used animal cancer model is mouse skin. This represents a convenient, well-developed way of investigating mechanistic questions in multistage carcinogenesis. Although it allows the study of potential risk factors on the process of cancer development, its results may not translate easily into information on the specific cancer type in humans. Other models, specifically for investigating the risk for leukemia, are valuable because a variety has been developed. Thus, considerable information is available about leukemia and lymphoma and its carcinogenic process in animals, and some similarities exist between the development of the disease in these models and in humans (Pattengale & Taylor, 1983).

4.1.1 One- and two-year bioassays

Lifelong studies of EMF as a complete carcinogen have been conducted in experimental animals in Canada, Japan, and the United States. The results are summarized in Table 4.1. The results of long-term bioassays can provide a general assessment of whether an agent is carcinogenic in an animal model. This type of study is therefore relevant to the initiation, promotion, and progression phases of cancer development, although it may not contribute much information on biological mechanisms. As indicated above, few have been carried out on exposure to EMF because of the time and the cost of such assays.

The most comprehensive study to date of EMF as a potential carcinogen was conducted at the IIT Research Institute for the National Toxicology Program (NTP, 1998b). In this study, which was conducted according to good laboratory practice (GLP), groups of 100 Fischer 344 rats and 100 B6C3F1 mice of each sex were exposed to one of several magnetic field conditions: 2 200, or 1000 μT continuously or 1000 μT intermittently (1 h on, 1 h off), 60 Hz linearly polarized magnetic fields; one group received sham exposure. Neither exposed nor control animals were exposed to transients. Exposure began when the animals were 6–7 weeks of age and continued for 18.5 h/d for two years. The animals were monitored and evaluated over the course of their lifetime for survival, body weight, and clinical signs of neoplasia. At death (average age, 112–113 weeks), all animals underwent complete necropsy and histopathological evaluation.

The survival of exposed rats (47–59% of males and 58–68% of females) was no different from that of control animals (57% males and 59% females). There were no exposure-related clinical findings. The only significant increase in tumor incidence in field-exposed rats was for thyroid gland C-cell adenomas and carcinomas combined in male rats, with incidences of 16% in sham-exposed controls, 31% in those at 2 μT ($p < 1.01$), 30% in those at 200 μT ($p < 0.01$), 25% in those at 1000 μT continuously ($p = 0.06$), and 22% in those at 1000 μT intermittently ($p = 0.15$). The incidence of mononuclear-cell leukemia in males was 50, 44, 47, 50, and 36% ($p < 0.05$, intermittent group) for the five groups, respectively.

The survival of exposed mice (72–84% in males and 74–79% in females) was similar to that of control animals (76% males and 70% females), except for male mice exposed to 1000 μ T which had significantly reduced survival (62/100, $p = 0.037$) in comparison with control mice (76/100). There were no exposure-related clinical findings. Significant differences in the incidence of neoplasms between field-exposed and sham-exposed mice included decreased incidences of alveolar/bronchiolar adenoma in males exposed to 2 μ T (11/99, $p = 0.007$) or 200 μ T (9/100, $p < 0.001$) and in female mice exposed to 200 μ T (0/99, $p = 0.002$). The incidences of adenoma and carcinoma combined were significantly lower in males (19/100, $p = 0.041$) and females (29/99, $p = 0.008$) exposed to 200 μ T than in controls (males, 30/100; females, 11/95). The incidence of malignant lymphoma in female mice exposed intermittently to 1000 μ T was significantly lower (20/100, $p = 0.035$) than that observed in the controls (32/100).

The authors concluded that under the conditions of these two-year studies with whole-body exposure there was equivocal evidence for the carcinogenic activity of 60 Hz magnetic fields in male Fischer 344/N rats, on the basis of the increased incidences of thyroid gland C-cell neoplasms in male rats exposed at 2 or 200 μ T. There was no evidence of carcinogenic activity in female rats or in male or female B6C3F1 mice exposed to 2, 200, or 1000 μ T continuously or to 1000 μ T intermittently.

A study similar to that described above was conducted in Canada (Mandeville *et al.*, 1997). In this study, groups of 50 female Fischer 344/N rats were exposed to 2, 20, 200, or 2000 μ T 60 Hz, linearly-polarized magnetic fields; there were also groups of sham-exposed and cage controls. The authors carefully excluded transients. Exposure began two days before birth and continued for 20 h/d for two years. The animals were monitored and evaluated over the course of their lifetime for survival, body weight, and clinical signs of neoplasia. At death, all of the animals were subjected to complete necropsy and histopathological evaluation of 50 organs and tissues from each animal, with specific attention to the incidences of mononuclear-cell leukemia, brain tumors, and mammary tumors.

The survival of rats at the end of the study was significantly lower among the sham-exposed controls (19/50, $p = 0.03$) and animals exposed to low field intensities (16/50, $p = 0.005$ for both 2 and 20 μ T groups) than in cage controls (30/50). The survival rates were not different for exposed and sham-exposed animals (16/50, 16/50, 24/50, and 25/50 in rats at 2, 20, 200, and 2000 μ T, respectively, versus 19/50 in sham-exposed). There were no consistent exposure-related clinical findings.

The two control groups had higher overall tumor incidences (45/50 in cage controls and 46/50 in sham-exposed) than exposed rats (42/50, 43/50, 43/50, and 41/50 in rats at 2, 20, 200, and 2000 μ T). In all groups of animals, the commonest tumor types were pituitary adenomas, mammary gland fibroadenomas, and mononuclear-cell leukemia. Following the pattern for overall tumor incidence, that of pituitary adenomas in the exposed animals varied between 40% (2 μ T; 20/50, $p = 0.04$) and 44% (2000 μ T; 22/50, $p = 0.07$) and was

statistically significantly lower than in the controls (31/49 in cage controls, 29/49 in sham-exposed). When the sham-exposed animals were compared with the exposed rats for mammary gland fibroadenomas, there was no significant difference (28/50 for sham-exposed and mice at 2 μ T versus 27/50, 24/49, and 21/50 for those at 20, 200, at 2000 μ T respectively). Mammary gland adenocarcinomas were rare in all groups of animals. The incidence of mononuclear-cell leukemia was relatively low and not significantly different in any group.

The authors concluded that there was no evidence for the carcinogenic activity of 60 Hz, linear sinusoidal, continuous waves at intensities of 2, 20, 200, or 2000 μ T in female Fischer 344 rats, suggesting lack of carcinogenicity. There were also no statistically significant, consistent, dose-related trend in the number of tumor-bearing animals per study group that could be attributed to exposure to magnetic fields.

The results of a carefully conducted, well-documented study to determine the carcinogenic effect of 50 Hz sinusoidal magnetic fields in rats throughout their lifetime have been reported (Yasui *et al.*, 1997). Groups of 48 Fischer 344/DuCrj rats of each sex were exposed to flux densities of 500 or 5000 μ T or sham fields from 5 to 109 weeks of age. The high dose was much higher than those used in the other two studies. The exposure design eliminated transients, and exposure was for 22.6 h/d day for two years. The animals were monitored and evaluated over their lifetime for survival, body weight, and clinical signs of neoplasia. At death, all animals underwent complete necropsy and histopathological evaluation.

The survival of exposed rats was no different from that of control animals. There were no exposure-related clinical findings. The only significant difference between exposed and sham-exposed rats in the incidence of neoplasms was an increase in fibroma of the subcutis in males at 5 mT (9/48 versus 2/48 in controls, $p = 0.05$). This increase in the incidence of a benign tumor was not significant in a comparison with historical controls. The incidences of leukemia, lymphoma, and brain and of adenomas of the pituitary and thyroid (changes noted in other animal studies) were no different between field- and sham-exposed animals.

Margonato *et al.* (Margonato *et al.*, 1995) investigated the exposure of groups of 256 animals male Sprague-Dawley rats to a 50 Hz field over 32 weeks. Exposure was for 22 h/d to 5 μ T magnetic fields or sham exposure. Although this study was not designed to address the issue of cancer *per se*, the biological end-points included hematological examinations for each animal and morphological and histological evaluation of the liver, heart, mesenteric lymph nodes, and testes. In two identical sets of experiments involving 128 rats per group per experiment, no significant difference in the investigated variables was found between exposed and sham-exposed animals. Although certain parameters differed between the two experiments, the exposure conditions were the same. The authors concluded that the results did not indicate any harmful effects of prolonged exposure to magnetic fields comparable to those measured close to power lines. [This

conclusion is limited to a selected number of markers within the portion of the life span of the animal corresponding to a high growth rate but not to the early developmental phase.]

Few long-term bioassays have been performed of the exposure of mice or rats to 50- or 60 Hz magnetic fields. In the largest and most comprehensive of the studies (Mandeville *et al.*, 1997; NTP, 1998b; Yasui *et al.*, 1997), few significant effects (both increases and decreases) of exposure on cancer development were seen, with the exception of isolated thyroid C-cell adenomas and carcinomas in male rats in the NTP study.

4.1.2 Multistep carcinogenesis

Carcinogenesis is a multistep, multifactorial process. The experimental approach most commonly used is the two-phase protocol, based on the two-stage hypothesis, which can be used to verify whether the agent of interest acts as an initiator or a promoter.

‘Initiation’ is considered to involve a genotoxic event in which the carcinogen interacts with target cells to affect DNA. ‘Promotion’ is associated with a number of subcellular events that are generally nongenotoxic and is responsible for the conversion or clonal expansion of initiated cells to a cancer. When EMF is being investigated for possible promotional effects, animals are treated with a known initiator (e.g. ionizing radiation or a chemical carcinogen such as 7,12-dimethylbenz[*a*]anthracene, DMBA) and subsequently exposed to EMF over a long period (months). Initiation–promotion approaches have the advantage of involving fewer animals, shorter time, and less cost. This approach may also provide information on dose–response relationships or answer questions about biological mechanisms. An initiation–promotion study may provide only general information on the specific effect of EMF on cancer development. A given model is usually limited to evaluating a specific type of cancer that may or may not be relevant to the agent of interest.

Neither the long-term studies of spontaneous tumor development studies summarized above nor shorter studies have given any indication that EMF are mutagenic. For this reason, investigations based on the multistage nature of carcinogenesis have focused on the promotional phases of the cancer process. The studies summarized below addressed the specific question of whether EMF acts as a promoter or co-promoter of tumorigenesis in models of mammary, skin, liver, and brain cancer and of lymphoma/leukemia and as an enhancer in a rat leukemia progression model.

4.1.2.1 Mammary Cancer

Several studies have been conducted to examine mammary cancer and exposure to magnetic fields (Table 4.2), because of the importance of breast cancer to the public and on the basis of a possible biological mechanism involving the hormone melatonin (Stevens, 1987) and EMF (Wilson & Matt, 1997).

(a) Initiation with N-methyl-N-nitrosourea

In the earliest reported study of this type, Beniashvili *et al.* (Beniashvili *et al.*, 1991) induced mammary tumors in five groups of 50 female rats by an intravenous injection of *N*-methyl-*N*-nitrosourea (MNU; 50 mg/kg body weight) at 55 days of age. After administration of the MNU, one group served as cage controls, and two groups were exposed to a 20 μ T, 50 Hz magnetic field for 30 or 180 min. each day, and exposure continued for the lifetime of the animals. Animals exposed to the 50 Hz field for 180 min/d had a higher incidence ($p < 0.05$) of mammary tumors than cage controls (43/46 vs. 27/46) and a larger number ($p < 0.05$) of total tumors (75 vs. 31 in controls). In addition, the mean latent period was shorter in the exposed animals (45.5 d) than in the MNU-injected controls (74.4 d). No differences were observed for the animals exposed to magnetic fields for 0.5 h/d.

As part of this study, 25 female rats were exposed to 50 Hz magnetic fields for 0.5 or 3 h/d with no MNU treatment. At the conclusion of the study after two years, limited information was collected at necropsy and histological examination. A significant increase ($p < 0.05$) in the incidence of mammary gland tumors was observed in rats exposed to 20 μ T for 3 h/d (7/25 animals) in comparison with those exposed for 0.5 h/d (1/25) and with unexposed animals (0/50). The latency for tumor appearance was 74 ± 15 d for controls, 65 ± 1 d for 0.5-h exposure, and 46 ± 12 d for 3-h exposure.

Anisimov *et al.* (Anisimov *et al.*, 1996), conducted a replication experiment in which groups of 40 outbred white rats were field- or sham-exposed to 50 Hz, 20 μ T magnetic fields for life (generally less than five months). Rats received 50 mg/kg MNU intravenously at three-week intervals with either magnetic field exposure or sham exposure for 3 h/d. Mammary adenocarcinomas (identified histologically) were found in 7/22 sham-exposed and 15/33 field-exposed (not significant). The mean latent period for tumor development was 166 ± 4 d for sham-exposed and 125 ± 7 ($p < 0.05$) for field-exposed.

[The inadequate reporting of the method and experimental details prevents an assessment of the significance of either result.]

(b) Initiation with 7,12-dimethylbenz[a]anthracene

A fairly comprehensive series of studies of mammary tumor initiation and promotion was conducted by Löscher and Mevissen (Löscher *et al.*, 1993; Löscher *et al.*, 1994; Mevissen *et al.*, 1998a; Mevissen *et al.*, 1993). In all of their studies, female Sprague-Dawley rats were initiated by intragastric administration of DMBA in sesame oil at 52 days of age by a fractionated dosage of 5 mg per animal given over four weeks ($4 \times 5 = 20$ mg, total dose DMBA). In all of the experiments, animals were exposed for 13 weeks, 24 h/d, to 50 Hz horizontal magnetic fields. [No transients were expected from the design of the system.]

In the initial study (Mevissen *et al.*, 1993), female rats were exposed after DMBA administration to 30 mT (50 Hz) magnetic fields. The average mammary tumor incidences were 66% (range, 55–75%) in reference controls and 61% (range, 50–78%) in sham-exposed controls. Exposure to magnetic fields resulted in tumors in 19/36 sham-exposed and 20/33 field-exposed animals, and the total number of tumors was 51 in treated animals and 36 in sham-exposed (not statistically significant). When the latter experiment was repeated with only eight or nine animals per group, no difference was found between the exposed and control groups. When groups of 36 DMBA-treated rats were exposed to a gradient (0.3–1.0 μ T) 50 Hz field, no difference in tumor incidence was seen, and the exposed animals had 47 tumors versus 60 in the sham-exposed (not statistically significant) (Löscher *et al.*, 1994; Mevissen *et al.*, 1993). The authors concluded that these experiments indicate that magnetic fields at high flux densities act as a promoter or co-promoter of breast cancer. [This conclusion must be considered only tentative because of the limitations of this study, particularly the small sample size used for exposure to magnetic fields.]

In the next set of experiments, a much larger number of animals (99 rats/group) was used (Löscher *et al.*, 1993). All rats received the four weekly doses of 5 mg DMBA beginning at 52 days of age. One group of 99 rats was then exposed to magnetic fields at a flux density of 100 μ T, while another group of 99 rats served as sham-exposed controls. After three months of exposure, the number of tumor-bearing animals (macroscopically visible tumors at necropsy) was 34 in the sham-exposed group and 51 in the exposed animals ($p < 0.05$). The tumors were not significantly larger ($p = 0.08$) in the exposed group (median, 707 mm³; interquartile range, 168–1885) than in the controls (367 mm³; 101–1178; $p = 0.07$), and no difference was found in the number of tumors per tumor-bearing rat. The authors stated that the data demonstrate that long-term exposure of DMBA-treated female rats to an alternating magnetic field of low flux density promotes the growth and increases the incidence of mammary tumors. [The study is well documented and adequately addresses the problem of the earlier study. No histopathological data are presented.]

An extension of the previous study was conducted in which a complete histopathological examination was performed (Baum *et al.*, 1995). Histological examination of the tumors from the previous experiment revealed more tumors than were detected by palpation, the incidence of histologically verified DMBA-induced lesions being 57/99 in sham-exposed controls and 65/99 in animals exposed to magnetic fields. When tumors and hyperplasia were combined [an unusual combination], the numbers were 74/99 in sham-exposed controls and 65/99 in field-exposed rats; the incidence did not significantly differ between the groups. The authors concluded that exposure did not alter the incidence of mammary lesions but accelerated tumor growth, consistent with a co-promoting effect of EMF. There was a significant increase ($p < 0.05$) in the number of adenocarcinomas in exposed animals (62/99 in field-exposed versus 49/99 in sham-exposed controls). [Adenocarcinoma are not normally separated from carcinoma *in situ* for evaluation in the mammary gland.] After assessing the histological data, the authors concluded that long-term exposure of DMBA-treated female rats to EMF promotes the size and progression of mammary

tumors (treated: median, 733 mm³; interquartile range, 183–2994; controls: 367 mm³; 101–1178; $p < 0.05$), while tumor incidence is not affected.

In the next experiments in this series of studies (Mevisen *et al.*, 1996a), an effort was made to determine if a dose–response relationship exists with field intensity. Ninety-nine animals per group were exposed to 10 μ T for 13 weeks. DMBA induced palpable tumors in 55/99 of sham-exposed and 60/99 field-exposed animals. At autopsy, these numbers were 61 and 67%, respectively; neither was statistically significant. The size, number per animal, incidence, and latency of tumors were similar in the two groups. The authors concluded that at this field intensity, magnetic fields had no effect.

In the next experiment in this series (Mevisen *et al.*, 1996b), groups of 99 rats were exposed to 50 μ T. At autopsy, 55% of sham-exposed controls and 69% ($p < 0.05$) of those exposed to magnetic fields had tumors, but the size and the number of tumors per animal were similar in the two groups. The author concluded that at this field intensity, magnetic fields had no effect.

Mevisen *et al.* (Mevisen *et al.*, 1998a) conducted a replication experiment in which 99 female Sprague-Dawley rats were field-exposed or sham-exposed to a 100 μ T, 50 Hz magnetic field. All of the rats received a total of 20 mg of DMBA (4 x 5 mg fractionated dose) beginning at 52 \pm 2 days of age. After three months of exposure, the rats were sacrificed and mammary tumors identified by macroscopic evaluation at necropsy. Small tumors were examined histologically to confirm diagnosis as adenocarcinomas. Macroscopically visible tumors were found in 82 field-exposed and 61 sham-exposed rats ($p < 0.05$). The total number of tumors was 230 in controls and 297 in exposed animals; no difference was observed in the number of tumors per animal or in tumor size.

[In this series of studies of DMBA-initiated breast cancer in Sprague-Dawley rats promoted with 10–100 μ T magnetic fields, a higher number of total tumors was found in field-exposed groups in most studies. These effects often did not reach statistical significance, and in none of the studies was there a difference between field-exposed and sham-exposed animals in the number of tumors per tumor-bearing rat. The exposure resulted in a decreased latency in several but not all studies, and this effect was often seen only during part of the study. Increased tumor size was seen with exposure to magnetic fields but not consistently across the studies. Although the rats were initiated with a very high dose of DMBA (20 mg/rat), the 34–61% tumor incidence in the controls is much lower than would have been expected in Sprague Dawley rats in US studies. This may reflect a differences in the rat strain.]

In an effort to replicate these results (NTP, 1998a), Battelle Pacific Northwest Laboratories attempted to simulate the design and experimental method of the studies as closely as possible, with four weekly doses of 5 mg DMBA beginning at 52 days of age given by intragastric intubation to female Sprague-Dawley rats. Exposure was for 18.5 h/d, 7 d per week for 13 weeks at field intensities of 100 and 500 μ T (50 Hz) and 100 μ T

(60 Hz) linearly polarized horizontal sinusoidal magnetic fields. The study was conducted under GLP conditions and included documentation of fields and exposure characteristics. A 26-week study at a lower single dose of 10 mg DMBA was also conducted. As all rats given DMBA in the first 13-week study had mammary gland neoplasms at incidences, determined by palpation, > 80%, a second 13-week study was conducted with four weekly doses of 2 mg DMBA.

Additional groups were included which were exposed at 500 μ T (50 Hz) and 100 μ T (60 Hz) for 18.5 h/d; all environmental conditions (temperature, light, relative humidity, and noise) were regulated and monitored continuously. Full gross pathological analysis and complete histopathological examination of mammary tumors were conducted.

In the first 13-week study, no difference in the onset of tumors or tumor size was found by gross palpation. The skin and the mammary glands were transluminated to identify all potential lesions; all gross lesions were counted, measured in two directions and sampled for histology. The incidences of mammary gland carcinomas were 92% in sham-exposed rats, 86% in those at 100 μ T 50 Hz, 96% in those at 500 μ T 50 Hz, and 96% in those at 100 μ T 60 Hz magnetic fields. The numbers of mammary gland carcinomas verified histologically were 691 in sham-exposed and 528 ($p < 0.05$ negative trend), 651 (not significant), and 692 (not significant) for rats at 100 and 500 μ T 50 Hz and 100 μ T 60 Hz, respectively.

The high tumor incidence in all groups (86–94%) seen with the same dosing regime as used in the Lüscher studies decreased the sensitivity of the first 13-week study to detect a promoting effect. In the second 13-week study, at 8 mg DMBA (2 mg x 4 weekly doses), the mean body weights and clinical findings (attributable to DMBA administration) were not different between field-exposed and sham-exposed groups. There was no difference in the time to onset of tumors or in tumor size by gross palpation. The incidences of mammary gland carcinomas were 43, 48, and 38% for the sham-exposure and for exposure to 100 or 500 μ T, 50 Hz magnetic fields, respectively, and the numbers of mammary gland carcinomas verified histologically were 102, 90, and 79, respectively. At necropsy, > 99% of the palpated tumors were shown histologically to be mammary gland carcinomas. The tumor incidence, total number of tumors, number of tumors per tumor-bearing rat (average, 1.7–2), and tumor size were not increased by exposure.

In the 26-week study, survival was similar in the sham- and field-exposed groups. In addition, no consistent differences in clinical findings were seen between groups exposed to DMBA plus magnetic fields and DMBA controls. Mammary gland carcinomas and multiple carcinomas were observed in all groups, but the rats exposed to magnetic fields had consistently fewer mammary tumors than the DMBA controls (Table 4.3); the 100 μ T, 60 Hz group had a significantly lower incidence than controls ($p < 0.05$). The numbers of tumors per tumor-bearing animal showed a similar pattern, the 100 μ T, 60 Hz group having lower values than controls. Most of the palpable tumors in all groups were

shown histologically to be mammary gland carcinomas and fibroadenomas. The numbers of mammary gland carcinomas verified histologically were 649 (sham-exposed), 494 (100 μ T, 50 Hz) ($p < 0.05$ negative trend for poly-3 test), 547 (500 μ T, 50 Hz), and 433 (100 μ T 60 Hz) ($p < 0.05$ negative trend for poly-3 test). The tumor sizes were similar in all groups.

Table 4.3. Incidences of mammary gland lesions in female rats exposed to 10 mg DMBA plus sham exposure or exposure to magnetic fields

Lesion	Sham-exposed	50 Hz		60 Hz
		100 μ T	500 μ T	100 μ T
Hyperplasia	1	1	0	1
Adenoma	2	0	0	0
Carcinoma	96	90	95	85*
Fibroadenoma	71	76	73	68

^a 100 animals/exposure group

* $p < 0.05$ (decrease)

In both the 26-week and the 13-week studies, the authors found no evidence that magnetic fields promote the development of mammary gland neoplasms. [The rats exposed to EMF showed a decrease in the number of tumors and in the incidence of DMBA-initiated tumors. Because of the large number of tumors generated by the dose of DMBA used in the first 13-week study, the sensitivity of the assay to pick-up small promotor effects was limited.]

A further study was conducted to examine the effects of magnetic fields on mammary tumor development in rodents (Ekström *et al.*, 1998). Although the intensities of the magnetic fields used in this study were similar to those in the studies described above, 250 and 500 μ T at 50 Hz, there were also some significant differences. In this study, a transient-producing, intermittent field was used (15 s on, 15 s off). In addition, the fields were used in a strictly ‘promotional’ design, exposure beginning one week after DMBA administration rather than simultaneously with the DMBA. Fifty-two-day-old Sprague-Dawley female rats were treated with DMBA (7 mg/animal) and, once started, the exposures continued for 19–21 h/d for 25 weeks. As in the other studies, the end-points were tumor incidence, number of tumors per animal, and tumor volume and weight.

This incidences of tumors were 43/60, 42/60, and 42/60 for the sham-exposed, 250 μ T and 500 μ T 50 Hz groups, respectively. The numbers of tumors and tumors per animal were also similar between all the groups, with 111 tumors in the DMBA controls and 102 at 250 μ T and 90 at 500 μ T in the exposed groups. The rate of tumor appearance and tumor volume were the same in all groups. The authors concluded that magnetic fields had no effects in this study. [The interpretation of these results is made uncertain by the lack of histopathological data.]

(c) *Comments*

Several studies have been conducted in rats to examine the effect of 50 and 60 Hz magnetic fields on mammary tumor promotion. In all of these studies, mammary gland carcinomas were initiated by treating female rats with a known chemical carcinogen; they were then exposed to various intensities of magnetic fields. Since promotion is generally a process of long duration, the short duration of these experiments greatly limits the possibility of detecting a potential modifying effect of EMF on the action of a strong carcinogen such as DMBA. The series conducted by Mevissen and Löscher appear to suggest that mammary cancer promotion in the rodent model is enhanced by exposure to magnetic fields. Although there was an apparent increase in the tumor incidence, the number of tumors per rat did not increase with exposure to magnetic fields. There is concern about the lack of consistency of the data, the lack of a dose–response to exposure to EMF in the individual studies, the low carcinogenic response to DMBA, and the lack of histological detail. The NTP study, specifically designed to replicate the Löscher studies, produced some results similar to those of Löscher but could not verify a promotional effect of exposure to EMF because of lack of sensitivity in one experiment. Conditions that might account for these results are the source of animals and feed, the quality of DMBA, possible exposure to field transients, different length of exposure. Within the limits of the experimental model used, the results of the ensemble of experiments do not provide convincing evidence for a promoting effect of EMF on chemically induced mammary cancer.

4.1.2.2 Skin tumor models

Skin tumor development in mice is a well-accepted, convenient model for the study of multistage carcinogenesis. Although human epidemiological studies do not indicate that skin tumors occur as a result of exposure to EMF, this model is useful for exploring general cancer development. In the most highly developed, two-stage model, the protocol involves DMBA treatment of the skin on the back of mice as an initiator and then treatment with an active phorbol diester, 12-*O*-tetradecanoyl phorbol 13-acetate (TPA), which is used as a promoter. Selected mouse strains, e.g. SENCAR (SENSitive to CARcinogenesis) mice, are used. After initiation and repeated application of TPA, morphological changes are observed. The main tumor type is squamous-cell papilloma, which begins to appear after five or six weeks of TPA treatment. Many substances have been found to act as promoters or co-promoters in this model (DiGiovanni, 1992). Studies with this model to examine EMF as a possible promoter or co-promoter are outlined in Table 4.4.

Skin tumor promotion after initiation with DMBA was examined in groups of 32 female mice exposed to a 2000 μ T, 60 Hz continuous magnetic field for 6 h/d five days per week for up to 21 weeks (McLean *et al.*, 1991). Mice were initiated with DMBA (10 nmol in 200 μ l of acetone) on the dorsal skin and were then exposed to the magnetic field with or without TPA promotion (1 μ g per week for 21 weeks). As none of the field-exposed or

sham-exposed mice developed papillomas in the absence of TPA, the authors concluded that magnetic fields did not act as a tumor promoter. A slight, nonsignificant decrease in the time of appearance of tumors was observed in animals treated with TPA plus EMF, in comparison with animals treated with TPA and sham exposed. [The number of animals with tumors at 21 weeks was extremely high (> 90% in both exposed and control groups) and essentially precluded a judgment as to whether EMF could affect the incidence of skin papillomas.]

In a second study, two groups of 48 mice were similarly initiated with DMBA and promoted with 0.3 µg (4.9 nmol) TPA for 23 weeks, with or without magnetic field exposure (Stuchly *et al.*, 1992). The onset of tumor development occurred earlier in mice ($p < 0.05$ for weeks 16, 17, and 18) that were treated with TPA plus magnetic fields when compared with the TPA plus sham-exposed mice. Although a difference in the cumulative number of mice with tumors was observed during the experiment, neither the number of animals affected nor the number of tumors per animal was statistically different between the two groups at the end of the study.

In a third study, the protocol was similar to that in the study described above, except that sham or field exposure continued for 52 weeks, whereas TPA treatment was discontinued after week 23. McLean *et al.* (McLean *et al.*, 1995) reported that while there was no overall increase in total tumors associated with exposure to fields, more field-exposed animals had malignant tumors (8/48) than sham-exposed animals (1/48, $p < 0.03$). [No indication of the number of tumors per animal was given.] A review of three independent studies involving a total of 288 SENCAR mice used to study the effects of 60 Hz magnetic fields on the growth and development of skin tumors showed mixed results: in one study, more tumors were seen in field-exposed (86) than sham-exposed mice (48), while two studies showed the opposite effect (33 magnetic field-exposed versus 50 sham-exposed and 27 magnetic field-exposed versus 86 sham-exposed; $p = 0.01$). The authors concluded that the results did not support a role of magnetic fields as tumor co-promoters (McLean *et al.*, 1997).

In a lifespan study of skin carcinogenesis in NMRI/HAN mice exposed to sinusoidal magnetic fields, no evidence was found that magnetic fields promote the formation of skin tumors (Rannug *et al.*, 1993a). Groups of 30 mice were initiated with DMBA (25.6 µg applied topically to the shaved dorsal skin of each mouse) and exposed from seven weeks of age to either 50 Hz sinusoidal magnetic fields with flux densities of 50 or 500 µT for 103 weeks for 19–21 h/d or sham conditions. There was no increase in tumor promotion with exposure to magnetic fields. [The flux densities used in this study were lower than those used by McLean *et al.*] (McLean *et al.*, 1995)

As part of this study, a group of animals was exposed to fields for two years in the absence of treatment with DMBA or TPA and were then monitored and evaluated over the course of their lifetime for survival and the appearance of skin tumors; at death, they were assessed by complete necropsy and histopathological evaluation of skin tumor

types. The survival of mice treated with DMBA and TPA but exposed to 500 μT was shorter than that of controls or 50 μT -treated animals (median survival, 74 versus 94.5 and 87.5 weeks, respectively). There were no skin tumors in either control or field-exposed groups, and no significant differences were observed between sham-exposed and field-exposed groups in the incidences of other neoplastic lesions or leukemia.

In a second study, this group investigated the tumor promoting effects of continuous and intermittent magnetic fields in sensitive female SENCAR mice (Rannug *et al.*, 1994). Groups of 40 mice were treated with DMBA (2.6 μg) one week before exposure to continuous and intermittent (15 s on/off) 50 Hz horizontal, AC fields with flux densities of 50 and 500 μT for 19 or 21 h/d for 104 weeks. Untreated, DMBA-treated, and TPA-promoted control groups were included. No tumors were found in animals treated with DMBA with no co-promotion by TPA and exposed to continuous fields of 50 or 500 μT . Four tumors in four animals were found at 50 μT and 13 tumors in five animals at 500 μT given intermittently, with two tumors in DMBA-treated sham-exposed animals. These increases were not significantly different when the two intermittent exposure groups were compared with the sham-exposed group. The time to first tumor was shortened in the intermittently exposed animals when compared with the DMBA-treated controls. [There were far fewer tumors in the field-exposed groups (< 5%) than in the TPA-treated positive control animals (> 97%). No hyperplastic response was seen with the magnetic field exposures. The results did not support the hypothesis that magnetic fields promote skin carcinogenesis in SENCAR mice at flux densities of 50 and 500 μT .]±

A further study was conducted in SENCAR mice (Sasser *et al.*, 1998) as a collaborative effort between Battelle and the M.D. Anderson Cancer Center. Mice were exposed to DMBA (10 nmol in 200 μL acetone) and then to TPA at 0.85, 1.7, or 3.4 nmol. They were then exposed to 2000 μT , 60 Hz magnetic fields for 23 weeks. Skin tumor incidence and multiplicity were monitored, and the tumors were histologically evaluated at the end of the study. Papillomas were seen in 15 of 48 field-exposed and 10 of 48 sham-exposed mice. These differences were not significantly different. The overall conclusion of the authors was that, within the sensitivity limits imposed by the animal model and the exposure parameters employed, no co-promotional effect of field could be demonstrated.

[Several studies of promotion and co-promotion have been conducted in mice to examine the effect of 50 and 60 Hz magnetic fields on the development of skin carcinomas and papillomas. In all of these studies, skin carcinomas were initiated by treating the animals with a known chemical carcinogen; they were then exposed to various intensities of magnetic field or combinations of magnetic fields with a known chemical promoter (TPA). Within the constraints of all five studies, there were no significant promotional effects of magnetic fields on skin tumor development.]

4.1.2.3 Liver cancer models

Rat liver is the most commonly used experimental model for investigating multistage carcinogenesis in tissues other than the epidermis (Dragan & Pitot, 1992). The protocol used in these studies typically requires a mitogenic stimulus, often a partial hepatectomy, in tandem with a subcarcinogenic dose of an initiator (usually *N*-nitrosodiethylamine, NDEA). The inclusion of a promoter (e.g. phenobarbital) is necessary to obtain expression of liver foci. The basis of using the rat liver model to study EMF exposure is similar to that for the skin tumor model: to determine whether EMF will promote or co-promote liver tumors. Two studies of this type have been conducted, as described below (Table 4.5).

In a series of experiments, Rannug *et al.* (Rannug *et al.*, 1993b; Rannug *et al.*, 1993c) investigated the possibility that magnetic fields interact with known initiators or promoters of cancer to induce preneoplastic lesions in rats. They used partially hepatectomized male Sprague-Dawley rats treated with NDEA to initiate tumor development. The animals were then exposed to magnetic fields for 12 weeks, beginning one week after initiation, to determine whether growth of enzymatically altered foci would be promoted in liver cells. In two studies, groups of nine to 10 rats were initiated with NDEA and then promoted with 50 Hz horizontal magnetic fields with flux densities of 0.5 or 50 μ T (experiment 1) or 5 or 500 μ T (experiment 2). A slight increase in staining for γ -glutamyltranspeptidase was reported in the first experiment at 50 μ T ($p < 0.01$) but not in the second experiment.

In a third study, groups of 10 rats were exposed to magnetic fields with flux densities of 0.5 or 500 μ T both during initiation with NDEA and throughout co-promotion with phenobarbital (300 ppm in diet) (Rannug *et al.*, 1993c). The magnetic field inhibited, although not significantly, the size and number of focal lesions. The authors concluded that there was no evidence of a promotional or co-promotional role of magnetic fields.

4.1.2.4 Leukemia/lymphoma model

Two types of study have been conducted: exposure to EMF after induction of leukemia/lymphoma by initiation with X-rays or DMBA or progression of the disease under the influence of EMF after introduction of leukemia cells into the animal. These studies are summarized in Table 4.6.

(a) Mice

In the largest of these studies, over 2000 C57Bl/6J mice were exposed to fractionated doses of ionizing radiation (cobalt-60) at 0, 350, 475, or 600 rads (Babbitt *et al.*, 1998). Eight groups of 195–450 male and female mice were exposed to a circularly polarized magnetic field of 1.4 mT from the first day of irradiation, continuing for 18 h/d for the

two-year duration of the study. This study was conducted under GLP, and extensive monitoring of exposure parameters was conducted; no transients were present during exposure. The incidence of lymphoma was not affected by exposure to magnetic fields (Table 4.7). A full morphological and histopathological evaluation and analysis was performed on all animals. No statistically significant, consistent effects of exposure were reported at any dose of ionizing radiation. Evaluation of the various lymphoma subsets produced similar conclusions. The authors reported no significant effects of exposure to magnetic fields over the natural lifespan of this strain of mouse with regard to either the incidence of all leukemias/lymphomas at death or the rate of death with leukemia/lymphoma present. [This study should have been sensitive enough to detect small differences due to exposure to magnetic fields.]

Table 4.7. Lymphoma incidence in mice treated with ionizing radiation and EMF

Ionizing radiation (rads)	Percent lymphomas	
	Sham-exposed ^a	60 Hz 1.4 mT ^b
0	35 ± 7	37 ± 5
350	40 ± 7	34 ± 5
475	38 ± 7	41 ± 5
600	52 ± 7	46 ± 5

^a 190 control mice per ionizing radiation group (760 total)

^b 380 exposed mice per ionizing radiation group (1520 total)

As an addition to the study of Babbitt *et al.* (Babbitt *et al.*, 1998), sections of brain were examined from mice exposed to 0, 350, 475, or 600 rads of ionizing radiation in four fractionated doses with and without subsequent exposure to 1.4 mT of circularly polarized 60 Hz magnetic fields. Hematoxylin and eosin-stained sections were prepared of the brain and were reviewed for primary proliferative lesions. Seven primary brain tumors or hamartous lesions (lipomas) were found in treated animals, with no apparent correlation with exposure to either radiation or magnetic fields. The authors concluded that this study provides no evidence of an effect of magnetic fields on primary brain tumors in female C57BL/6 mice (Kharzi, submitted manuscript).

[The sensitivity of this mouse model for agents that cause brain cancer has not been established, and ionizing radiation did not affect brain tumor incidence.]

A study in which DMBA was used as an initiator was conducted in newborn male and female Swiss-Webster mice (Shen *et al.*, 1997). Each pup received a subcutaneous injection of 35 µg DMBA within 24 h of birth. Two weeks later, the mice were separated into either a sham-exposed group or a group exposed to a 1 mT, 50 Hz magnetic field. Exposure was continued for 3 h/d, 6 d per week for 16 weeks. The percentages of animals with thymic lymphomas and lymphomatous leukemia were 30% (50/165) of field-exposed and 30% (46/155) of sham-exposed mice. The authors reported no evidence for a promotional effect of a 1 mT, 50 Hz magnetic field on lymphoma/leukemia induced by DMBA in mice.

(b) Rats

A study of the progression of disease was conducted in Fischer rats with large granular lymphocytic leukemia cells (Anderson *et al.*, 1997; Sasser *et al.*, 1996). Spleen cells shown to be predominately with large granular lymphocytic leukemia cells were taken from diseased, aged Fischer 344 rats and transplanted into young male rats. The leukemia developed into full-blown disease within six to eight weeks, as indicated by enlarged palpable spleens and various hematological parameters. In the first study (Sasser *et al.*, 1996), 72 rats were randomly assigned to four treatment groups as follows: 1 mT, sham-exposure, ambient controls, and positive controls exposed to 5 Gy whole-body γ -irradiation (cobalt-60). At initiation of field or sham exposure, all rats were injected intraperitoneally with 2.2×10^6 fresh leukemia cells. Magnetic fields were present for 20 h/d seven d per week for approximately 18 weeks. An additional 18 rats per group (field- or sham-exposed) bled serially to evaluate hematological indicators of disease progression. In general, no significant or consistent differences were seen between rats exposed to magnetic fields and ambient-field controls, in either the size of palpated spleens or the hematological parameters evaluated for leukemia. The 1 mT, continuous 60 Hz field did not significantly alter the clinical progression of the disease.

In the second study (Anderson *et al.*, 1997), a similar protocol, exposure, and end-points were used. Leukemia cells were inoculated at 2.2×10^6 or 2.2×10^5 , and intermittent field presentation (3 min on, 3 min off) was added, with replication of the continuous field exposures. Again, no significant exposure-related differences were observed for continuous fields at either level of cell inoculum or for intermittent fields at the lower cell inoculum; however, with intermittent fields at the higher inoculum an apparent decrease in the latency to disease (from 60 to 45 days) was observed in comparison with the sham-exposed animals. The authors reported that, taken together, the results for both inoculae argue for a lack of effect of magnetic fields on the progression of leukemia in this model. There remains, however, the slight effect of intermittent exposure, particularly when in animals with a higher load of injected leukemia cells.

(c) *Transgenic animal models*

[Neither studies in which an initiating event such as γ -irradiation or a chemical carcinogen was used nor studies of progression of leukemia after injection of viable leukemic cells showed an effect of exposure to magnetic field at a variety of intensities. The absence of an increased incidence of leukemia/lymphoma in the long-term bioassay is consistent with these results.]

(c) *Transgenic animal models*

Pim mice, which carry the *pim-1* oncogene, are highly sensitive to *N*-ethyl-*N*-nitrosourea (ENU)-induced lymphoma. Groups of 30 male and female Pim mice were treated with ENU (25 mg/kg bw) and then exposed to 0 (sham exposure), 2 200, or 1000 μ T, 60 Hz

magnetic fields for 23 weeks. Histological evaluation revealed no differences in lymphoma incidence between field- and sham-exposed mice. In a second experiment, groups of 30 male and female TSG-p53 heterozygote transgenic mice were exposed to 0 (sham-exposure) or 1000 μT , 60 Hz magnetic fields for 23 weeks. There was no evidence of an effect of magnetic fields on the lymphoma incidence (McCormick *et al.*, 1998; Table 4.8). [The usefulness of transgenic mice for detecting environmental carcinogens has not been established. It was also noted that the p53 transgenic mice were evaluated at only one field intensity, and the low tumor incidence in the p53 controls suggest that the study may have been too short for this model.]

Table 4.8. Leukemia/lymphoma in transgenic mice exposed to 60 Hz magnetic fields

Strain	Sex	Sham	No. of affected mice ^a			
			2 μT	200 μT	1000 μT	1000 μT (I) ^b
Pim1	Male	15	14	13	7*	17
Pim1	Female	14	13	13	14	16
p53	Male	1	NT	NT	0	NT
p53	Female	1	NT	NT	2	NT

NT, not tested

^a Number of mice diagnosed with leukemia/lymphoma; 30 mice/group

^b Intermittent exposure for 1 h on, 1 h off during the 18.5-h exposure period

* $p < 0.05$ vs sham-exposed

Groups of approximately 100 E μ -Pim1 transgenic mice were exposed to 50 Hz magnetic fields at intensities of 0, 1, 100, or 1000 μT for up to 18 months (Harris *et al.*, 1998). Animals that died during the study were subjected to histological evaluation. No difference in lymphoma incidence was seen between field- and sham-exposed mice. The authors concluded that long-term exposure to 50 Hz magnetic fields had no tumorigenic effect in the lymphoma-prone mice. The authors assumed that the animals did not have leukemia.

[Transgenic mouse models have not been fully evaluated for their predictive value for testing carcinogens. The design is also unusual in that the ‘healthy’ animals (nearly 50% of the animals) were discarded at the end of the study without examination. It was further noted that during the in-life portion of the study more than 7% of the animals were autolysed and discarded without diagnoses.]

4.1.3 Summary

Two long-term bioassays demonstrated no carcinogenic response, and one showed an equivocal response at one tumor site in animals of one sex of one species. Within the limits of the experimental model of multistage mammary carcinogenesis, the results of the ensemble of experiments do not provide convincing evidence for a promoting effect of EMF on chemically induced mammary cancer. In another commonly investigated model,

skin carcinogenesis, exposure to magnetic fields had no effect. EMF did not promote leukemia or lymphoma in mice or rats in several studies.

In several long-term bioassays, no association was found between exposure to magnetic fields and brain cancer; however, the sensitivity of rodent models for assaying brain cancer has not been well established.

Most of the investigations carried out until now have followed the pattern of the traditional testing of chemical agents suspected to be carcinogenic. While additional traditional studies are fully justified and may produce useful results, it is conceivable that investigations of the role of the factors involved in the multistep, multifactorial carcinogenesis process (perhaps including EMF) may require different approaches than those used until now.

The overall conclusion of the Working Group is that most of the studies suggest a lack of carcinogenicity, and the few with borderline positive results are inadequate to conclude that exposure to magnetic fields at the magnitude and field configurations at which they were investigated increases the incidence of cancer in rodents.

There is inadequate evidence in experimental animals for carcinogenicity from exposure to extremely low frequency electromagnetic fields.

[This conclusion was supported by 19 members of the Working Group; there were 8 votes for 'lack' of carcinogenicity, 1 abstention and 1 absent.]

[There was a minority report written on this opinion; this report is in Appendix B]

Table 4.1 Results of long term chronic bioassays in rodents exposed to EMF

Reference	Species/Strain	No. of animals	EMF exposure	Time/other	Results reported by authors
(NTP, 1998b)	F344 rats B6C3F ₁ mice	100 males, 100 females/species/ group	2, 200, 1000 μ T continuously (60 Hz) & 1 mT intermittently (60 Hz, 1 hour on, 1 hour off)	2 years, GLP (18.5 h/d)	No increase in carcinogenesis (brain, mammary gland, or leukemia) in male or female rats or mice
(Mandeville <i>et al.</i> , 1997)	F344/N rats	50 females/group	2, 20, 200, 2000 μ T (60 Hz)	2 year, GLP (20 h/d)	No increase in carcinogenesis
(Yasui <i>et al.</i> , 1997)	F344 rats	48 females/group	0.5, 5 mT (50 Hz)	2 year chronic, (22.6 h/d)	No increase in carcinogenesis
(Margonato <i>et al.</i> , 1995)	Sprague-Dawley albino rats	256 males/group	5 μ T (50 Hz)	32 weeks (22 h/d)	No increase in carcinogenesis

GLP, good laboratory practice

Table 4.2 Assays of co-initiation and of promotion of: mammary cancer

Reference	Species / strain	No. of animals	Initiator	EMF exposure	Time / other	Results reported by authors
(Beniashvili <i>et al.</i> , 1991)	rats	50 females/group	MNU	20 μ T (50 Hz);	lifelong (0.5, 3 h/d)	Increase incidence, decreased latency of mammary tumors in rats exposed for 3 h/d; more malignant tumors
(Mevisse <i>et al.</i> , 1993)	Sprague- Dawley rats	18 females/group	DMBA	30 mT (50 Hz) (homogeneous field)	13 weeks (24 h/d)	Increase tumor number per animal (66 vs. 61%); not reproduced upon repeat
(Löscher <i>et al.</i> , 1994)	Sprague- Dawley rats	36 females/group	DMBA	0.3 - 1.0 μ T (50 Hz) (gradient field)	13 weeks (24 h/d)	No significant differences in histopathology; nocturnal melatonin significantly lower in exposed animals
(Löscher <i>et al.</i> , 1993)	Sprague- Dawley rats	99 females/group	DMBA	0.1 mT (50 Hz) (homogeneous field)	13 weeks (24 h/d)	50% increase in mammary tumor incidence (51% exposed vs. 34% in sham-exposed)
(Baum <i>et al.</i> , 1995)	Sprague- Dawley rats	99 females/group	DMBA	0.1 mT (50 Hz)	13 weeks (24 h/d)	No effect on incidence of mammary tumors; significant increase in malignant tumor size in exposed
(Mevisse <i>et al.</i> , 1996a)	Sprague- Dawley rats	99 females/group	DMBA	10 μ T (50 Hz) (homogeneous field)	13 weeks (24 h/d)	Negative (61% tumor incidence in sham vs. 66% in exposed)
(Mevisse <i>et al.</i> , 1996b)	Sprague- Dawley rats	99 females/group	DMBA	50, μ T (50 Hz) (homogeneous field)	13 weeks (24 h/d)	Significant increase in tumors in exposed animals (apparent dose-response reported)
(Mevisse <i>et al.</i> , 1998a)	Sprague-Dawley rats	99 females/group	DMBA	0.1 μ T (50 Hz) (homogeneous field)	13 weeks (24 h/d)	Significant increase in tumors in exposed animals; no change in tumor size
(NTP, 1998a)	Sprague- Dawley rats	100 females/group	DMBA	0.1- 0.5 mT (50 Hz) 0.1- 0.5 mT (50 Hz), 0.1 mT (60 Hz)	13 weeks (18.5 h/d) 26 weeks (18.5 h/d)	Negative (43% tumor incidence in sham vs. 48% in 0.1 mT exposed and 38% in 0.5 mT exposed) Negative (96% tumor incidence in sham vs 90% in 0.1 mT (50 Hz) exposed and 95% in 0.5 mT exposed)
(Ekström <i>et al.</i> , 1998)	Sprague- Dawley rats	60 females/group	DMBA	0.25 - 0.5 mT (50 Hz) (intermittent, 15 s, on/off)	25 weeks (19-21 h/d)	Negative (71% tumor incidence in sham vs. 70% in exposed; exposure 1 week after DMBA)

MNU, N- methyl - N - nitrosourea; DMBA, 7, 12-dimethylbenz [a] anthracene

Table 4.4 Studies of promotion and co-promotion of skin cancer

Reference	Species / strain	No. of animals	Initiator / promoter	EMF exposure	Time other	Results reported by authors
(McLean <i>et al.</i> , 1991)	SEN CAR mice	32 females/group	DMBA ± TPA (1 µg/week)	2 mT (60 Hz)	21 weeks (6h/d)	Negative at 22 weeks
(Stuchly <i>et al.</i> , 1992)	SEN CAR mice	48 females/group	DMBA/TPA (0.3 µg/week)	2 mT (60 Hz)	21 weeks (6 h/d)	Decreased tumor latency, increased tumor incidence
(McLean <i>et al.</i> , 1995)	SEN CAR mice	48 mice/group	DMBA/TPA (0.3 µg/week)	2 mT (60 Hz)	52 weeks (6 h/d)	Increased fraction with malignant tumors in exposed; non-significant increase in overall tumor incidence
(Rannug <i>et al.</i> , 1993a)	NMR/HAN mice	30 females/group	DMBA	50, 500 µT (50 Hz) (continuous field)	103 weeks (19-21 h/d)	Negative
(Rannug <i>et al.</i> , 1994)	SEN CAR mice	50 females/group	DMBA	50, 500 µT (50 Hz;) continuous or intermittent 15 s on/off	104 weeks (19-21 h/d)	Negative for continuous; dose trend of increased tumors/tumor-bearing animal in intermittently exposed
(Sasser <i>et al.</i> , 1998)	SEN CAR mice	100 females/group	DMBA/TPA	2 mT (60 Hz)	23 weeks (18.5 h/d)	Negative

DMBA, 7,12 dimethylbenz[a]anthracene; SEN CAR, SENsitive to CARcinogenesis; TPA, 12-O-tetradecanoyl phorbol 13-acetate

Table 4.5 Studies of promotion and co-promotion of liver cancer

Reference	Species / strain	No. of animals	Initiator / promoter	EMF exposure	Time / other	Results reported by authors
(Rannug <i>et al.</i> , 1993b)	Sprague-Dawley rats	10 males/group	NDEA	0.5, 5, 50, 500 μ T (50 Hz)	12 weeks (19 h/d)	Negative
(Rannug <i>et al.</i> , 1993c)	Sprague-Dawley rats	10 males/group	NDEA phenobarbital	0.5 and 500 μ T	13 weeks (19 h/d)	Exposed and a decrease in no. of foci. (0.5 mT), mean focus area and volume of foci

NDEA, N-nitrosodiethylamine

Table 4.6 Studies of promotion of: lymphoma/leukemia

Reference	Species / strain	No. of animals	Initiator / promoter	EMF exposure	Time / other	Results reported by authors
(Babbitt <i>et al.</i> , 1998)	C57Bl/6J mice	195-450 males or females/group	X-irradiation (0, 350, 475, 600 R)	1.4 mT circularly polar. 1 mT horizontal and vertical (60 Hz)	2 year chronic (18 h/d)	Negative
(Shen <i>et al.</i> , 1997)	Swiss-Webster mice	165 exposed 155 sham-exposed	DMBA within 24 h of birth	1 mT (50 Hz)	32 weeks (3 h/d, 6 d/week)	No difference in lymphoma/leukemia between groups; increased liver infiltration in exposed
(Sasser <i>et al.</i> , 1996)	Fischer 344 rats	72 males/group	Leukemic cells injected (2.2×10^7)	1 mT (60 Hz) continuous	18 weeks (20 h/d)	Negative
(Anderson <i>et al.</i> , 1997)	Fischer 344 rats	72 males/group	leukemic cells injected (2.2×10^7 or 2.2×10^6)	1 mT (60 Hz) continuous and intermittent	18 weeks continuous and intermittent	Negative for continuous, decrease in latency for intermittent exposure in 10^7 cell inoculum

4.2 Epidemiological studies of carcinogenicity in adults

Epidemiological studies are implemented to investigate the associations between health effects and exposure to a presumed disease agent. A well-designed and -conducted epidemiological study involves several steps. First, the population base is identified within which the relationship between the exposure of interest and the disease are to be investigated. Identification of the population base includes specifying the study population and the follow-up period during which disease status is to be assessed. Only subjects who are free of the disease of interest at the time of enrollment can be included in the study base. During the follow-up period, all new cases of the disease must be identified. In observational studies, exposure occurs through the natural course of events. In a cohort study, information on exposure is collected for the entire study base. In studies of rare diseases, a case-control design is used in which the exposure prevalence is investigated in all cases and in a random sample of disease-free individuals (controls) in the study base. It is crucial that the control sample accurately reflect the prevalence of exposure in the study base.

Inability to randomly assign exposures means that investigators must design their study such that the cases resemble the controls, except for exposure, in order to limit possible bias. Control selection bias is introduced if exposure is related to characteristics that would make persons more or less likely to be sampled, or, once sampled, to participate. In the Nordic countries, comprehensive national population registries can be used for selecting controls. All residents of each country are listed in these population registries, and participation rates are typically high, such that epidemiological studies of these populations are not compromised by control selection bias. In the USA, investigators often use random-digit dialing methods to identify controls, because no comprehensive registries are available. Random-digit dialing leads to difficulty in identifying, contacting, and recruiting controls of low socioeconomic status. The impact and possible bias introduced by enrolling fewer controls of low socioeconomic status is described by Poole and Trichopoulos (Poole & Trichopoulos, 1991).

Case selection bias may occur in studies that are based on mortality records (death certificates). Studies of mortality rather than incidence are subject to bias if the survival rate of the exposed and unexposed subjects differs. This may occur if, for example, the exposure is related to socioeconomic status, and different socioeconomic groups have different survival rates for the studied disease. In addition, for diseases that are easily cured or allow patients to live with the disease for a long time and die of some other cause, use of death certificates leads to severe limitations for the identification of cases. Apart from limiting the power of the study (a severe limitation in studies of rare diseases), there is a large potential for selection bias in the identification of cases.

The inability to randomly assign exposures also introduces the possibility of confounding. Confounding is a mixing of effects between the exposure of interest and extraneous risk factors; it is not a product of the design or conduct of the study but

results from an association among risk factors (Rothman, 1986). In order to be a confounder, a risk factor must be related to both the studied exposure and the disease. For example, consider a study to determine whether alcohol drinkers have a greater incidence of oral cancer than abstainers. Smoking is related to the incidence of oral cancer; it is also associated with alcohol consumption, and there is a greater proportion of smokers among alcohol drinkers than among nondrinkers. Since smoking increases the incidence of oral cancer, alcohol drinkers will have a greater incidence than nondrinkers, quite apart from any effect of alcohol drinking itself but simply as a consequence of the greater prevalence of smoking among alcohol drinkers. Thus, the apparent effect of alcohol drinking is distorted by the effect of smoking, and smoking is thus a confounding factor. Confounding can produce bias in either direction, artificially increasing or decreasing relative risk estimates, depending on the direction of the association between the exposure, the disease, and the confounder. When identified, confounding can be controlled through statistical methods.

Another limitation of observational epidemiological studies is that exposure occurs through the natural course of events rather than being assigned and controlled for by the investigator. Thus, determination of exposure is subject to inaccuracies, i.e. exposure misclassification. Exposure misclassification may distort measures of association seen in the study and may occur at several levels. For example, in occupational epidemiological studies, errors may occur in assigning job titles. Measurement errors that are dependent on either disease or exposure are termed 'differential misclassification', i.e. the exposure assignment differs for diseased and non-diseased subjects or disease classification differs for exposed and unexposed persons. Information on exposure can be obtained either prospectively (before the disease has occurred) or retrospectively (after the occurrence of the disease). In the former situation, there is no potential for differential misclassification of the exposure. In the latter situation, the recall of exposures that occurred before diagnosis may be influenced by the disease, if the patient's recollection of the exposure is required for its assessment.

In this report, the Working Group critically reviewed observational epidemiological studies of exposure to EMF that were of sufficient quality and reliability in respect of the aforementioned limitations.

4.2.1 Occupational exposure

Epidemiological study of diseases in relation to occupational exposure to EMF has a long history. Reports of various health problems in high-voltage substations in the former USSR initially focused attention on ELF electric fields (Asanova & Rakov, 1966). After Wertheimer and Leeper (Wertheimer & Leeper, 1979) suggested that occupational exposure to magnetic fields might be carcinogenic, Milham (Milham, 1982) examined the association between electrical jobs and leukemia risk. The significant association reported in his first study led to over 100 epidemiological investigations of workplace exposure to

EMF and various diseases. The early studies were based on job titles assumed to entail exposure but lacked measurement-based validation.

After a number of these studies showed associations between cancer and electrical work, epidemiologists in several countries undertook studies with personal magnetic field monitors. All of the studies included measurements of exposure to ELF magnetic fields, and in some studies exposures to ELF electric fields and pulsed EMF (PEMF) at higher frequencies were studied. Accompanying the improvements in assessment of exposure to EMF, these newer studies had more reliable epidemiological designs: cohort and case-control. Since the literature is so voluminous, this review covers only the studies that meet the criteria for exposure assessment listed in Table 4.9.

Table 4.9. Minimal exposure assessment required for a study to be included in this review

Disease	Exposure assessment
All cancers	
Leukemia and brain cancer	Full-shift monitoring*
Breast cancer	Job titles of electrical workers**
Other cancers	Full-shift monitoring
Central nervous system tumors from parental exposure	Job titles of electrical workers

* Worker wears personal EMF monitor for a complete work shift

** Includes one or more studies with full-shift measurements

4.2.1.1 All cancers combined

Tynes *et al.* (Tynes *et al.*, 1992) studied a cohort of 37 945 working-age men in Norway who were identified from the Norwegian Central Bureau of Statistics as having held jobs in which they could be exposed to EMF. This cohort was linked the Cancer Registry of Norway to identify 3806 incident cancer cases that occurred between 1961 and 1985. High exposure to EMF was assumed to occur in 12 electrical jobs (Table 2.4). Standardized incidence ratios (SIR) for the electrical workers were calculated with the working population as reference and adjusting for age and calendar period. The SIR was 1.1 (95% CI, 1.0–1.1; see Table 4.10) [No field measurements were made in this study.]

Sahl *et al.* (Sahl *et al.*, 1993) studied a cohort of utility workers in the USA comprising the 36 221 permanent employees who had worked for Southern California Edison (Edison) for at least one year between 1960 and 1988. Vital status was ascertained through the National Death Index, Social Security Administration, and the California Automated Mortality Linkage System. Workers were classified as ‘electric’ or ‘non-electric’ workers on the basis of their longest-held occupation at Edison. Electrical workers were defined as ‘craft occupations who work near energized equipment’; non-electrical workers included all other non-managerial, non-electrical jobs. The age-adjusted relative risk (RR) for electrical occupations was calculated for all cancers combined (261) and was not significant (1.1; 95% CI, 0.92–1.3). [The limitations of the study are its relatively small

sample size and potentially incomplete follow-up of the small percentage of former employees who left California before 1979.]

Savitz and Loomis (Savitz & Loomis, 1995) conducted a retrospective cohort mortality study of 138 905 men who had been full-time permanent employees of one of five participating electric utility companies for at least six months during the period 1950-86. A complete work history was assembled from company records for each worker. Men who had worked for their entire career in a utility's nuclear division were excluded from the cohort. Vital status to 1988 was determined for more than 99% of the men by searching Social Security Administration, Death Benefit Records, Health Care Financing Administration Records, and Drivers License records. Death certificates were obtained for 97% of the deceased. Subjects lost to follow-up were considered lost at the date of the last record showing they were alive. Exposures, measured with an AMEX-3D, were assessed for 2842 full shifts for a random sample of workers in 28 occupational categories. Exposure to potential confounding factors was evaluated by asking industrial hygienists and expert panels to assess exposures to a number of known or suspected carcinogens, including solvents, polychlorinated biphenyls, sunlight, and wood preservatives. In all analyses, the investigators adjusted for age, calendar year, race, social class, and work status (active versus inactive).

For total cancers (4833), a slight significant increase in risk was observed in the higher exposure categories (Table 4.10), adjusted for age, calendar year, race, social class, work status, and exposure to polychlorinated biphenyls and solvents. [The main limitation is the reliance on death certificates for diagnosis and the use of a magnetic field meter that could record only TWA exposures and not other metrics.]

Thériault *et al.* (Thériault *et al.*, 1994) examined cancer occurrence in relation to exposure to magnetic fields among workers at three large electric utility companies: Hydro Québec and Ontario Hydro in Canada, and Electricité de France (EDF). A nested case-control approach within these three cohorts was used to study all cancers combined among the male population of the three companies (total: 223 000; EDF, 170 000; Ontario Hydro, 31 543; Hydro Québec, 21 749). The cohorts at the two Canadian companies included both active and retired workers employed between 1970 and 1988, although the Ontario Hydro cohort included only retired workers from 1970-73. The EDF cohort included only actively employed workers and covered the period 1978-89. There were 4151 new cases of cancer in the combined cohort between 1970 and 1989. At Ontario Hydro, cases were ascertained through the Ontario Cancer Registry; at Hydro Québec, ascertainment was made through the company's medical files, the Québec Tumor Registry and death certificates; at EDF, only cancers in active workers were identified through the company's specific epidemiological data base of sickness benefits.

To estimate cumulative exposure to magnetic fields, the authors combined the job history of each case and control with TWA exposure to magnetic fields estimated from a JEM for each job (see section 2.4). The JEM for each utility was based on an extensive program of measurements among its employees. For this study, 2066 workers in the three utilities

wore a Positron exposure to EMF meter for a five-day work week. The Positron measures ELF EMF and was also thought to measure PEMF (see section 2.3.1). Only the data on ELF magnetic field were used in this study; the other fields were analyzed in subsequent publications. In the protocol used by Hydro Québec and EDF, workers were selected for measurements in job categories determined *a priori* on the basis of EMF sources, and the sample sizes were representative of the utility's worker distribution among those categories. In Ontario Hydro's measurement protocol, the sample of workers was representative of the job titles and work locations of the cases and controls.

Potential confounders examined included smoking and exposure to ionizing radiation, chemical agents, and sunlight. Data on smoking were available from medical histories for some subjects at Hydro Québec but not for the other two companies. Information on cumulative individual occupational dose of ionizing radiation was obtained from company radiation surveillance records. Occupational hygienists at each of the companies then developed JEMs for chemicals and sunlight. In an approach similar to that used to estimate exposure to EMF, each individual's job history was combined with the JEM to obtain a cumulative exposure estimate for each chemical agent. When available, data from exposure monitoring were used; otherwise, exposure to confounders was assessed by expert judgment. No association was found between the risk for all cancers combined and cumulative exposure to ELF magnetic fields (Table 4.10), overall (OR, 1.0; 95% CI, 0.91–1.1 for exposures \geq median compared with $<$ median) or in any of the cohorts.

Guénel *et al.* (Guénel *et al.*, 1996) reanalyzed the data from this cohort study with information on exposure to electric fields. There was a marginally significant decrease in risk for all cancers combined (Table 4.10). [As a person's exposure to electric fields depends on posture, grounding, and nearby objects, accurate measurement requires more sophisticated instruments and measurement protocols than those used in this and other epidemiological studies.]

4.2.1.2 Leukemia

Floderus *et al.* (Floderus *et al.*, 1993) conducted a large population based case-control study of occupational exposure to magnetic fields and leukemia and brain tumors. The study base was all men (20–64 years old in 1980) who were alive at the time of investigation and living in Sweden's more densely-populated counties, representing about half the male population of the country. Cases of leukemia (426) and brain cancer (424) that occurred during 1983-87 were identified from the national cancer registry. Of the leukemia patients, 325 were contacted, and 250 agreed to participate. Two controls, matched on age and alive at the time of investigation were selected for each case from the 1980 census. Full job histories were obtained from responses to questionnaires mailed to the subjects or proxies (64% of the cases required proxies). The response rates were 77% for leukemia patients and 72% for controls.

Exposure to magnetic fields was determined from JEMs for the longest-held job during the 10 years prior to diagnosis of the case, and 1015 full-shift measurements were conducted at the subject's job or a similar one. Because measurements were not available for everyone, all subjects were assigned exposure based on the averages for all measurements for their job. JEMs were constructed in 169 occupational categories for the TWA, median, standard deviation (SD), and time exposed to $> 0.2 \mu\text{T}$, computed from these one-day measurements. Exposures to potential confounders were evaluated from workplace interviews.

Age-adjusted odds ratios were calculated from an unmatched analysis of all controls for both leukemia and brain cancer cases. The relative risks for leukemia were significantly associated with the estimated TWA exposure to magnetic fields in the job held longest during the 10 years before diagnosis (Table 4.11). Although no formal testing of the trend is reported, the relative risks increased with quartiles of exposure, reaching significance for the highest exposure. For all leukemias combined, the highest risk was seen in the group with TWA exposure $> 0.41 \mu\text{T}$ (OR = 1.7; 95% CI, 1.0–2.7). Analysis by leukemia subtype revealed no increased relative risk for acute myeloid leukemia (AML) but an increase in the risk for chronic lymphocytic leukemia (CLL) with greater exposure. The odds ratios for CLL in the highest TWA exposure categories were even higher and statistically significant (TWA $\geq 0.41 \mu\text{T}$: OR = 3.7; 95% CI, 1.8–7.7). The relative risks for CLL in the highest category of exposure to magnetic fields increased somewhat when adjusted for exposure to benzene (OR = 4.1; 95% CI, 2.0–8.5), solvents (4.2; 1.9–9.4), and ionizing radiation (4.7; 2.2–9.7). Because the authors were concerned about a possible information bias due to the large number of proxy respondents among the cases, they also carried out analyses based on average daily exposure estimated from occupational information from the 1980 census. Although the odds ratios were slightly reduced, increases were observed with increasing exposure category: 1.0 (0.5–2.1), 1.9 (1.0–3.6), 2.3 (1.2–4.3), and 2.6 (1.3–5.4), respectively, for exposure to 0.16–0.19, 0.20–0.28, ≥ 0.29 , and $\geq 0.41 \mu\text{T}$. Concern about a possible bias linked to the high non-response rate was addressed by repeating the analyses with the occupation stated in the census for the entire population of cases and controls, including non-respondents. The odds ratios were further reduced, and, although increased, were no longer statistically significant: 0.9 (0.5–1.6), 1.6 (0.9–2.7), 1.6 (0.9–2.7), and 1.7 (0.9–3.3). These results are due to the larger proportion of unexposed subjects among non-respondents and indicate the presence of a differential bias.

[This study is unique in assessing EMF cancer risks in the general working population. In industry, magnetic fields are likely to be more diverse in their characteristics than the single-frequency fields usually found around electric power facilities. Another unique feature of this study is the effort to measure magnetic fields at the same job and workplace (or a close proxy) where the subjects had worked before their cancer diagnosis. For logistical reasons, the measurement protocol was changed during the course of the study, resulting in more measurements in case work places than in those of controls. Exposures were not based on an entire work history. The results of analyses during two different jobs, however, are similar. The analyses based on census occupational

information, including non-responders, indicate the presence of a bias which could lead to an overestimate of risk among respondents.] (Bowman & Methner, 1998)

Matanoski *et al.* (Matanoski *et al.*, 1993) conducted a case–control study of mortality from leukemia nested in a cohort of 1 300 000 active workers and 200 000 retirees of the American Telephone & Telegraph Co. (AT&T). Cases of primary leukemia (except CLL) were determined from AT&T’s mortality records for 1975–80. To be included in the study, cases had to be in white males who had worked at AT&T for at least two years. For each case, three controls without leukemia were matched on retirement status at the age of the patient’s death, gender, date of birth, and date of hire. Sporadic data on the subjects’ employment histories were obtained from AT&T data tapes and from records of some participating regional phone companies which were separated from AT&T after the study period. Although 124 matched sets of cases and controls were identified, some analyses were based on smaller numbers since records specifying the last job could be obtained for only 75 sets of cases and controls (60%), and complete job histories were found for 35 sets (28%).

Full-shift measurements of magnetic fields were made with an EMDEX-C monitor from samples taken on 15-61 present-day workers in four categories of telephone line jobs (cable splicers, installers, central office technicians, and supervisors) and a sample of non-line jobs. For central office technicians, measurements were taken at switching facilities where either solid-state techniques or electromechanical relay crossbars were used; the latter began to be replaced during 1975–80. The older relay switching results in higher exposure than the new solid-state technique. The data on magnetic fields were used to construct JEMs with the TWA and peak exposures averaged for each job category. Odds ratios were calculated by conditional logistic regression for the last job held (relative to non-line workers) and for cumulative exposure (relative to values below the median). To assess exposure–response relationships, one-tailed tests for positive trend were performed on odds ratios for quartiles of cumulative exposure. For cumulative TWA exposures, the relative risk was elevated but not significant (OR = 2.5; 95% CI, 0.7-8.6), and there was no exposure–response relationship (p for trend = 0.27; based upon means of logs of exposures in each quartile). A marginally significant exposure–response relationship was found among workers using the older style relay switching (p for trend = 0.06). [A large fraction of subjects were excluded because of missing job records, which is a potential source of bias and resulted in small sample size.]

Sahl *et al.* (Sahl *et al.*, 1993) conducted a nested case–control study in the cohort of employees at Southern California Edison (Edison) described in section 4.2.1.1, comprising 44 cases of leukemia identified from death certificates. Ten controls were selected for each case, frequency matched on age, gender, and race. For the case–control analysis, exposure to magnetic fields was assessed with a JEM based on 776 person days of exposure measurements made with an EMDEX II monitor among present-day Edison employees in 35 occupational categories. Several exposure metrics were computed from the measurements, including the arithmetic mean, geometric mean, 95th and 99th percentiles, and fraction of time exposed to > 1.0 or $5.0 \mu\text{T}$. An exposure score was obtained for each

subject by summing the product of the exposure metric from the JEM times years of employment. The odds ratios for leukemia in relation to the various exposure scores were close to 1 (Table 4.11) Further analyses at various time windows of exposure and latency did not reveal positive associations. [The limitations are discussed in section 4.2.1.1. They also include lack of information on potentially important confounding exposures to chemicals, ionizing radiation, and smoking and a reliance on death certificates for diagnosis. The failure to track the deaths of subjects outside California could also have introduced some slight negative bias.]

London *et al.* (London *et al.*, 1994) performed a case–control study of leukemia which focused on nine electrical occupations originally suggested by Milham (Milham, 1985); see Table 2.4. Cases were all 2355 working men, aged 20–64, in whom leukemia had been diagnosed in Los Angeles County during 1972–90 and whose last occupation was entered in the County’s cancer registry. Of these, 121 were electrical workers. The controls were 67 212 men from the same study base in whom other tumors, except of the central nervous system (CNS), had been diagnosed. They included 2665 electrical workers. Exposure to magnetic fields was estimated with a variety of meters from full-shift measurements taken on 278 Los Angeles workers in electric occupations and a random sample of 105 men in 18 other occupations. TWA magnetic fields were calculated for 24 different tasks with exposure to EMF. The proportion of time that electric workers usually spent at those tasks was estimated by interviews with expert panels at each workplace. From these data, task-weighted estimates of mean and standard deviation were calculated for each electrical occupation, for all electric occupations combined, and for all non-electrical occupations combined. Exposure to potential leukemogens in these occupations was also assessed by the expert panels.

Odds ratios were calculated by logistic regression adjusted for age. Men in electrical occupations as a whole had significantly greater exposure to magnetic fields than the sample of those in non-electrical jobs (mean TWA = $0.96 \pm 0.13 \mu\text{T}$ vs. $0.17 \pm 0.01 \mu\text{T}$), except for electrical engineers. A weak trend in risk for leukemia of marginal significance was observed with exposure to the TWA magnetic field (OR increase per $1 \mu\text{T} = 1.2$; 95% CI, 1.0–1.5). The trend with TWA was concentrated in the risk for chronic myelogenous leukemia (significant) and acute nonlymphocytic leukemia (nonsignificant); no increase in relative risk was seen for CLL. The limited information on exposure to confounders did not appear to explain the risk patterns. [The following limitations were identified: reliance on the single job specified in the registry to estimate exposure and a study design based on the proportion of leukemia among all cancers.]

Kheifets *et al.* (Kheifets *et al.*, 1997b) used the exposure measurements of London *et al.* (London *et al.*, 1994) to assess the risks for leukemia associate with exposure to ELF electric fields. Some of the EMF monitors also had electric field sensors, so that exposure to electric fields was known for 28% of the Los Angeles workers monitored in the original study. Although no measurements were taken on power line workers in Los Angeles, they were assigned to have high exposures ($> 20 \text{ V/m}$) on the basis of measurements done elsewhere. The authors noted additional difficulties in assessing exposure to electric fields,

in particular that a person's exposure varies with posture and grounding. [The fraction of workers with the electric field sensor was 14–93% across occupations, which is a large potential source of bias.]

In their study of three large electric utility companies, Thériault *et al.* (Thériault *et al.*, 1994) carried out a nested case–control study of leukemia. No significant association was found between cumulative exposure to magnetic fields and the risk for leukemia as a whole. In analyses of specific leukemia subtypes, only the risk for acute non-lymphocytic leukemia was found to be related to exposure to magnetic fields (OR = 2.4; 95% CI, 1.1–5.4) among workers with TWA exposures above the median compared to those below the median. When only AML was considered, the odds ratio among the half of workers with higher exposures increased to 3.2 (95% CI, 1.2–8.3). No significant exposure–response relationship was observed. The association with magnetic fields greater than or equal to the median was strongest for exposures received 20 or more years previously (OR = 4.6; 95% CI, 0.22–94), based on seven exposed cases. For other leukemia subtypes, no significant associations were reported. When analyses for all leukemias were restricted to individual cohorts, a significant association was observed between cumulative exposure above the median in Ontario Hydro (OR = 3.1; 95% CI, 1.1–9.7) but not in the other cohorts (Hydro Québec, OR = 0.29; 95% CI, 0.04–1.8; EDF, OR = 1.4; 95% CI, 0.61–3.1). The association was due mainly to AML. [The cohorts were defined and followed up differently: the EDF cohort included only active workers, while the Ontario Hydro cohort included only retirees for the first three years of the study. The levels of exposure were notably lower in the EDF cohort, probably due to the inclusion of gas workers. The JEMs were derived differently for each cohort, which may affect the interpretation of the results for the combined cohorts. The small numbers of cases by leukemia subtypes make interpretation of these results difficult.]

Guénel *et al.* (Guénel *et al.*, 1996) analyzed exposure to ELF electric fields in the EDF cohort and found no association with leukemia risk (OR = 0.4; 95% CI, 0.13–1.2). [See section 4.2.1.1 for comments on the limitations of this study and that of Thériault *et al.*]

Miller *et al.* (Miller *et al.*, 1996) re-analyzed the data on the Ontario Hydro cohort for exposure to both ELF electric and magnetic fields. An association with increasing exposure to electric fields was reported for all leukemias and leukemia subtypes; an increase was also seen in combination with magnetic fields (see Table 4.11). The JEMs at Ontario Hydro and the other two utilities were different, as noted above. Miller *et al.* found an association when exposures were derived from the JEM of the Ontario Hydro protocol, which disappeared with the JEM derived from the same measurements with the protocol used at the other two utilities. [The large 95% confidence intervals on the odds ratios prevent interpretation of these results.]

In their retrospective cohort study of exposure to magnetic fields and cancer in utility workers (described in section 4.2.1.1), Savitz and Loomis (Savitz & Loomis, 1995) identified 164 deaths from leukemia. No association was observed between leukemia risk and increasing cumulative exposure to magnetic fields (Table 4.11). Analysis by subtype

showed no association, although a nonsignificantly increased risk for AML was seen (based on five cases) in the highest exposure category ($\geq 4.3 \mu\text{T}\cdot\text{year}$). [Reliance on death certificates limits diagnoses, particularly for leukemia subtypes and cancers with long survival such as CLL; furthermore, the magnetic field meter used could record only TWA exposures and not other metrics. See section 4.2.1.1 for other comments on the limitations of this study.]

In a population-based case–control study, Feychting *et al.* (Feychting *et al.*, 1997) examined leukemia risk in relation to occupational and residential magnetic fields. They estimated occupational exposure to magnetic fields from information from census data on the last job held before cancer diagnosis and from the JEM constructed by Floderus *et al.* (Floderus *et al.*, 1996) in another study in Sweden. When analyses were restricted to subjects with little or no residential exposure, nonsignificant increases in the risk for leukemia as a whole and for AML and CLL were observed for occupational TWA exposure $\geq 0.2 \mu\text{T}$. The odds ratio for AML was greater for subjects with both residential and occupational exposure, based on three exposed cases (Table 4.11). Adjustment for possible confounding by motor fuel or exhaust, benzene, oil products, and welding fumes reported to interviewers did not change these associations. [The limitations are use of an exposure assessment based on a JEM for another population of working males and the large percentage of missing information on occupation, particularly for women, and the small numbers of subjects in the analysis by subtype and by joint occupational and residential exposures. See also section 4.2.2.1 for comments on the limitations on the residential study.]

Johansen & Olsen (Johansen & Olsen, 1998) conducted a retrospective cohort mortality study of electric utility workers in Denmark. The cohort consisted of 32 006 men and women who had been employed for at least three months at any of the 99 electric utilities in Denmark. Their employment history was obtained from utility records going back to 1909. Vital status was obtained from the Central Population Register and the National Death Certificate files for 1968–93, and cancer incidence was obtained from the Cancer Registry over the same period. A JEM was constructed by a panel of utility engineers who used 127 magnetic field measurements taken earlier (Skotte, 1994) to assign a TWA magnetic field exposure category (background, low, high, or unknown) to 475 combinations of job titles and work areas. Each subject was assigned the magnetic field exposure at their first job because $< 1\%$ of the employees had changed occupations within a utility, according to the company records. The SIRs for leukemia in men were calculated for different exposure with respect to the Danish male population, with adjustment for age, gender, and calendar year. No association between level of exposure to magnetic fields and leukemia risk was observed (Table 4.11). [The measurement database is far less comprehensive than those of most other studies, which had access to full-shift measurements.]

4.2.1.3 Brain cancer

In their large case–control study of occupational magnetic fields, Floderus *et al.* (Floderus *et al.*, 1993) also studied 346 cases of brain tumor (see section 4.2.1.2) that occurred during 1983–87, which were identified from the National Cancer Registry. The response rate to the questionnaire was 75% for cases, resulting in 261 cases for analysis. A weak association with TWA exposure to magnetic fields for the job held longest during the 10 years before diagnosis (Table 4.12) was observed, with no evidence of a trend. A significant increase was seen in an intermediate median exposure category (median ≥ 0.17 μT : OR = 1.5; 95% CI, 1.1–2.0). [See section 4.2.1.2 for comments on the limitations of this study.]

Sahl *et al.* (Sahl *et al.*, 1993) also considered brain cancer in their case–control study nested in the cohort of employees at Southern California Edison (see section 4.2.1.2). The analyses included 32 deaths from brain cancer. The odds ratios by cumulative exposure category were close to 1.0. Further analyses at various time windows of exposure and latency did not reveal any association. [See section 4.2.1.2 for comments on the limitations of the study.]

Thériault *et al.* (Thériault *et al.*, 1994) also examined the risk for brain cancer in their case–control study nested within a cohort of workers at three large electric utility companies (see section 4.2.1.1). In all, 250 cases of brain cancer were included in the study. A non-significant increase in risk of brain cancers as a whole was observed for workers with cumulative exposure to magnetic fields greater than the median (3.15 μT -years: OR, 2.0; 95% CI, 0.98–3.9) and the 90th percentile (15.7 μT -years: OR, 2.1; 95% CI, 0.80–5.7; see Table 4.12). A significantly increased risk was seen for astrocytoma among workers in the 90th percentile of cumulative exposure, based on five exposed cases. This association greatly diminished, however, when exact conditional logistic analyses were used [the appropriate method for analyzing data when such small numbers of cases are observed]. The analyses showed no significant differences across cohorts. [See section 4.2.1.2 for comments on the limitations of this study.]

In their re-analyses of the EDF cohort, Guénel *et al.* (Guénel *et al.*, 1996), found an increased risk for brain tumors (based on 69 cases) among utility workers exposed to electric fields. The increase was significant in the group that had exposure to electric fields in the 90th percentile of the exposure distribution (OR, 3.1; 95% CI, 1.1–8.7). The association remained significant after adjustment for confounding exposures (including magnetic fields) and was strongest in workers with ≥ 25 years' employment. [See section 4.2.1.2 for comments about the limitations of this study.]

In their reanalyses of the Ontario Hydro cohort (see section 4.2.1.2), Miller *et al.* (Miller *et al.*, 1996) also considered 69 cases of brain cancer. No association was seen with exposure to electric fields, based on two exposed cases in the 172–344 V/m-year category

and three in the ≥ 345 V/m-year category. [See section 4.2.1.1. for comments on the limitations of this study.]

In their retrospective cohort study of magnetic fields and cancer in utility workers (described in section 4.2.1.1), Savitz and Loomis (Savitz & Loomis, 1995) estimated exposure to magnetic fields for 144 workers who had died from malignant neoplasms of the brain and nervous system. An increased risk was seen in all exposure categories, which was statistically significant only in the highest category (≥ 4.3 μT : RR = 2.3; 95% CI, 1.2–4.6). The RR per μT -year was 1.1 (95% CI, 1.0-1.1). The association was slightly greater for cumulative exposures received 2–10 years previously (RR per μT = 1.9; 95% CI, 1.3-2.8). [See section 4.2.1.1 for comments on the limitations of this study.]

Feychting *et al.* (Feychting *et al.*, 1997) also considered brain cancer in their case–control study of cancer and occupational and residential exposure to magnetic fields in Sweden (see section 4.2.1.2). They identified 223 cases of central nervous system tumors from the Swedish Cancer Registry. No association was seen between CNS tumors and occupational exposure to magnetic fields among people with little or no residential exposure. Among those with both residential and occupational exposures ≥ 0.2 μT , no association was seen for CNS tumors as a whole, but a non-significant increase (OR, 2.2; 95% CI, 0.6–8.5) was reported for astrocytomas grades III and IV, based on three exposed cases. [See section 4.2.1.2 for comments on the limitations of this study].

Harrington *et al.* (Harrington *et al.*, 1997) conducted a case–control study of death from brain cancer nested in a cohort of 84 018 male and female electric utility workers who had been employed for at least six months between 1972 and 1984 at the Central Electricity Generating Board in the United Kingdom. The cohort was defined from computerized employment records, which started at different times over the period 1972–79 in various regions of England and Wales. Deaths from brain cancer were identified from death certificates, and 112 diagnoses of primary brain cancer were verified through the National Cancer Registry. Six controls per case were chosen from the cohort, matched on gender, who were alive at the time of death of the case and closest in age to the case. Workers' computerized job histories were coded blindly in terms of 11 job groups by two engineers with long experience in the industry. Exposure in different jobs and locations was assessed from measured exposures from a survey of 258 staff in the British electricity supply industry (Merchant *et al.*, 1994), in which both IREQ and Positron meters were used. In each job for which measurements were made, exposure was estimated as the TWA and the time-weighted geometric mean of the measurements made in this job. Various measures of the exposure of the cases and controls were calculated by combining job classifications with employment records (when available) and the estimated exposure in the relevant job. Exposure estimates could not be made for 86 subjects (18 cases and 68 controls) because of insufficient employment history. Information on 24 potential workplace carcinogens and neurotoxic agents was obtained from a JEM generated for this study. Statistical analyses were performed by conditional logistic regression. No association was observed between brain cancer and cumulative exposure to magnetic fields (measured either as TWA or time-weighted geometric mean) over the total career or over

the five years before death. A significant increase in risk was, however, observed among people whose exposure was not classifiable owing to insufficient employment history. No association between exposure to any of the 24 potential confounders and brain cancer was observed. [The limitations in the exposure assessment resulted in no exposure estimates for 16% of cases and 10% of controls.]

Johansen and Olsen (Johansen & Olsen, 1998) also considered brain cancer in their retrospective cohort mortality study of electric utility workers in Denmark (see section 4.2.1.2). No association was seen between death from brain cancer (72 cases) and exposure to magnetic fields (see Table 4.12). [See section 4.2.1.2 for comments on the limitations of the study.]

4.2.1.4 Breast cancer

The studies described in this section are summarized in Table 4.13 and 4.14.

(a) Men

Matanoski *et al.* (Matanoski *et al.*, 1991) first reported an excess of male breast cancer, based on two cases among central office technicians in a cohort of telephone employees. The peak exposure to magnetic fields of the technicians was a significant risk factor in the study of leukemia in telephone workers (Matanoski *et al.*, 1993). It was later reported that these technicians were probably exposed to ionizing radiation from radium gas tubes which were sometimes carried in their shirt pockets, a clear confounder (Malkin *et al.*, 1994). Nonetheless, this study provided the first anecdotal evidence for a risk for breast cancer and generated interest in further studies. In another brief communication, Loomis *et al.* (Loomis, 1992) reported an excess of breast cancer deaths among men under 65, based on a small number of cases.

Demers *et al.* (Demers *et al.*, 1991) assessed exposure to EMF for the men in a population-based case-control study of epithelial breast cancer (Jauchem *et al.*, 1992). The cases were determined from five years of records at cancer registries in six states and four metropolitan areas in the USA. Controls matched on age were selected by random-digit dialing for younger subjects and from Medicare records for those over 65. An interviewer asked about the subject's two longest-held occupation and possible risk factors for breast cancer. A subject was considered to have been exposed to EMF if his longest-held job was in one of five groups (Table 2.4). All exposed men had a twofold increase in relative risk, which increased in the electric utility trades (OR = 6.0; 95% CI, 1.7-21). Adjustment for known risk factors for breast cancer did not change these estimates appreciably. The relative risks were further elevated in subjects who were first exposed before the age of 30 and continued to be exposed for at least 30 years before cancer diagnosis. [This finding confirms the hypothesis that exposure to EMF is an early-stage carcinogen.] The study is the largest to look at male breast cancer and could therefore assess the timing of exposure to EMF and possible confounders, both of which

supported the association. [The job titles used as a surrogate for exposure to EMF were not validated by field measurements in the study population. In addition, the refusal rate was substantial, especially among controls, and the occupational histories were limited to jobs held the longest.]

Tynes *et al.* (Tynes *et al.*, 1992) studied a cohort of working-age men in Norway by linking census data on work histories to cancer registry data covering a 25-year period. Exposure to EMF was attributed for a list of 13 electrical job titles (Table 2.4). The SIRs for the electrical workers were calculated from the expected numbers of cancers for the entire cohort. The relative risks for male breast cancer were significantly elevated, being highest for men with jobs in electrical transport (only four cases), although the exposure to EMF is generally below the power frequency (e.g. 16.7 Hz for electric railways and DC magnetic fields for tram operators in the three largest Norwegian cities). [The job titles used as a surrogate for exposure to EMF were not validated by field measurements in the study population, and no information on potential confounders was available.]

Guénel *et al.* (Guénel *et al.*, 1993) conducted a population-based study of working men and women in Denmark, whose cancer incidence was examined from 18 years of data from the national registry. To estimate exposure to EMF, 3932 combinations of occupational and industrial categories were assigned by expert judgment to four exposure categories (none, intermittent ELF, continuous ELF, and other EMF frequencies). The highest exposure category was ELF magnetic fields continuously above 0.3 μT , which were attributed to 20 industry–job combinations (Table 2.4). Sex-specific cancer risks are calculated relative to the entire cohort of economically active subjects and are effectively SIRs. Guénel *et al.* reported relative risks for male and female breast cancer, neither of which were significantly elevated for either intermittent or continuous exposure to ELF EMF (see Table 4.13). The occupations considered to imply continuous exposure to ELF magnetic fields is unusual, as it includes jobs such as female shop assistants in the dairy products and bread industries and omits electric line workers, power station operators, and welders, who are combined with other metal workers in the Danish job classification system. The authors noted that these possible misclassifications would tend to lower the risk estimates. [The job titles used as a surrogate for exposure to EMF were not validated by field measurements in the study population, and no information on potential confounders was available.]

Rosenbaum *et al.* (Rosenbaum *et al.*, 1994) conducted a case–control study of male breast cancer in New York State. The cases were all 71 cases of histologically confirmed primary breast cancer in men from eight counties in western New York state reported to the New York State Tumor Registry between 1979 and 1988. Controls were 256 men from the same eight counties who participated in the Prevention-Detection Clinic, a voluntary cancer screening program; they were cancer-free and frequency matched to the cases by race, year of diagnosis (screening for the controls), and age. The ‘usual occupation’ was taken from hospital records (76%) for cases, and information on ‘type of work done’ was obtained by questionnaire from 95% of the controls before screening. Complementary information on occupation was obtained from city directories, resulting in occupational

data for 89% of the cases and 99% of controls. JEMs were constructed for occupational exposures to heat and EMF (Table 2.4). The risk for breast cancer was elevated for men exposed to heat but not for those exposed to EMF, based on six exposed cases, and could be adjusted only for heat exposure, age, and county of residence. [The job titles used as a surrogate for exposure to EMF were not validated by field measurements in the study population, and no information on potential confounders was available. In addition, the source and completeness of information on occupation differed for cases and controls, and the controls may not be representative of the population at risk.]

Floderus *et al.* (Floderus *et al.*, 1994) analyzed the risk for breast cancer among all Swedish men who had been employed as railway workers and were aged 20–64 in 1960. The cohort was defined on the basis of data on occupation from the 1960 Swedish census. Cases of breast cancer were ascertained from the 1960 Cancer Environment Registry, which comprises information from the Cancer Registry for the period 1960–79. SIRs for specific occupations were calculated with respect to the entire population of working men from the 1960 census data, adjusted for age in 10-year intervals. No account was made for cancer mortality or incidence during the follow-up period. Data for 1960–69 and 1970–79 were analyzed separately because changes in railway work practices had reduced the size of train crews and how often individuals worked on trains. Exposures were assessed by the railroad job titles that were associated with high exposure to ELF magnetic fields according to earlier personal monitoring (Floderus *et al.*, 1993). Significantly increased relative risks were reported for men in the most exposed occupations (Table 2.4): engine drivers, engine drivers and conductors, and railway workers in the first decade, based on two, three, and four cases, respectively (Table 4.13). In the second decade, only four cases of breast cancer were seen, none of which was in men with the occupations listed above. The authors discussed the differences between the two time periods and proposed several hypotheses, in particular an effect of reduction of exposures. [The very small number of cases and the improper follow-up of the cohort make interpretation of these results difficult.]

In an extension of their previous case–control study of leukemia and brain cancer (Floderus *et al.*, 1993), described in section 4.2.1.2, Stenlund and Floderus (Stenlund & Floderus, 1997) also considered male breast cancer and testicular cancer. They identified 56 cases of breast adenocarcinoma from the Swedish Cancer Registry for the period 1985–91 from all of Sweden. The 1700 controls used in the study were from the previous case–control study of brain and leukemia. The participation rate was 82% for cases and 72% for controls. Exposure assessment was based on the use of the JEM, as described above, which was obtained in the previous case–control study on a different study population (Floderus *et al.*, 1993) and complemented by 15 additional measurements in this study population. No association was observed between the risk for male breast cancer and exposure to magnetic fields (see Table 4.14). [The limitations are transporting JEMs across study populations, the low participation rates, limited information on potential controls, and the fact that the controls came from a different study and were therefore not matched on age or region with the cases in this study.]

(b) Women

Female breast cancer has been the subject of one study in which exposure was assessed by measurements and three studies in which exposure to EMF was assessed by job titles (Table 4.13 and 4.15).

Loomis *et al.* (Loomis *et al.*, 1994b) used a large database of death certificates in the USA for the period 1985–89. Among 27 814 cases of breast cancer and 112 749 controls, 68 cases and 199 controls had been employed in traditional electrical occupations, resulting in a small but significantly increased risk (mortality odds ratio = 1.4; 95% CI, 1.0-1.8) in the electrical occupations originally defined by Milham (Milham, 1982). Since this restrictive definition of electrical work applied to only about 0.2% of women, Loomis *et al.* (Loomis *et al.*, 1994b) examined other occupations in which more women might be exposed to EMF (Table 2.4), but saw no elevated associations. [The study had the following limitations: reliance on death certificates for occupation and diagnosis, use of other deaths as controls, assessment of exposure to EMF by a group of electrical occupations, and an inability to control for other risk factors for breast cancer.]

Cantor *et al.* (Cantor *et al.*, 1995a) used the same death certificate data set, adding one more year of follow-up. Exposure to EMF was assessed by an industrial hygienist [no details were given]; however, this new classification resulted in twice as many women being defined as 'highly' exposed. They found no association for white women but a significant increase for black women with medium or high probability of exposure to ELF fields (see Table 4.15). [The absence of detail about the more liberal ELF exposure assessment makes evaluation of the differences in results from Loomis *et al.* difficult.]

Coogan *et al.* (Coogan *et al.*, 1996) studied occupational exposure to 60 Hz magnetic fields in a large case–control study of breast cancer in the USA (Newcomb *et al.*, 1994). The cases were over 6800 cases of breast cancer diagnosed between 1988 and 1991 among women 74 years of age or younger from the cancer registries in Maine, Wisconsin, and Massachusetts. The controls were frequency-matched on age from drivers' license records (if < 65) and the Health Care Financing Administration's list of Medicare beneficiaries (if 65–74). The occupation most representative of the subject's career was obtained by telephone interview, with information on reproductive history and other breast cancer risk factors. The participation rates were 81% (6888) for cases and 84% (9529) for controls. Usual occupations were grouped into three categories (low, medium, and high) of potential exposure to 60 Hz magnetic fields above background by an industrial hygienist (Table 2.4); the remaining occupations were aggregated into a 'background' category. Conditional logistic regression stratified on age and state was used to calculate odds ratios, with adjustment for risk factors for breast cancer. The odds ratios by category were 1.0 (95% CI, 0.91–1.2) for low exposure, 1.1 (0.83–1.4) for intermediate exposure, and 1.4 (0.99-2.1) for high exposure. [There are problems in assessing exposure to EMF by expert judgment for workers in broad sectors of the economy (see section 2.4 for further discussion).]

Johansen and Olsen (Johansen & Olsen, 1998) also considered breast cancer in women in their retrospective cohort mortality study of electric utility workers in Denmark (see section 4.2.1.2). No association was seen between death from breast cancer (96 cases) and exposure to magnetic fields, based on very small numbers of exposed cases: two in the low-exposure category (0.1–0.29 μT), none in the intermediate category, and one in the highest category ($\geq 1.0 \mu\text{T}$). [No information on risk factors for breast cancer was available. See section 4.2.1.2 for comments on the limitations of the study.]

4.2.1.5 Lung cancer

The Positron meter used by Thériault *et al.* (Thériault *et al.*, 1994) also measured exposures to ELF electric fields and high-frequency EMF transients (or PEMF; see section 2.3.1). They examined the risk for lung cancer in their case–control study nested within the cohort of workers at three large electric utility companies (see section 4.2.1.1). In all, 772 cases of lung cancer were included in the study. No association between risk for lung cancer and cumulative exposure to magnetic fields greater than the median ($\geq 3.2 \mu\text{T}$ -years: OR, 0.92; 95% CI, 0.70–1.2; Table 4.16). [See section 4.2.1.2 for comments on the limitations of this study.]

Armstrong *et al.* (Armstrong *et al.*, 1994) examined the associations between exposure to PEMF and cancer among the Hydro Québec and EDF cohorts included by Thériault *et al.* (Thériault *et al.*, 1994). This analysis was based on about 1000 person–weeks of measurements of exposure to these high-frequency electromagnetic transients, 508 lung cancer cases, and 508 controls. Smoking status was available from medical histories for some of the subjects at Hydro Québec but not at EDF. A significant association was observed between the risk for lung cancer and cumulative exposure to PEMF (OR, 3.1; 95% CI, 1.6–6.0 among workers with exposure $>$ 90th percentile). This association was confined to the Hydro Québec workers (OR, 2.4; 95% CI, 1.1–5.3 for PEMF exposures $>$ median and OR, 5.6; 95% CI, 2.0–16 for exposures $>$ 90th percentile), despite a low standardized mortality ratio (SMR, 0.85) for lung cancer in that cohort. The association among Hydro Québec workers became stronger after adjustment for current smoking status and exposure to asbestos and other occupational agents (OR = 10; 95% CI, 3.2–31 for the highest exposure). The authors noted that the levels of exposure to both PEMF and ELF magnetic fields were considerably lower among EDF workers than among Hydro Québec workers. They also noted the incomplete and apparently incorrect characterization of the Positron’s PEMF channel, which is more sensitive to radiocommunication signals (see section 2.3.1) (Heroux, 1991). [The information on smoking was incomplete.]

Miller *et al.* (Miller *et al.*, 1996) also analyzed the risk for lung cancer in the Ontario Hydro cohort of Thériault *et al.* in relation to exposure to both ELF electric and magnetic fields (see description of study in section 4.2.1.2). No significant association was seen between the occurrence of lung cancer (263 cases) and exposure to electric or magnetic

fields. [See section 4.2.1.2 for comments on the limitations of this study; in addition, there was no information on smoking.]

Savitz *et al.* (Savitz *et al.*, 1997) subsequently re-examined the cohort from the study of five US utilities of Savitz and Loomis (Savitz & Loomis, 1995) in order to test the association between lung cancer and exposure to PEMF reported by Armstrong *et al.* (Armstrong *et al.*, 1994). A total of 1692 deaths from lung cancer had occurred over the study period. The PEMF JEM from the Canada–France study was adapted with some approximation to the job categories of the five US utilities. No association was seen between the risk for lung cancer and exposure to 60 Hz magnetic fields. The risks associated with exposure to PEMF were slightly but significantly elevated in all exposure categories (Table 4.16); there was no indication of a trend with exposure. No data on smoking were available. The risk for lung cancer was still significantly elevated after adjustment for socioeconomic status. [Transposition of a JEM from the Canada–France study to this population is problematic.]

4.2.1.6 Other cancers

A number of studies based on job titles alone have investigated the occurrence of various cancer types. Sporadic reports of elevated risks for malignant melanoma, have come out, but interpretation of these results is difficult because of the lack of measurements and the problem of multiple comparisons. The studies are therefore not described here.

In the case–control study described above (section 4.2.1.3), Stenlund and Floderus (Stenlund & Floderus, 1997) also used the Swedish JEM to analyze the relative risks for testicular cancer. A total of 144 cases (94 seminomas and 50 non-seminomas) were identified from the Swedish Cancer Registry for the period 1985–87 in central Sweden. A small increase in risk was observed in all quartiles of TWA exposure to magnetic fields. The analyses were adjusted for age, education, and exposure to solvents. The odds ratios were 1.3 (95% CI, 0.7–2.4) for TWA exposure in the range 0.16–0.19 μT , 1.4 (0.8–2.7) for 0.20–0.28 μT , and 1.3 (0.7–2.5) for $\geq 0.29 \mu\text{T}$. The risk was significantly increased among workers with exposures $>$ 90th percentile ($\geq 0.41 \mu\text{T}$: OR = 2.1; 1.0–4.3), particularly among men under the age of 40 (OR = 3.9; 95% CI, 1.4–11). A significantly increased risk in the 90th percentile was seen for non-seminomas in men below the age of 40 (OR = 16; 2.7–95, based on seven exposed cases and overall when workers were also probably exposed to solvents (OR = 3.8; 95% CI, 1.1–13.1). The authors regretted their inability to test for confounding by exposure to heat, a possible risk factor for testicular cancer. [See section 4.2.1.3 for comments on the limitations of this study.]

Thériault *et al.* (Thériault *et al.*, 1994) also examined the occurrence of a number of other cancer types in relation to exposure to magnetic fields in a case–control study nested within the cohort study of workers at three large electric utility companies (see section 4.2.1.1). No association was seen with lymphoma, multiple myeloma, melanoma, or any of the other 13 cancer groupings considered. No association with exposure to electric

fields was seen for cancers other than those of the brain and lung cancer by Miller *et al.* (Miller *et al.*, 1996). [See section 4.2.1.1 for comments on the limitations of these studies.]

Schroeder and Savitz (Schroeder & Savitz, 1997) studied mortality from lymphoma and multiple myeloma in association with the JEM for magnetic fields and the cohort mortality data from Savitz and Loomis (Savitz & Loomis, 1995). In total, 154 deaths from non-Hodgkin's lymphoma, 87 from CLL (classified as low and intermediate or high grade), 29 from Hodgkin's disease, and 84 from multiple myeloma occurred during the study period. No association was found between levels of exposure to magnetic fields and the risk for CLL, Hodgkin's disease, or multiple myeloma. An association was found for non-Hodgkin's lymphoma, however, which was significant in the two intermediate exposure categories. The relative risks, adjusted for exposure to solvents, were 1.5 (0.9–2.4), 1.8 (1.1–2.9), 1.8 (1.1–3.1), and 1.3 (0.7–2.8) for cumulative exposure categories of $0.6 \leq 1.2$, $1.2 \leq 2.0$, $2.0 \leq 4.3$, and ≥ 4.3 μT -years, respectively. No association was seen for cumulative exposures in the previous 2–10 years. [Information on other risk factors for lymphomas was lacking. See also section 4.2.1.1 for comments on the limitations of the Savitz and Loomis study.]

4.2.1.7 Central nervous system cancers in the offspring of parents exposed to electromagnetic fields

Seven studies have addressed the risks for cancers of the central nervous system (CNS) among children of parents exposed to EMF (Table 4.17). Six are population-based case-control studies in which exposure to EMF was assessed by job titles, and the seventh is a cohort study that included childhood cancers in a study of male reproductive effects.

In an exploratory study, Spitz and Johnson (Spitz & Johnson, 1985) investigated death from neuroblastoma. The jobs of controls and parents were obtained from the Texas birth certificate registry. Controls were selected so as to match the case's birth year distribution. Exposure to EMF was assigned to electrical jobs, with both a 'narrow' and a 'broad' definition (see Table 2.4). The relative risks were elevated with both definitions of exposure but reached significance only with the broad definition. [The broad definition included electrical equipment salesmen and repairmen, who are unlikely to have high exposure to magnetic fields. No adjustment was made for potential confounding exposures.]

The same Texas records were examined by Johnson and Spitz (Johnson & Spitz, 1989) for mortality from all CNS tumors (intracranial and spinal cord), which include the neuroblastomas studied by Johnson and Spitz (Spitz & Johnson, 1985). The methods were similar to those of the earlier study, except that controls were frequency-matched on gender and race as well as birth year. The relative risks in electrical occupations were not significantly elevated. [Their new definition of electrical occupations is perhaps the most

questionable devised, as it includes jobs such as radio and television performer and electrical goods and appliance salesmen.]

Nasca *et al.* (Nasca *et al.*, 1988) conducted a study of the incidence of CNS tumors; controls were selected from birth certificates for the same geographical region and were matched on gender, race, and year of birth. Parental job histories were obtained by telephone interviews with the mothers (85% participation rate for cases and 70% for controls). Exposures to EMF and ionizing radiation were assigned to industry–occupation combinations (see Table 2.4). Some increase in risk was observed among children whose parents were employed in industries with exposure to ionizing radiation, and they were excluded as controls in the EMF analysis. The relative risks from exposure to EMF were not significantly elevated for either the broad or narrow definition. Power calculations indicated that the sample sizes were large enough to permit detection of relative risks as low as 2.5–2.8.

Bunin *et al.* (Bunin *et al.*, 1990) studied the incidence of neuroblastomas in comparison with controls selected by random-digit dialing and with occupational histories ascertained by phone interviews. The controls were matched to cases on race, date of birth, and the first five digits of their telephone numbers (i.e. locality). Exposure to EMF was assigned to the electrical occupations defined by Spitz and Johnson (Spitz & Johnson, 1985). No increase in risk was observed.

Wilkins and Hundley (Wilkins & Hundley, 1990) studied the incidence of neuroblastomas in Columbus, Ohio. Controls and parental occupations were determined from birth certificates, and controls were matched on birth year, race, gender, and mother’s county of residence. Electrical occupations of the fathers were defined in several ways, including those of Deapen and Henderson (Deapen & Henderson, 1986) and Lin *et al.* (Lin *et al.*, 1985). No significant associations were seen with any definition.

Wilkins and Wellage (Wilkins & Wellage, 1996) studied the same population in Ohio for the association between exposure to EMF and risks for CNS tumors. Random-digit dialing was used to recruit controls, who were matched on gender and race (but not telephone exchange). Occupational histories and exposures to potential risk factors were ascertained by interviewing both biological parents. Exposure of the fathers to EMF was ascribed for a group of electrical occupations (Table 2.4). No association was seen with tumor risk. When welders were analyzed separately, the relative risk, based on only six cases, was marginally significant (OR = 3.8; 95% CI, 0.95-16). No evidence was seen for confounding by childhood or maternal exposure to X-rays, parental smoking, or household pesticides. [Confounding from welding fumes and solvents is a potential explanation for the association.]

Tornqvist (Tornqvist, 1998) examined cancers in the children of members of retrospective and prospective cohorts of electrical workers in the power industry. Details of the study design are given in section 4.5.1. The retrospective study found an equal number of

cancers among children of fathers who had had electrical jobs in the censuses before and after the birth ('exposed') and the remainder of the cohort ('unexposed'). [On the basis of the number of cancers expected in the paper, the Working Group calculated the risk ratio as 0.75 (95% CI, 0.24-2.3), showing no association with the father's apparent electrical work at the time of conception.] Six of the 12 cancers were located in the CNS and were also found equally in exposed and unexposed children. No cancers were reported among the children in the prospective study. [As the paper did not report the number of cancers expected in this population, this finding is hard to interpret.]

4.2.1.8 Meta-analyses of brain cancer and leukemia

Kheifets *et al.* (Kheifets *et al.*, 1997a; Kheifets *et al.*, 1995) have explored the patterns of the brain cancer and leukemia in relation to exposure to EMF in meta-analyses and combined their results to obtain pooled risk estimates.

(a) Brain cancer

Kheifets *et al.* (Kheifets *et al.*, 1995) identified 52 studies of occupational exposure to EMF and brain cancer through an English-language literature search. The criteria for inclusion in the meta-analyses were as follows:

- For studies that were updates or re-analyses of previously reported studies, only the study with the most inclusive study population was selected, unless more specific information on exposure or disease was used for a subset. Six studies were excluded on the basis of this criterion.
- Quantitative information had to be available on exposure and risk. Twelve studies were excluded on the basis of this criterion.
- Five studies were not included in most analyses because they were not published or presented only preliminary results.

Of the studies with results pertaining to occupational exposure to EMF and brain cancer, 29 independent studies were selected for this analysis. [The studies of Guénel *et al.*; Miller *et al.*; Feychting *et al.*; Harrington *et al.*; and Johansen and Olsen, reviewed above, were not included in the meta-analyses as they were published later.] (Feychting *et al.*, 1997; Guénel *et al.*, 1996; Harrington *et al.*, 1997; Johansen & Olsen, 1998; Miller *et al.*, 1996)

In order to assess heterogeneity, the authors scored 15 individual study characteristics that were thought to predict the results, including study quality and design. The characteristics were scored by two independent epidemiologists who were blinded to the authors and the results of the studies. Because most of the completed studies contained

limited information on exposure, the authors attempted to evaluate the relationship between exposure and disease by using additional information or measured exposure to EMF by job classification obtained from several large surveys of exposure in the workplace. These data were used to rank job categories and to compare exposure to the risk estimates for those job categories. The risk estimates of the 29 studies and various subsets are summarized by weighted averages in which the weight is the inverse of the variance of the estimate. A heterogeneity test, q statistic, and random-effects and fixed-effects summaries were computed. To investigate the sensitivity of the results to the weights used, several additional weighting schemes were used.

The pooled odds ratio from the 29 studies for a broad group of electrical occupations was 1.2 (95% CI, 1.1-1.3). [The pooled results for the broad group of electrical occupations includes data from studies in which no measurements of magnetic fields were made and which are therefore not reviewed in this document.] The authors observed lower risks in the Nordic cohort and incidence-based studies included in the meta-analyses. To assess exposure–response relationships, the authors pooled the risk estimates for the high, medium, and low categories of exposure from the available studies in which magnetic fields were measured. These included the results of Floderus *et al.* (Floderus *et al.*, 1993), Thériault *et al.* (Thériault *et al.*, 1994), and Savitz and Loomis (Savitz & Loomis, 1995). Although an increased risk was seen in all exposure categories, there was no evidence of an exposure–response relationship across the three exposure categories. [A limitation of this analysis is the combination of results across studies with different exposure categorizations. For example, the high exposure category in the study of Floderus *et al.* in the general industry may correspond to a medium exposure level in an electrical industry, possibly resulting in exposure misclassification.]

(b) Leukemia

Using the same methods, Kheifets *et al.* (Kheifets *et al.*, 1997a) also reviewed 70 studies on leukemia. The criteria for inclusion were:

- For studies that were updates or re-analyses of previously reported studies, only the study with the most inclusive study population was selected, unless more specific information on exposure or disease was used for a subset; 15 studies were excluded on the basis of this criterion.
- Quantitative information had to be available on exposure and risk. Eleven studies were excluded on the basis of this criterion.
- One study was excluded because it was a meta-analysis.
- Three studies were not included in most analyses because they were not published or presented only preliminary results.

- One study was not published in English.

Of the studies reporting results pertaining to occupational exposure to EMF and leukemia, 38 independent reports were selected for this analysis; the study of Thériault *et al.* (Thériault *et al.*, 1994) was treated as three independent studies. [The studies reviewed by Kheifets *et al.* did not include those of London *et al.*, Guénel *et al.*, Miller *et al.*, Feychting *et al.*, and Johansen and Olsen, as the results were not yet available for analysis.] (Feychting *et al.*, 1997; Guénel *et al.*, 1996; Johansen & Olsen, 1998; Kheifets *et al.*, 1997a; Miller *et al.*, 1996)

The pooled odds ratio from the 38 data sets (in 22 of which exposure was assessed by job titles alone) for leukemia was 1.2 (1.1-1.3) for a broad group of electrical occupations. Among the leukemia subtypes, a significant association was seen for both AML (OR = 1.4; 95% CI, 1.2–1.7) and CLL (OR = 1.6; 95% CI, 1.1–2.2). There was no evidence of heterogeneity of risk across the studies; in particular, the studies judged to have included better exposure assessment and design did not show a different risk.

In order to assess possible exposure–response relationships, the authors pooled the risk estimates for the high, medium, and low categories of exposure from studies in which magnetic fields had been measured and which were published at that time. The analyses included results from Floderus *et al.* (Floderus *et al.*, 1993), Thériault *et al.* (Thériault *et al.*, 1994), Savitz and Loomis (Savitz & Loomis, 1995), and Matanoski *et al.* (Matanoski *et al.*, 1993) and two studies that included spot measurements (Tynes *et al.*, 1992; Tynes *et al.*, 1994). For both brain cancer and leukemia, the pooled relative risks showed no exposure–response relationship across the three exposure categories. An increased risk was seen in all exposure categories, although there was no evidence of an exposure–response relationship. [See comments on the limitations of these analyses in the discussion of the meta-analysis of brain cancer, above.]

4.2.1.9 Summary

This review focuses on the best of the epidemiological studies that were available to the Working Group, i.e. those of exposure from full-shift measurements of extremely low frequency (ELF) magnetic and electric fields. The one exception is the studies of breast cancer, in which exposure was assessed only by job title.

Leukemia

Leukemia was the first cancer to be associated with occupational exposure to EMF, and at least 70 epidemiological studies have provided evidence relevant to this cancer. Most of these were based on job titles, and judgments were made about which occupational categories involve high exposure to EMF. In a meta-analysis, a small but significantly increased relative risk for leukemia and its main subtypes was found for a broad group of electricity-associated occupations.

Separate evaluations were made for the two major leukemia subtypes, chronic lymphocytic leukemia (CLL) and acute myelogenous leukemia (AML), and for all leukemias.

Chronic lymphocytic leukemia: The association between exposure to magnetic fields and CLL was considered in three studies of incidence, two in Sweden (Feychting *et al.*, 1997; Floderus *et al.*, 1993) and one in Canada and France involving three separate cohorts (Thériault *et al.*, 1994), and in one of mortality in the USA (Savitz & Loomis, 1995).

No association was found in the US mortality study. The diagnoses were, however, based on death certificates, which is problematic for leukemia subtypes and particularly for CLL, because of the long survival time.

In the Canada–France incidence study of electric utility workers, a nonsignificantly increased risk was seen overall and in two of the three cohorts. A significant increase was seen in both of the Swedish studies. One of these (Feychting *et al.*, 1997) provides unique information on the potential importance of combining occupational and residential exposures for adults, but it suffers from small numbers. In addition, their exposure assessment was based on a job–exposure matrix derived from magnetic field measurements for a different population of male workers, so their occupational exposures were not validated, especially for female workers. In the other Swedish study (Floderus *et al.*) of male workers in all occupations, the risk increased with increasing exposure; the risk was particularly strong for the highest exposure category and was increased somewhat when adjusted for exposure to potential confounders. The refusal rate in that study, however, could have introduced bias into the results.

Although each of these studies has its limitations, the limitations are different across studies, as are the designs and exposure assessment methods. Taken together, the studies of incidence suggest an association between exposure to magnetic fields and CLL.

Acute myelogenous leukemia: The association between exposure to magnetic fields and AML was considered in the same studies as for CLL. A nonsignificant increase in risk was found in the US mortality study, although the use of diagnoses from death certificates is problematic, as mentioned above.

In the Canada–France study, a significantly increased risk was seen overall for exposures above the median; this association is due mainly to a very high risk in one cohort, whereas a much smaller risk was seen in another cohort. The differences in definition and follow-up between the three studies, however, limit interpretation of the results. A nonsignificant increase in risk was seen in the study of Feychting *et al.* (Feychting *et al.*, 1997), which became significant when restricted to the very small number of subjects who had both high occupational and high residential exposures. Although the study of Feychting *et al.* provides unique information on the potential importance of combining occupational and residential exposures in adults, it suffers from small numbers and

weaknesses in exposure assessment, particularly for women. In the study of Floderus *et al.* (Floderus *et al.*, 1993), no association was seen between exposure to magnetic fields and the risk for AML.

Leukemia: The association between exposure to magnetic fields and risk for leukemia in general was considered in the same studies. No association was found in either of the two US studies of mortality. The limitations of death certificate diagnoses mentioned above are less critical for leukemia in general than they are for specific subtypes. In the Canada–France study, no significant association was seen overall, although a significant association was seen in one cohort. The differences in definition and follow-up among three studies, however, limit interpretation of the results. A marginally significant association was seen in both Swedish studies; in the study of Feychting *et al.* (Feychting *et al.*, 1997), when the analyses were restricted to subjects with high occupational and residential exposures, a significant elevation in risk was seen, based on nine cases. Although the study of Feychting *et al.* provides unique information on the potential importance of combining occupational and residential exposures in adults, it suffers from small numbers and weaknesses in exposure assessment, particularly for women.

Brain cancer

The association between exposure to magnetic fields and brain cancer was considered in the same studies.

One US study found a significant association in the highest exposure category and evidence for an exposure–response trend. The smaller US study showed no association. Both studies are based on diagnoses from death certificates, which is problematic for brain cancer owing to the difficulty in distinguishing primary cancers from metastases.

A nonsignificant elevation in risk was seen in the Canada–France study and in each of the cohorts in that study. In the study of Floderus *et al.* (Floderus *et al.*, 1993), an association was reported between exposure to magnetic fields and brain cancer, which was significant only in one of the intermediate exposure categories; no evidence for a dose–response relationship was observed. No association was observed in the study of Feychting *et al.*

Although each of these studies has its limitations, the limitations are different across studies, as are the designs and exposure assessment methods. Taken together, the studies suggest an association between exposure to magnetic fields and brain cancer, although the results are somewhat inconsistent.

Male breast cancer: The relationship between the risk for male breast cancer and exposure to magnetic fields has been examined in only one study, in Sweden, in which exposures were assessed with a JEM derived from full-shift measurements of magnetic fields. No association was observed, although no adjustment for potential confounders was made.

This association was also considered in nine studies in which only job titles were used to classify workers by exposure. Only one study involved large numbers of cases and took into account risk factors for male breast cancers. In that study, a two-fold increase of borderline significance was seen among men in all exposed occupations combined; a significant increase was seen for the category of workers in electrical trades. The exposure assessment based on job title was not validated by measurements. The other studies, which were based on smaller numbers and had various limitations, gave inconsistent results. Most of these studies were not designed *a priori* to test this hypothesis.

Female breast cancer: The relationship between the risk for breast cancer in women and exposure to magnetic fields assessed with a JEM derived from full-shift measurements has been examined in only one study, in Denmark. No association was observed, but no adjustment was made for potential confounders.

Three other studies, in the USA, were based on job titles; in two, these were classified by experts into categories of probable exposure to EMF. These studies, which have methodological limitations mainly because they were not designed *a priori* to test an association with EMF, had mixed results.

Other cancers

Other cancer outcomes (including cancer in the offspring of exposed workers) were considered in some studies. Increased incidences of specific types of cancers were observed in some studies but were not found consistently. Many of the studies suffer from methodological limitations, which hamper interpretation of the results.

Cancers at all sites

The risk for cancers at all sites associated with occupational exposure to magnetic fields were assessed in one US mortality study and one incidence study in Canada and France. These two studies were based on cohorts of male electric utility workers, and exposures were assessed by job–exposure matrixes derived from contemporary full-shift monitoring of the cohort members. The mortality study reported a very weak but significant elevation in risk, with an exposure–response relationship. The study of incidence in the Canadian and French utilities found no increased risk overall, although a small, nonsignificant elevation was observed in the Hydro Québec cohort.

Evaluation

There is limited evidence that occupational exposure to extremely low frequency magnetic fields is carcinogenic to adults. This evaluation is based on the results of studies of chronic lymphocytic leukemia.

[This conclusion was supported by 14 members of the Working Group; there were 11 votes for ‘inadequate’ evidence, 2 abstentions, and 2 absent.]

There is inadequate evidence for all other cancers.

[This conclusion was supported by 22 Working Group members; there were 2 votes for ‘limited’ evidence, 1 vote for ‘lack’ of evidence, 2 abstentions, and 2 absent.]

4.2.2 Residential exposure

4.2.2.1 All cancers

Wertheimer and Leeper (1987) (Wertheimer & Leeper, 1987) carried out a seminal case-control study of adult cancer in the towns of Boulder and Longmont and the city and suburbs of Denver in Colorado, USA. The cases were all deaths from cancer that had occurred between 1967 and 1975 and were identified from death certificates in Boulder and Longmont, all survivors in these two towns of ‘life-threatening’ cancers from the Colorado Cancer Registry diagnosed in the previous five years and alive in 1979, and a sample of 1977 cancer deaths from Denver and its suburbs comprising all deaths from cancers other than lung among people under the age of 62 and half of the deaths from lung cancer and half of the deaths from all cancers in people over the age of 62. Only subjects for whom an address could be traced in the sampling area for at least four years before diagnosis were included. Controls for the deaths in Boulder and Longmont were chosen from the next three death certificates for non-cancer deaths, matched to the cases for gender, age, year of death, and, in most cases, socioeconomic level. Controls for the cancer survivors were drawn at random from a list of subjects included in an unrelated random telephone survey in Longmont and Boulder and matched on gender, age, and socioeconomic level. Controls for the Denver cancer deaths were chosen at random from the 1970 city directory among persons whose addresses were within two blocks of the case addresses. [It is unclear whether these controls were matched to the cases on the same factors.] Each residence was categorized by presumed level of EMF exposure on the basis of wire coding (VHCC, ordinary high and ordinary low current configuration, and Endpole); the same approach was used as for the study of childhood cancer (Wertheimer & Leeper, 1979). In all, 1977 cancer cases were included in the study. The proportion of case-control pairs for which the wire codes were higher in case residences than in control residences was significantly elevated overall. There was a tendency for the proportion of case-control pairs in which the wire codes were higher in case residences than in control residences to increase with increasing wiring configuration level (40% for Endpole, 49% ordinary low current configuration, 53% ordinary high current configuration, and 59% VHCC). [This is an important hypothesis-generating paper; however, its usefulness for hypothesis testing was compromised because of unblinded assessment of exposure, the unusual statistical method used, potential overmatching for the Denver cases, and the unusual and complex selection of controls.]

Verkasalo *et al.* (1996a) (Verkasalo, 1996) tested the hypothesis of a relationship between cancer risk and exposure to magnetic fields from high-voltage transmission lines in a cohort study in Finland. Information was obtained by linkage between the Finnish Cancer Registry, data on residential exposure to magnetic fields from the Finnish Transmission Line Cohort Study, and residential data from the Central Population Register and the 1970 Population Census. The study cohort consisted of all persons who had resided in a building with a calculated magnetic field of $\geq 0.1 \mu\text{T}$ for any period between 1970 and 1989. Follow-up was from 1 January 1974 to 31 December 1989. Internal analyses were carried out by Poisson regression on data grouped on age (five-year categories), cumulative exposure, and social class [cumulative exposure was defined as cumulative exposure at the end of follow-up and was not treated as a time-dependent variable in the analysis]. In addition, SIRs were calculated with respect to the Finnish general population. The study cohort was very large, consisting of 383,700 persons (189,300 men) who contributed 2.5 million person-years of follow-up after age 20. Overall, 8415 cancer cases were observed (4082 in men). There was no association between cumulative level of exposure and the risk for all cancers (incidence rate ratio, IRR, 0.98 per μT -year; 95% CI, 0.96–1.0) or for any specific cancer type studied. The authors reported that skin melanoma was the only cancer for which the risk was somewhat increased throughout the three highest cumulative exposure categories: the IRR per μT -year was 0.91 (0.58–1.4), 1.5 (1.0–2.3), 1.5 (0.80–2.9), and 1.3 (0.59–2.7) for exposure to 0.2–0.39, 0.4–0.99, 1.0–1.99, and ≥ 2.0 compared with $< 0.2 \mu\text{T}$, respectively, in people of each sex. A marginally significant increased IRR was seen for multiple myeloma in men (IRR, 1.2 per μT -year; 95% CI, 1.0–1.5), and a nonsignificant decrease was observed for women (IRR, 0.87 per μT -year; 95% CI, 0.57–1.3). A significant increase in the risk for colon cancer was seen in women (IRR, 1.2 per μT -year; 95% CI, 1.0–1.3) but not in men. [No measurements were made to validate the calculated fields, and no distinction was made between apartments and single-family dwellings. The lack of information on other sources of residential exposure to EMF might have resulted in substantial exposure misclassification. In addition, no information on other risk factors, apart from age and sex, was available].

4.2.2.2 Leukemia

The studies summarized in this section are presented in tabular form in Tables 4.18 (design characteristics) and 4.19 (results).

Preston-Martin *et al.* (Preston-Martin *et al.*, 1988) investigated the risk for leukemia associated with use of electric blankets (see section 2.1) by including questions in questionnaires that were being used in two recently started case-control studies of AML and chronic myelogenous leukemia (CML) in Los Angeles County in the USA. The patients were residents of the area, aged 20–69 years, with histologically confirmed AML or CML diagnosed between July 1979 and June 1985, identified through the Los Angeles County population-based cancer registry. Both cases and controls had to be alive and to be able to be interviewed in English. One neighborhood control was matched individually to each case on gender, race, and birth year (within five years). The cancer registry

contained 858 eligible cases, of whom 485 were alive. A physician's permission to contact a patient was obtained for 415. The participation rate of patients was 61% (68 could not be located, and 52 refused to be interviewed). [The response rate of controls is not given.] Controls could not be found in three neighborhoods. In all, 293 matched pairs were included in the analysis, including 156 cases of AML and 137 cases of CML. As information on use of electric blankets was included after the beginning of the study, this information was available for only 224 matched pairs. Neither AML nor CML appeared to be related to any regular use of electric blankets: the ORs were 0.9 (95% CI, 0.5–1.6) for AML and 0.8 (95% CI, 0.4–1.6) for CML. Cases and controls did not differ by average duration of use, year of first regular use, or year since last use. Adjustment for other risk factors found in the study did not change the results. [There was no indication of whether blankets had been used only for warming the bed or continuously throughout the night.]

Severson *et al.* (Severson *et al.*, 1988) carried out a population-based case–control study of ANLL in adults in relation to residential exposure to power-frequency magnetic fields in King, Pierce, and Snohomish counties in western Washington State in the USA. The cases were identified through the cancer registry of the Fred Hutchinson Cancer Research Center, which is part of the SEER program. Cases were restricted to those of people aged 20–79 in whom ANLL had been diagnosed between 1 January 1981 and 31 December 1984. Both living and deceased patients were included, for a total of 164 cases. Random-digit dialing was used to select 204 controls in the same three geographical areas, who were frequency matched to the patients by gender and age (in five-year groups). A detailed questionnaire was administered to patients (or their next-of-kin if the patients had died) and controls; the questionnaire covered complete residential history and use of electric appliances. Exposure was assessed in three ways. First, the wire coding method of Wertheimer and Leeper (Wertheimer & Leeper, 1979) was used to classify all addresses in the study area in which the subject had resided in the previous 15 years. On the basis of maps of the residences and the wiring configuration, magnetic fields inside the residence were also estimated by a method developed by Kaune *et al.* (Kaune *et al.*, 1987). In addition, one-time measurements of the 60 Hz magnetic fields were made inside and outside the residence using a Power-frequency Field Meter Model 111 at the time of the interview if the subject had lived there for a continuous period of one year or longer immediately prior to the reference date (date of diagnosis for the cases). The measurements were made in the kitchen, the subject's bedroom, and the family gathering room, in both 'low power' and 'high power' configurations (i.e. with all major appliances that could conveniently be turned on and off). Finally, 24-h measurements were made in a limited sample of residences.

The response rates were 70% for cases and 65% for controls. For cases, most of the non-responses were due to physician refusal (17%), and only 4.9% of the subjects refused to be interviewed. The percentage of refusals among controls was much higher: (27%). The final analyses included 114 cases, with 91 cases of AML, and 133 controls. The patients tended to be of lower socioeconomic status than the controls and to smoke more; these factors were therefore adjusted for in subsequent analyses. There was no association

between the risk for leukemia and electrical wiring configuration by the Wertheimer and Leeper scheme, either in the residence inhabited the longest in the 3–10 years before the reference date or in the residence closest to the reference date. There was also no association with magnetic fields calculated by the model of Kaune *et al.* One-time measurements were available for only 56% of homes, since many subjects had moved after the reference date. A non-significant increase in odds ratio was observed for mean exposures of 0.2 μT or more, in both low-power (OR, 1.5; 95% CI, 0.48-4.7) and high-power conditions (1.6; 0.49-5.0). When weighted mean exposure was considered, the increase was no longer apparent in low-power conditions and was reduced in high-power conditions (1.3; 0.35-4.5). No association was found with use of electric blankets, electric water-bed heater, or electric mattress pads. [The participation rates were low, and the type of refusal differed between cases and controls. Also, information on electric blanket use was limited.]

Lovely *et al.* (Lovely *et al.*, 1994) further analyzed the data obtained in this case–control study, focusing on information obtained by questionnaire on use of motor-driven personal appliances (electric razors, hair dryers, and massage units), for which it was judged that use would represent higher exposures to peak magnetic fields than most other home appliances. Information was available on whether subjects had ever used such appliances, on the number of years (in the 10 years before diagnosis) they had had such appliances, and on the daily length of reported use. The authors also characterized magnetic fields produced by several models of hair dryers, electric razors, and massage units and found that partial body exposure could exceed 0.5 μT at rates of change exceeding 10 T/s. Massage units resulted in the highest average peak magnetic flux densities (0.35 $\mu\text{T} \pm 0.15$); electric razors were in the middle range (0.19 $\mu\text{T} \pm 0.17$), and hair dyers in the lowest (0.03 $\mu\text{T} \pm 0.004$).

There was no association between ever using one of these appliances and the risk for leukemia (unadjusted OR, 0.71; 95% CI, 0.41–1.2 for ever vs. never used). When the appliances were considered individually, massage units had been used more frequently by cases (3.0; 1.4–6.3, based on 24 exposed cases), while hair dryers had been used more frequently by controls (0.38; 0.22–0.66). There was a nonsignificantly increased risk for leukemia among ever users of electric razors (1.3; 0.80-2.2). A positive trend ($p < 0.05$) was seen for reported daily of use of electric razors; the unadjusted odds ratios were 0.70 (0.32–1.5) for use up to 2.5 min/d, 1.6 (0.76–3.25) for use 2.5–7.5 min/d, and 2.4 (1.1–5.5) for use > 7.5 min/d in comparison with never use. No pattern of risk with length of use was seen for massage units [the numbers of exposed cases and controls were quite small for this analysis] or hair dryers. The authors noted that information on use may have been limited, since the majority of leukemia patients in the study had died before the interview and information on reported duration of use was obtained from proxy respondents.

Data from this study were further analyzed by Sussman *et al.* (Sussman *et al.*, 1996) to assess the likelihood that the observed association with duration of use of electric razors was due to a bias related to the fact that proxy respondents had been used only for cases

and not for controls. Of 110 patients for whom information on duration of use of electric razors was available, only 24 had provided this information themselves. On the basis of this small number of cases, there was no association between ever use of electric razors and the risk for leukemia (OR, 0.7; 95% CI, 0.3-1.7). There was also no association with reported daily length of use: the odds ratios were 0.6 (0.2–2.3; three exposed cases) for use up to 2.5 min/d, 0.6 (0.1–2.6; two exposed cases) for 2.5–7.5 min/d, and 0.9 (0.2–4.7; two exposed cases) for > 7.5 min/d in comparison with never use. When analyses were restricted to proxy respondents, however, the odds ratio for ever use was 1.6 (0.9-2.8), and a significant trend with daily duration of use was observed. The authors suggested that the association reported by Lovely *et al.* was therefore an artifact due to proxy response. [The number of patients for whom information was obtained directly is too small to rule out similar odds ratios].

A population-based case–control study was carried out in Sweden by Feychting and Ahlbom (Feychting & Ahlbom, 1992; Feychting & Ahlbom, 1994) to assess the impact on the risk for leukemia of exposure to magnetic fields from high-voltage transmission lines. The methods used were similar to those used in their case–control study of childhood leukemia (Feychting & Ahlbom, 1993). The study base consisted of all persons aged 16 years or more who had lived at least one year on a property located within 300 m of any of the 220 and 400 kV transmission lines in Sweden during the period 1960–85. These individuals were identified from maps of the Central Board for Real Estate Data to identify properties at least partially located on the corridor and the Population Registry to identify the approximately 400 000 residents of these properties. The case–control study was nested in this study base. Cases of leukemia were identified by record linkage with the Swedish Cancer Registry for the period 1960–85. For each case, two controls were selected at random from the cohort among those who had lived in the power-line corridor at least one year before the reference date and who lived near the same power line as the case. The controls were matched to the case on age (within five years), gender, parish of residence, and year of the diagnosis.

A detailed description of the exposure assessment method is given in section 2. It included spot measurements and calculations of fields generated by the power line. For each case and control, the historical field was then calculated from the average load for the relevant years preceding the diagnosis. Calculations were made for the year of diagnosis, or closest to diagnosis if the subject had moved, and for 1, 5, and 10 years before diagnosis. These estimated levels were used to assign an average magnetic field exposure in microtesla for each year the subject had lived in the power corridor over the previous 15 years. Information on the following confounding factors was available: age, gender, year of diagnosis, residence in the county of Stockholm or not, type of housing (single-family vs. apartment), and socioeconomic status.

A total of 325 cases of leukemia (72 AML, 57 CML, 14 ALL, and 132 CLL) and 1091 controls were included in the analysis. There was no association between the risk for all leukemia and calculated exposure to magnetic fields closest to the time of diagnosis. For AML and CML, however, non-significantly increased odds ratios were seen for fields of

$\geq 0.2 \mu\text{T}$ in comparison with $\leq 0.09 \mu\text{T}$ (AML: OR, 1.7; 95% CI, 0.8–3.5; based on nine exposed cases; CML: 1.7; 0.7–3.8; based on seven exposed cases). For analyses based on calculated cumulative exposure during the 15 years preceding the diagnosis, the odds ratios for all leukemia were 1.0 (0.6–1.8) for cumulative exposures of 1.0–1.9 μT -years, 1.5 (1.0–2.4) for $\geq 2.0 \mu\text{T}$ -years, and 1.5 (0.9–2.6) for $\geq 3.0 \mu\text{T}$ -years, in comparison with $\leq 0.99 \mu\text{T}$ -years. Elevated odds ratios were seen at exposure $\geq 2.0 \mu\text{T}$ -years for both AML (2.3; 1.0–4.6) and CML (2.1; 0.9–4.7). Although these results were not adjusted for age or socioeconomic status, the authors reported that they were not greatly changed when adjustment was carried out. The authors also presented the results of matched analyses, which were similar to those of the unmatched analyses. The results of analyses based on spot measurements yielded odds ratios close to unity for all categories of exposure and leukemia subtypes, except for CML in the $\geq 0.2 \mu\text{T}$ category (1.5; 0.7–3.2). The authors commented on the small number of cases, which prevented further analyses of duration of exposure, and on the lack of information on exposure to EMF from other sources, particularly occupational. [It is difficult to estimate exposures over a long period of follow-up.]

In a follow-up to this study, Feychting *et al.* (Feychting *et al.*, 1997) obtained information on occupation from the censuses performed by Statistics Sweden every fifth year. Exposure was assessed from the occupation held in the year prior to the reference date (date of diagnosis for the cases) and a JEM developed from workday measurements in a large number of jobs held by a sample of the general male population within the framework of an occupational case–control study (see section 4.2.1.2). No information was available on the occupations of 43% of the women.

No association was seen between the risk for all leukemia and calculated residential exposure to magnetic fields after exclusion of subjects who were not exposed residentially but who were exposed to $\geq 0.13 \mu\text{T}$ occupationally. Again, however, elevated odds ratios were seen for AML (OR, 2.4; 95% CI, 0.9–5.7) and CML (2.1; 0.8–5.5) among patients in the highest exposure category ($\geq 0.2 \mu\text{T}$) compared with the lowest ($< 0.1 \mu\text{T}$). When the analyses were restricted to people who had only residential exposure in the highest category (compared with ‘unexposed’ subjects with $< 0.1 \mu\text{T}$ residential and $< 0.13 \mu\text{T}$ occupational exposure), the odds ratios for AML and CML were no longer elevated (AML: 1.3; 0.4–5.0; based on three exposed cases; CML: 0.5; 0.1–3.9), although the very small number of cases prevents any interpretation of these results. The odds ratios for patients who had both high occupational and high residential exposure were much higher than those who had either (6.3; 1.5–27 for AML and CML based on three exposed cases of each subtype). [The limitations of the previous study apply here as well. This study is the first to combine both residential and occupational exposures (see section 4.2.1 for more discussion). The validity of extrapolating occupational information, particularly for women, is questionable.]

In a very large cohort study in Finland, described in detail in section 4.2.2.1), Verkasalo (Verkasalo, 1996) considered the risk for leukemia associated with calculated exposure to magnetic fields from transmission lines. These data were analyzed in more detail in case–

control analyses [mistakenly referred to as case-cohort analyses]. A total of 196 cases of leukemia were included, with 60 of AML, 12 of ALL, 30 of CML, 73 of CLL, and 21 of other or unknown subtype. For each case, 10 controls were selected from the cohort and matched on gender, age at diagnosis (within one year), and whether they were alive in the year of diagnosis of the case. The statistical analyses were based on conditional logistic regression, adjusted for type of municipality. Several exposure measures were used: cumulative exposure and exposure 0–4, 5–9, and ≥ 10 years before diagnosis; annual average magnetic fields 1–20 years before diagnosis; highest annual average magnetic field and in windows of 0–4, 5–9, and ≥ 10 years before diagnosis; and age at first exposure to annual average magnetic field greater than a specified level and duration and time since exposure to annual averages above that level.

No association was seen between the risk for all leukemia or for specific subtypes and cumulative exposure or highest annual average exposure. Adjustment for type of housing or for occupational exposure (none vs. possible or probable, based on expert judgment) did not affect the results. For CLL, a significant increase was seen with dichotomized cumulative exposures of ≥ 0.2 μT -years and ≥ 0.4 μT -years for ≥ 10 years before diagnosis and for durations of exposure to fields of ≥ 0.10 μT for ≥ 12 years, based on three exposed cases. No association was seen for other types of leukemia. [The limitations noted for the study of Verkasalo *et al.* apply here as well; however, type of residence was examined in this analysis.] (Verkasalo, 1996)

In a case-control study described in detail in section 4.2.1.2, Li *et al.* (Li *et al.*, 1997) studied 1135 histologically confirmed incident cases of leukemia in northern Taiwan which were identified from the National Cancer Registry between 1987 and 1992. Controls were chosen among people with cancers other than those potentially related to exposure to magnetic fields. Eleven case-control pairs were excluded after verification of hospital records and a further 416 because one of the members of the pair resided in one of the 14 districts for which maps were not available and therefore exposure could not be assessed. The addresses of the remaining cases and controls were plotted on detailed maps with information on utility routes; distance to the nearest transmission line was then estimated to within 10 m. Average and maximum residential magnetic fields were assessed on the basis of distance from the lines and information on distance between wires, height of wires above the ground, annual and maximum loads on the lines in 1987–92, current phase, and geographical resistivity of earth. The calculated magnetic fields were validated by direct 30–40-min indoor measurements made at low-power conditions in 407 residences. With results grouped in three categories (< 0.1 , 0.1 – 0.2 , > 0.2 μT), the agreement (κ) between measured and calculated fields was 0.64 (95% CI, 0.5–0.78), which increased to 0.82 (0.79–0.86) when analyses used cut off points 0.5–1 μT and were restricted to houses in which both the measured and the calculated fields were > 0.2 μT . Limited information was available on potential confounders because of restrictions on interviews for the study.

The odds ratios were increased for patients in the middle and highest categories of calculated exposure to magnetic fields in the year of diagnosis: 1.3 (0.8–1.9) for 0.1–0.2

μT and 1.4 (1.0–1.9) for $> 0.2 \mu\text{T}$, compared with $< 0.1 \mu\text{T}$. In analyses by leukemia subtype, the odds ratios varied between 0.8 and 2.8. [The numbers of exposed cases by subtype were too small for these results to be interpreted; calculations of magnetic field were limited to the year of diagnosis because previous addresses were not available (see section 2 for comments on the exposure assessment in this study). Only limited information on confounders was available. Although the authors excluded cancer types thought to be potentially related to exposure to EMF, use of cancer cases as controls is still a concern.]

4.2.2.3 Breast cancer

In a case–control study in western New York, USA, Vena *et al.* (Vena *et al.*, 1991) studied the role of electric blankets in postmenopausal breast cancer. The cases were newly diagnosed, histologically confirmed, in women aged 41–85 and admitted to hospitals in the study area (Niagara and Erie counties) between 1987 and 1989. The controls were randomly selected from the community from the drivers' license rosters of the New York State Motor Vehicle Bureau for women under 65 and from the rosters of the Health Care Financing Administration for older women, and matched on age. The participation rate was low: 56% among cases (permission was denied by the physician for 28%; of the remaining 72%, 18% refused to participate, and 4% were too ill to be interviewed) and 46% among controls. Detailed home interviews were carried out; the questionnaire included questions about electric blanket use in the previous 10 years, the frequency of use by season, and the mode of use. Information was obtained for 382 cases and 439 controls.

The odds ratio for breast cancer with use of electric blankets was 0.89 when adjusted for age and education and 1.0 after further adjustment for risk factors for postmenopausal breast cancer: body mass index, age at first pregnancy, number of pregnancies, age at menarche, family history of breast cancer, and history of benign breast disease. There was no trend in odds ratio with increasing years or frequency of use. In the analysis of the general mode of use of the electric blankets, a slightly increased risk was found for women who reported using electric blankets continuously throughout the night compared with never users (OR adjusted for all risk factors, 1.5; 95% CI, 0.96–2.2). Further analyses showed a slightly increased risk in the heaviest users (only 8% of cases and 6% of controls), i.e. those who had used electric blankets continuously throughout the night, daily during the season over the previous 10 years (1.4; 0.77–2.4). The authors concluded that there was no association between use of electric blankets and risk for postmenopausal breast cancer, although the increased risk among heaviest users should be investigated further. [Interpretation of this study is complicated by the very low response rates, particularly among controls, the lack of information on the type and age of the electric blankets, and the absence of information on other source of exposure to ELF EMF.]

In a complementary study, Vena *et al.* (Vena *et al.*, 1994) also studied the role of electric blankets in women aged 40 or more with premenopausal breast cancer diagnosed between

1986 and 1991. Women were considered premenopausal if they were still menstruating or not menstruating due to medical intervention yet retained one ovary and were under the age of 50. Controls were drawn from the drivers' license rosters and frequency matched on age to the cases. The response rates were again low: 66% among cases (72% of thenon-interviewed cases were due to denial of permission to interview by physician) and 62% among controls. Interviews were carried out at home with a lengthy questionnaire including questions about electric blanket use. The odds ratio for use of an electric blanket at any time in the previous 10 years was 1.2 (95% CI, 0.83–1.7) after adjustment for age, education, and other risk factors, as in the study of postmenopausal breast cancer. There was no trend in risk with number of years of use. A slight increase in risk was observed among women reporting daily use during a season in comparison with never users (1.3; 0.86–1.9) and among those who reported using electric blankets continuously throughout the night (1.4; 0.94–2.2). The odds ratio among the heaviest users (continuously throughout the night, daily during the season over the previous 10 years) was 1.1 (0.59–2.1). [The interpretation of this study is complicated by the low response rates, the lack of information on the type and age of the electric blankets, and the absence of information on other sources of exposure to ELF EMF.]

In a letter to the Editor, Stevens (Stevens, 1995) commented on the results of these two studies. He suggested that they should be combined, thus increasing their statistical power and the likelihood that the small increases in risk noted for continuous use throughout the night in both studies would reach statistical significance. He further commented on the possible mechanisms by which EMF could affect the risk for breast cancer, suggesting that if they reversed the oncostatic effect of melatonin at the site of action in breast tissue they would be more important for estrogen receptor-positive tumors. Vena *et al.* (Vena *et al.*, 1995) responded that pre- and postmenopausal tumors had been separated because of their different etiologies. The *a priori* hypothesis of these studies was that EMF differentially affect premenopausal and postmenopausal tumors on the basis of Stevens' (Stevens, 1987) hypothesis that they affect risk through the pineal–melatonin pathway, which is more relevant for premenopausal women. Vena *et al.* (Vena *et al.*, 1995) nevertheless presented the results of combined analyses. The odds ratio was 1.1 (95% CI, 0.85–1.4) for ever use, 1.2 (0.90–1.5) for daily use, and 1.5 (1.1–1.9) for continuous use throughout the night. Analysis by duration of continuous use throughout the night showed no association. The authors cautioned about over interpretation of these results because of the limited capacity of the study to address such issues and the retrospective nature of the exposure assessment.

A case–control study of several adult cancers and residential exposure to 60 Hz magnetic fields from transmission lines was carried out in northern Taiwan by Li *et al.* (Li *et al.*, 1997) (see section 4.2.2.2). A total of 2407 histologically confirmed incident cases of breast cancer reported between 1990 and 1992 were identified from the National Cancer Registry. The same number of controls were drawn from the registry among women with cancer, excluding leukemia, brain cancer, breast cancer, cancers of the hematopoietic and reticuloendothelial system, skin, ovary, fallopian tube, and broad ligament. They were matched one-to-one to cases on date of birth (within five years) and date of diagnosis

(within six months). Twenty-two case–control pairs were excluded after verification of hospital records and a further 823 because one of the members of the pair resided in one of the 14 districts for which maps were not available, leaving 1562 case–control pairs for analysis. An index of urbanization was derived on the basis of local population density, age, mobility, economic activity, family income, educational level, and sanitation facilities. There was no association with calculated exposure to magnetic fields in the year of diagnosis (OR, 1.1 for exposure to > 0.2 or $0.1\text{--}0.2$ μT in comparison with < 0.1 μT). [See comments on the limitations of this study in section 4.2.2.2.]

In the Finnish cohort study described in section 4.2.2.1, Verkasalo *et al.* (Verkasalo *et al.*, 1996) also examined the risk for breast cancer in relation to calculated residential exposure to magnetic fields. Overall, 1229 cases of breast cancer were found among women in the cohort. No association was seen with risk, with SIRs of 1.1 (0.98–1.1) for exposure to < 0.2 μT , 1.1 (0.88–1.3) for exposure to $0.20\text{--}0.39$ μT , 0.89 (0.71–1.1) for exposure to $0.40\text{--}0.99$ μT , 1.2 (0.89–1.6) for exposure to $1.00\text{--}1.99$ μT , and 0.75 (0.48–1.1) for exposure to ≥ 2.00 μT . [See comments on the limitations of this study in section 4.2.2.2.]

In their population-based nested case–control study described in detail above (section 4.2.2.2), Feychting *et al.* (Feychting *et al.*, 1998) also considered the effect of magnetic fields from high-voltage transmission lines on the risk for breast cancer, using 699 cases in women and nine in men, identified from the Swedish Cancer Registry. Controls were selected at random from the study base among people who had lived in the power-line corridor for at least one year before the reference date and who lived near the same power line as the case. The controls were matched to the cases on age (within five years), gender, and parish of residence in the year of the diagnosis. Matching was one-to-one for female breast cancer cases and one-to-eight for male breast cancer cases. A detailed description of the method of exposure assessment is given in section 4.3.1). Information on the estrogen-receptor status of the tumor was obtained from medical records and was available for only 82 of the 699 cases.

There was no association between the risk for breast cancer in women and calculated exposure to magnetic fields closest in time to the diagnosis (OR, 1.0; 95% CI, 0.7–1.5 for ≥ 0.2 μT compared with < 0.1 μT). A nonsignificantly elevated risk was observed among women with cumulative exposures ≥ 3.0 $\mu\text{T}\text{-years}$ in the six years immediately preceding diagnosis (1.6; 0.8–3.2). A nonsignificant increase was also observed among women aged < 50 (1.8; 0.7–4.3) (≥ 0.2 μT vs. < 0.1 μT) and among women who were estrogen receptor-positive (1.6; 0.6–4.1) (≥ 0.1 μT vs. < 0.1 μT), with an exposure cut-point of 0.1 μT . Among estrogen receptor-positive women under 50, the odds ratio was 7.4 (1.0–180), based on six exposed cases and one exposed control. In males, a nonsignificant increase in risk was observed (2.1; 0.3–14) for calculated exposure to magnetic fields ≥ 0.2 μT closest to the time of diagnosis. [In addition to the limitations described in section 4.2.2.1, no information was available on important risk factors for breast cancer, since all of the data were obtained from registry and hospital files. Information on estrogen-receptor status, moreover, was available for only a limited number of cases.]

4.2.2.4 Tumors of the central nervous system

In their population-based nested case-control study, described in detail in section 4.2.2.2, Feychting and Ahlbom (Feychting & Ahlbom, 1992; Feychting & Ahlbom, 1994) also considered the effect of exposure to magnetic fields from high-voltage power lines on the risk for tumors of the CNS. Cases were identified from the Swedish Cancer Registry. For each case, two controls were selected at random from the cohort among people who had lived in the power-line corridor for at least one year before the reference date and who lived near the same power line as the case. The controls were matched to the case on age (within five years), gender, and parish of residence in the year of the diagnosis. A detailed description of the exposure assessment method is given in section 4.3.1. Sixty-six cases of glioma and 157 of glioblastoma were included in the analysis. There was no association with any measure of exposure to ELF EMF. The authors noted the small number of cases, which prevented further analyses by duration of exposure, and on the lack of information on exposure from other sources, particularly occupational.

In a follow-up to this study, Feychting *et al.* (Feychting *et al.*, 1997) obtained information on occupation from the censuses performed by Statistics Sweden as described in detail in section 4.2.2.2. No association was seen between the risk for tumors of the CNS and calculated residential exposure to magnetic fields after excluding subjects who were not exposed residentially but were exposed to $\geq 0.13 \mu\text{T}$ occupationally; and no association was seen when the analyses were restricted to people who had only residential exposure (OR, 0.7; 95% CI, 0.3–1.7; seven exposed cases).

In a case-control study described in detail in section 4.2.2.2, Li *et al.* (Li *et al.*, 1997) studied 705 histologically confirmed incident cases of brain tumor (ICD-O 191) in northern Taiwan identified from the National Cancer Registry between 1987 and 1992. Controls were chosen among people with cancer, excluding cancer types potentially related to exposure to magnetic fields. Nine case-control pairs were excluded after verification of hospital records and a further 241 because one of the members of the pair resided in one of the 14 districts for which maps were not available. No association was seen with calculated exposure to magnetic fields in the year of diagnosis (OR, 0.9; 95% CI, 0.5–1.7 for exposure to 0.1–0.2 μT ; 1.1; 0.8–1.6 for exposure to $> 0.2 \mu\text{T}$, compared with $< 0.1 \mu\text{T}$). In analyses by tumor subtype, the odds ratios varied between 0.6 and 2.8. [See comments in section 4.4.2 on the limitations of this study.]

In the study of Verkasalo *et al.* (Verkasalo *et al.*, 1996) described in section 4.2.2.1, the risk for gliomas and meningiomas was also analyzed. Over the study period, 301 cases of tumors of the CNS were observed. The incidence was not different from that of the Finnish population, and no association with calculated cumulative exposure to magnetic fields was observed. The SIRs with respect to the general population were 0.94 (95% CI, 0.8–1.1, 238 cases) for $< 0.2 \mu\text{T}$, 1.1 (0.77–1.5; 35 cases) for 0.2–0.39 μT , 0.64 (0.37–1.0, 16 cases) for 0.4–0.99 μT , 0.55 (0.18–1.3, five cases) for 1.00–1.99 μT , and 0.92 (0.37–1.9, seven cases) for $\geq 2.00 \mu\text{T}$. Although separate analyses were carried out for gliomas and meningiomas, and the authors reported only that the results were consistent with

those for cancer of the nervous system as a whole. [See comments on the limitations of this study in section 4.4.2.]

4.2.2.5 Summary

Leukemia

The risk for leukemia associated with use of electrical appliances was considered in two case-control studies in the USA. Because of limitations in design and exposure assessment, neither study provides information for evaluation of an association.

Magnetic fields were calculated on the basis of distance from transmission lines, historical loads, and line configuration in three case-control studies, from Finland, Sweden, and Taiwan. No information on other sources of residential exposure was available in any of these studies. In the Swedish study, no association was observed between the risk for any leukemia and exposure to magnetic fields, either for calculated fields closest to the time of diagnosis or for cumulative exposure over 15 years. A slight increase in risk for acute myelogenous leukemia (AML) and chronic myelogenous leukemia (CML), but not for chronic lymphocytic leukemia (CLL), was seen with calculated fields. The increase for AML disappeared when the analyses were restricted to subjects with no or very low occupational exposure, based, however, on a very small number of cases. The risk of people with both high residential and high occupational exposures was increased. In the Finnish study, no association was seen between either all leukemias or specific subtypes and highest annual or cumulative exposure to magnetic fields. A significant increase in the risk for CLL (but not for other leukemia subtypes) was seen in association with cumulative exposure to ≥ 0.20 or ≥ 0.40 μT -years for 10 years or more before diagnosis. In the study in Taiwan, a small increase in risk for leukemia was seen in association with exposure to 0.1–0.2 or > 0.2 μT of magnetic fields during the year of diagnosis.

In one study in the USA, in which wire coding was used to estimate exposure, no association was seen with the risk for leukemia.

Direct measures of magnetic fields in the homes of the study subjects were used in two studies. In the US study, a small, nonsignificant increase was seen in association with mean exposure but not with weighted mean exposure; measurements were made, moreover, in only a fraction of homes. In the Swedish study, no association was seen between spot measurements of exposure to EMF and the risk for leukemia.

Breast cancer

The association between use of electric blankets and the risk for breast cancer was considered in a large study in the USA of pre- and postmenopausal women. A modest, nonsignificant increase in risk was seen in both groups, which reached statistical

significance when the two were combined; however, there was no evidence for an association with duration of exposure.

Calculated fields were used in three studies, in Finland, Sweden, and Taiwan. In the Finnish and Taiwanese studies, no association was seen between exposure to magnetic fields and the risk for breast cancer. In the Swedish study, although no association was seen overall, nonsignificant increases were observed in the highest cumulative exposure category among young women, particularly those who were estrogen receptor-positive (based on very small numbers).

The Swedish study also considered the risk for male breast cancer. Although the number of cases was extremely small, a two-fold, nonsignificant increase was observed.

Cancers of the central nervous system

The association between calculated exposure to extremely low frequency magnetic fields and the risk for cancer of the brain was considered in one study in Taiwan, and the association with cancers of the central nervous system in general was assessed in one study in Finland and one in Sweden. No association was seen in any of these studies.

Considerations

None of the associations between cancer and residential exposure to magnetic fields was by itself convincingly positive; however, the quality of exposure assessment is a serious limitation in all these studies. Omission from consideration of occupational exposure is likely to lead to substantial misclassification. Studies that simultaneously address both exposures are needed to address this limitation.

Evaluation

There is inadequate evidence that residential exposure to extremely low frequency magnetic fields is carcinogenic to adults.

[This conclusion was supported by 24 Working Group members; there was one vote for 'lack' of evidence, 1 abstention, and 3 absent.]

Table 4.10 Epidemiological studies of exposure to EMF and cancer at all sites

Reference; type of study; country	Cohort description	Exposure classification	All cancers		Comments
			No. of cases	RR for cases ^a (95% CI)	
(Tynes <i>et al.</i> , 1992); cohort, Norway	37945 male workers (age 20-70) followed 1961-85 in the Cancer Registry of Norway	12 electrical occupations	3806	1.1 (1.0-1.1)	SIR adjusted for age
(Sahl <i>et al.</i> , 1993); cohort, California (USA)	Southern California Edison Company utility workers, mortality from 1960-88, 36221 workers in cohort	Electrical occupations in utility	261	1.1 (0.92-1.3)	Internal cohort RR, adjusted for age
(Thériault <i>et al.</i> , 1994); case-control, Canada and France	Male utility workers in 3 large companies: base population of 223292; 4151 cancer cases; 6106 controls. Cumulative exposure from job history and magnetic field JEM	Cumulative magnetic fields \geq median \geq 3.1 mT - year	2158	1.0 (0.91-1.1)	OR, adjusted for social class from case-control analysis with magnetic field JEM
		\geq 90th percentile \geq 16 μ T - year	443	1.0 (0.86-1.2)	
(Savitz & Loomis, 1995); cohort, USA	138905 men employed for > 6 months in 5 electric utilities were followed for mortality from 1950-86	Cumulative magnetic fields highest category, > 4.3 μ T-year exposure response, RR/ μ T-year	505	Total exposure: 1.2 (1.1-1.4)	Internal cohort RR, adjusted for age, year, race, class, work status, PCBs, and solvent exposures
			4833	1.0 (1.0-1.0)	
		highest category > 0.7 μ T-year exposure response, RR/ μ T-year	746	Past 2-10 years: 1.1 (1.0-1.3)	
			4833	1.1 (1.0-1.2)	
(Guénel <i>et al.</i> , 1996) case-control, France	EDF cohort of (Thériault <i>et al.</i> , 1994); 170000 men in cohort with 1915 cases of cancer matched to 7568 controls	Cumulative electric fields highest category > 414 V/m-year	195	0.89 (0.74-1.1)	OR, adjusted for social class
		exposure response, OR per 500 V/m-year	986	0.89 (0.75-1.0)	

PCB, polychlorinated biphenyls

^a All RRs are normalized to the null hypothesis = 1.0

Table 4.11 Epidemiological studies of leukemia with full-shift measurements of magnetic fields

Reference, type of study, country	Study population	Exposure assessment method	Magnetic field exposures category/magnitude/exposure metric/category		Risk estimates		Comments
					No. of cases	OR (95% CI)	
(Floderus <i>et al.</i> , 1993) case-control, Sweden	All male workers in a large region of mid-Sweden who were 20-64 year old in 1980. 250 leukemia cases from cancer registry, 1121 controls matched on age from census records	Exposures from JEMs for TWA and 3 other metrics in job held the longest in the 10 years before diagnosis. JEMs for 169 job categories based on 1015 magnetic field measurements taken at subject's workplace and job (or surrogate)	TWA		AML		OR with highest EMF exposure as high as 4.7 (2.2-9.7) after adjusting for ionizing radiation, benzene, and solvents. No change after adjusting for smoking, or pesticides
			2nd quartile	0.16-0.19 μ T	24	1.0 (0.5-1.8)	
			3rd quartile	0.20-0.28 μ T	18	0.8 (0.4-1.6)	
			4th quartile	$\geq 0.29 \mu$ T	23	1.0 (0.6-1.9)	
			≥ 90 th percentile	$\geq 0.41 \mu$ T	8	0.9 (0.4-2.1)	
					CLL		
			2nd quartile	0.16-0.19 μ T	17	1.1 (0.5-2.3)	
			3rd quartile	0.20-0.28 μ T	33	2.2 (1.1-4.3)	
4th quartile	$\geq 0.29 \mu$ T	41	3.0 (1.6-5.8)				
≥ 90 th percentile	$\geq 0.41 \mu$ T	22	3.7 (1.8-7.7)				
(Matanoski <i>et al.</i> , 1993) case-control, USA	Cohort of white males who were employed by AT&T or pensioned during 1975-80. Cases were deaths from leukemia (except CLL) whose job histories were obtained. For each case, 3 controls without leukemia were matched on gender, date of birth, date of hire, work status, and local telephone company	Cumulative exposures from job histories and JEMs for TWA and peaks from magnetic field measurements on 204 workers. Different exposures noted for central office technicians from old relay switches and new solid-state switches	Cumulative exposure		Leukemias (except CLL)		3 tests for trend (one-tailed) done over exposure quartiles measured by quartile ordinals, means, and log of means
			TWA \geq median	test for trend	35	2.5 (0.7-8.6) <i>p</i> = 0.21-0.35	
			Peak \geq median (w/ all switches)	test for trend	35	1.6 (0.5-4.9) <i>p</i> = 0.12-0.28	
Peak \geq median (w/ old switches)	test for trend	35	2.6 (0.8-8.6) <i>p</i> =0.04-0.06				
(Sahl <i>et al.</i> , 1993) case-control, California (USA)	36221 southern California Edison Company utility workers. Cancer mortality determined for 1960-88. 10 controls per case matched on date of birth, gender, and race	Exposure based on job history and JEMs for TWA and 4 other metrics from 776 person-days of magnetic field measurements	Total cumulative exposure		Leukemia		OR increase per defined exposure magnitude calculated by conditional logistic regression
			TWA 25 μ T-year		13	1.1 (0.80-1.5)	
			Median 3.5 μ T-year		10	1.0 (0.75-1.4)	
2-12 years before death		--	0.63 (0.32-1.2)				
Median 3.5 μ T-year							

Table 4.11 (continued)

Reference, type of study, country	Study population	Exposure assessment method	Magnetic field exposures category/magnitude/exposure metric/category	Riskestimates		Comments	
				No. of cases	OR (95% CI)		
(London <i>et al.</i> , 1994); case-control, Los Angeles County (USA)	Men age 20-64 years with cancer diagnosis and occupation in LA County tumor registry. 2355 leukemia cases (121 among electrical workers) compared with all other cancers with the exception of CNS tumors	Exposure based on job title reported on hospital records and on JEM for the TWA and 2 other metrics derived from full-shift magnetic field measurements on 278 electrical workers and 105 non-electrical workers. Current measurements adjusted based on estimates of time spent on tasks 15-20 years previously	TWA	Leukemia		No confounding detected with chlorinated hydrocarbon solvents, ionizing radiation, benzene or gasoline exhaust	
			highest category $\geq 0.81 \mu\text{T}$	30	1.4 (1.0-2.0)		
			exposure-response OR/ μT	2355	1.2 (1.0-1.5)		
			ANLL	10	1.3 (0.7-2.3)		
			highest category $\geq 0.81 \mu\text{T}$	853	1.2 (0.8-1.6)		
			exposure-response OR per μT	CLL	4		0.8 (0.4-1.5)
highest category $\geq 0.81 \mu\text{T}$	534	1.0 (0.6-1.5)					
exposure-response OR per μT	CML	10	2.3 (1.4-3.8)				
highest category $\geq 0.81 \mu\text{T}$	487	1.6 (1.2-2.0)					
(Thériault <i>et al.</i> , 1994); case-control, Canada and France	Cohorts of male utility workers in 3 large companies: base population of 223292; 4151 cancer cases determined from cancer registries, company records, etc. 6106 controls matched to cases by utility and date of birth	Cumulative exposure based on job history plus JEMs from 2066 workweek EMF measurements (50/60 Hz magnetic fields, electric fields and pulsed EMF). JEMs for TWAs adjusted for past practices constructed for 260 job titles	Cumulative TWA exposure	AML		Trend calculated over 4 exposure groups. No significant confounding detected for benzene, gasoline, paint, solvents, or ionizing radiation	
			\geq median $\geq 3.1 \mu\text{T}\cdot\text{year}$	26	3.2 (1.2-8.3)		
			$\geq 90\text{th percentile} \geq 16 \mu\text{T}\cdot\text{year}$	4	2.7 (0.5-15)		
			OR for trend	47	1.5 (0.31-7.6)		
			\geq median $\geq 3.1 \mu\text{T}\cdot\text{year}$	CLL	24		1.5 (0.5-4.4)
			$\geq 90\text{th percentile} \geq 16 \mu\text{T}\cdot\text{year}$	6	1.7 (0.44-6.7)		
OR for trend	41	1.4 (0.44-4.1)					
(Savitz & Loomis, 1995); case-control, USA	138,905 men employed for > 6 months in 5 electric utilities followed for mortality in 1950-86	Cumulative magnetic field exposure estimated from job history plus JEM based on 2842 magnetic field measurements	Cumulative TWA exposure	AML		Risks adjusted for PCB and solvent exposures. Ionizing radiation exposure insignificant	
			highest category $\geq 4.3 \mu\text{T}\cdot\text{year}$	5	1.6 (0.51-5.1)		
			exposure-response RR/ $\mu\text{T}\cdot\text{year}$	49	1.0 (0.93-1.2)		
			highest category $\geq 2.0 \mu\text{T}\cdot\text{year}$	CLL	5		0.55 (0.17-1.8)
exposure-response RR/ $\mu\text{T}\cdot\text{year}$	34	0.96 (0.78-1.1)					

Table 4.11 (continued)

Reference, type of study, country	Study population	Exposure assessment method	Magnetic field exposures category/magnitude/exposure metric category		Risk estimates		Comments
					No. of cases	OR (95% CI)	
(Feychting <i>et al.</i> , 1997); case-control, Sweden	Combined occupational and residential exposure assessment: approximately 400000 subjects living within 300 m of transmission lines; 325 leukemia cases	Residential magnetic field exposure from a physical model of distance from transmission line and historical reconstruction of power loads. Occupational exposure for job on census before diagnosis was estimated from JEM developed from measurements of Floderus (Floderus <i>et al.</i> , 1993)	TWA		AML		CML risks also significant with occupational + residential exposures $\geq 0.2 \mu\text{T}$ [OR 6.3, (1.5-27)]. Crude estimates of confounding from smoking and chemical exposures did not change results
			Occupational exposures only	0.13-0.19 μT $\geq 0.2 \mu\text{T}$	26 14	1.7 (0.9-3.2) 1.8 (0.9-3.8)	
			Occupational exposures $\geq 0.2 \mu\text{T}$				
			Residential exposures	$< 0.2 \mu\text{T}$ $\geq 0.2 \mu\text{T}$	11 3	1.5 (0.6-3.6) 6.3 (1.5-26)	
			Occupational exposures only	0.13-0.19 μT $\geq 0.2 \mu\text{T}$	37 28	1.2 (0.7-1.9) 1.7 (1.0-2.9)	
(Miller <i>et al.</i> , 1996); case-control, Ontario (Canada)	Ontario Hydro cohort of (Thériault <i>et al.</i> , 1994), 1484 cancer cases, 50 leukemia	Cumulative exposures estimated from job history in company records combined with JEMs for EMF derived from Ontario Hydro measurements taken by (Thériault <i>et al.</i> , 1994).	Cumulative TWA exposure		Leukemia		ORs adjusted for EMF interactions, benzene, herbicides, and ionizing radiation. Without EMF interaction, OR for highest exposure is 3.5 (0.56-22)
			magnetic fields	3.2-7 μT -years $\geq 7.1 \mu\text{T}$ -years	16 24	1.7 (0.58-4.8) 1.6 (0.47-5.2)	
			electric fields	172-344 V/m-years	2	1.2 (0.10-15)	
			magnetic fields	3.2-7 μT -years $\geq 7.1 \mu\text{T}$ -years	6	7.8 (1.1-58)	
			electric fields	$\geq 345 \text{ V/m-years}$	8	11 (1.5-84)	
(Johansen & Olsen, 1998); cohort, Denmark	Employees of 99 Danish utility companies, 32 006 total	Magnetic field exposures for subject's first job taken from a JEM based on expert judgment and 24-h measurements on 129 workers at 6 companies. JEM has 5 exposure categories (including background and unknown) for 25 job titles and 19 sites	TWA		Leukemia, men		Risks calculated as an SIR adjusted for age, gender, and date of diagnosis relative to background
			low exposure	0.1-0.29 μT	16	1.0 (NS)	
			medium	0.3-0.99 μT	16	0.9 (NS)	
			high	$\geq 1.0 \mu\text{T}$	12	1.1(NS)	

Table 4.11 (continued)

Reference, type of study, country	Study population	Exposure assessment method	Magnetic field exposures category/magnitude/exposure metric category	Risk estimates		Comments
				No. of cases	OR (95% CI)	
(Kheifets <i>et al.</i> , 1997a); Meta-analysis	38 studies of leukemia in EMF-exposed worker populations	Indicators of EMF exposure varied from a single job (e.g. welding) to magnetic field measurements	Electrical occupations or high EMF exposures (broadly defined)	AML	1.4 (1.2-1.7)	Significant heterogeneity ($p < 0.05$) among AML and CLL studies with broad definitions of EMF exposure
				18 studies		
			CLL	12 studies	1.6 (1.1-2.2)	
			All leukemia (6 studies)	1.2 (0.94-1.6)		
			Magnetic field measurements			
			low exposure 50th-75th %		1.4 (1.1-1.8)	
			medium 75th-90th %		1.3 (1.0-1.7)	
			high \geq 90th %			

OR, odds ratio; CI, confidence interval; TWA, time-weighted average; JEM, job-exposure matrix; AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; ANLL, acute non-lymphocytic leukemia; PCB, polychlorinated biphenyls

Table 4.12 Epidemiological studies of brain cancer with full-shift measurements of magnetic fields

Reference, type of study, country	Study population	Exposure assessment method	Magnetic field exposures category/magnitude/ exposure metriccategory	Riskestimates		Comments
				No. of cases	OR (95% CI)	
(Floderus <i>et al.</i> , 1993); case-control, Sweden	All male workers in a large region of mid-Sweden who were 20-64 years old in 1980. 346 brain cancer cases from cancer registry, 1121 controls matched on age from census records.	Exposures from JEMs for TWA and 3 other metrics in job held the longest in the 10 years before diagnosis. JEMs for 169 job categories based on 1015 magnetic field measurements taken at subject's workplace and job (or surrogate).	TWA	All brain tumors		With 90th percentile of the median magnetic fields, risk for all brain tumors is 1.6 (1.0-2.6). No change significant in risks after adjustment for benzene, ionizing radiation, or solvent exposures
			2nd quartile 0.16-0.19 μ T	59	1.0 (0.7-1.6)	
			3rd quartile 0.20-0.28 μ T	72	1.5 (1.0-2.2)	
			4th quartile \geq 0.29 μ T	74	1.4 (0.9-2.1)	
			\geq 90th percentile \geq 0.41 μ T	24	1.2 (0.7-2.1)	
			Astrocytoma III-IV			
2nd quartile 0.16-0.19 μ T	48	1.3 (0.8-2.0)				
3rd quartile 0.20-0.28 μ T	57	1.7 (1.1-2.7)				
4th quartile \geq 0.29 μ T	52	5 (1.0-2.4)				
\geq 90th percentile \geq 0.41 μ T	14	1.1 (0.5-2.1)				
(Sahl <i>et al.</i> , 1993); case-control, California (USA)	36221 southern California Edison Company utility workers. Cancer mortality determined from 1960-88. 10 controls per case matched on date of birth, gender, and race with 32 brain cancer cases	Exposure based on job history and JEMs for TWA and 4 other metrics from 776 person-days of magnetic field measurements in the current electric utility working environment	Cumulative TWA exposure (total)	Brain cancer		OR increase per defined exposure magnitude calculated by conditional logistic regression
			TWA 25 μ T-year	4	0.81 (0.48-1.4)	
			Median 3.5 μ T-year 2-12 years before death	7	0.95 (0.62-1.5)	
			Median 3.5 μ T-year		1.1 (0.62-2.0)	
(Thériault <i>et al.</i> , 1994) case-control, Canada and France	Cohorts of male utility workers in 3 large companies: base population of 223292; 4151 cancer cases (250 brain cancer) determined from cancer registries, company records, etc. 6106 controls matched to cases by utility and date of birth	Cumulative exposure based on job history plus JEMs from 2066 work-week EMF measurements (50/60 Hz magnetic fields, electric fields and pulsed EMF). JEMs for TWAs adjusted for past practices constructed for 260 job titles	Cumulative TWA exposure \geq median \geq 3.1 μ T-year \geq 90th percentile \geq 16 μ T-year	Malignant brain cancer		Trend calculated over 4 exposure groups. Astrocytoma OR in high exposure group much reduced when calculated by exact method for small sample.
			OR for trend	48	1.5 (0.85-2.8)	
				12	2.0 (0.76-5.0)	
				108	1.7 (0.68-4.1)	
			Astrocytoma			
			\geq median \geq 3.1 μ T-year \geq 90th percentile \geq 15.7 μ T-year	12	0.97 (0.34-2.8)	
			OR for trend	5	12 (1.1-140)	
				41	9.4 (1.1-83)	
			Benign brain cancer			
			\geq median \geq 3.1 μ T-year \geq 90th percentile \geq 15.7 μ T-year	19	2.3 (0.79-6.7)	
	4	1.6 (0.35-7.6)				

Table 4.12 (continued)

Reference, type of study, country	Study population	Exposure assessment method	Magnetic field exposures category/magnitude/ exposure metriccategory	Riskestimates		Comments	
				No. of cases	OR (95% CI)		
(Savitz & Loomis, 1995) Historic cohort study, USA	138905 men employed for > 6 months in 5 electric utilities followed for mortality 1950-86;; 144 deaths from brain and CNS cancers	Cumulative magnetic field exposure estimated from job history plus JEM based on 2842 magnetic field measurements. JEM constructed for 28 occupational categories (120 location-specific categories) collapsed into 5 exposure groups for TWA	Cumulative TWA exposure (total)			Risks adjusted for PCB and solvent exposures. Ionizing radiation exposure insignificant.	
			highest category $\geq 4.3 \mu\text{T-year}$	Brain cancer	16		2.3 (1.6-4.6)
			exposure-response RR per $\mu\text{T-year}$		144		1.1 (1.0-1.1)
			2-10 year window				
			highest category $\geq 0.7 \mu\text{T-year}$		43	2.6 (1.4-4.9)	
			exposure-response RR per $\mu\text{T-year}$		144	1.9 (1.3-2.8)	
(Feychting <i>et al.</i> , 1997); case-control, Sweden	Combined occupational and residential exposure assessment.: approximately 400000 subjects living within 300 m of transmission lines; 223 CNS tumor cases.	Residential magnetic field exposure from physical model of historical fields from transmission lines. Occupational exposure estimated from JEM developed by (Floderus <i>et al.</i> , 1993)	TWA			CNS tumors	
			Occupational 0.13-0.19 μT		79		1.2 (0.8-1.7)
			exposures only $\geq 0.2 \mu\text{T}$		43		1.2 (0.8-1.9)
			Occupational exposures $\geq 0.2 \mu\text{T}$				
			Residential < 0.2 μT		40	1.2 (0.7-1.9)	
			exposures $\geq 0.2 \mu\text{T}$		3	1.3 (0.3-4.8)	
(Harrington <i>et al.</i> , 1997); case-control, UK	84018 utility workers at the Central Electricity Generating Board of England and Wales. 112 deaths from primary brain cancers matched to 654 controls by gender and date of birth.	Magnetic field exposure estimated from computerized job histories and a JEM based on limited measurements on 127 workers. Many subjects unclassifiable because of gaps in job records or JEM.	Cumulative TWA exposure (total)			Primary brain cancers	
			highest category $\geq 6.0 \mu\text{T-year}$		27		0.97 (0.53-1.8)
			trend OR/ $\mu\text{T-year}$		94		0.92 (0.68-1.2)
			0-5 year before diagnosis				
			highest category $\geq 6.0 \mu\text{T-year}$		11	0.59 (0.25-1.4)	Unclassifiable cases and controls had an OR = 2.0 (CI = 1.1-4.4). No associations with 24 potential confounders
		trend OR/ $\mu\text{T-year}$		40	0.78 (0.51-1.2)		

Table 4.12 (continued)

Reference, type of study, country	Study population	Exposure assessment method	Magnetic field exposures category/magnitude/ exposure metriccategory	Riskestimates		Comments
				No. of cases	OR (95% CI)	
(Johansen & Olsen, 1998); Retrospective cohort, Denmark	Male and female employees of 99 Danish utility companies, 46284 total.	Magnetic field exposures for subject's first job taken from a JEM based on expert judgment and 24-h measurements on 129 workers at 6 companies. JEM has 5 exposure categories (including background and unknown)	TWA	CNS tumors, men		Risks calculated as SIR relative to background. For women employed ≥ 10 years, the risk for low exposure is significant (SIR = 9.2 for 2 cases)
			low exposure 0.1-0.29 μ T	17	0.9 (NS)	
			medium 0.3-0.99 μ T	13	0.7 (NS)	
			high $\geq 1.0 \mu$ T	8	0.7 (NS)	
			low exposure 0.1-0.29 μ T	3	3.3 (NS)	
			medium 0.3-0.99 μ T	0	--	
high $\geq 1.0 \mu$ T	4	1.4 (NS)				

OR, odds ratio; CI, confidence interval; TWA, time-weighted average; JEM, job-exposure matrix; PCB, polychlorinated biphenyls; CNS, central nervous system

Table 4.13 Cohort studies of breast cancer and occupational exposure to EMF

Reference, country	Cohort description	Exposure classification	Males		Females		Comments
			No. of cases	RR (95% CI)	No. of cases	RR (95% CI)	
(Tynes <i>et al.</i> , 1992); Norway	37 945 male workers (aged 20-70) followed 1961-85 in the Cancer Registry of Norway	12 electrical occupations Electric transport work (ISCO codes 631-632, 641, 693)	170 4	2.1 (1.1-3.6) 4.0 (1.1-10)	NA		SIR
(Guénel <i>et al.</i> , 1993); Denmark	All actively employed Danes (aged 20-64) in 1970 followed 1970-87 in the cancer registry. 172 000 men and 83 000 women in jobs exposed to magnetic fields were compared with reference workers in unexposed jobs	Jobs with intermittent magnetic field exposure Jobs with continuous exposure	23 2	1.2 (0.77-1.8) 1.5 (0.16-4.9)	1526 55	0.96 (0.91-1.0) 0.88 (0.68-1.2)	SIR relative to economically active subjects
(Floderus <i>et al.</i> , 1994); Sweden	Male railway workers (aged 20-64) in the 1960 census compared with all employed men (17 150 940 person-years in 1960-69). Cancers for 1960-69 and 1970-79 obtained from Cancer-Environment Registry.	Engine drivers Conductors Railway workers (and station masters, dispatchers & linemen)	2 1 4	8.3 (2.0-34) 2.7 (0.4-20) 4.3 (1.6-12)	NA		SIR adjusted for age. All cases occurred in 1960-69 follow up period (none in the 1970s)

RR, relative risks; CI, confidence interval; NA, not applicable; SIR, standardized incidence ratio; SMR, standardized mortality ratio; PIR, proportional incidence ratio

Table 4.14 Case-control studies of male breast cancer and occupational exposure to EMF

Reference, country	Study population	Exposure classification	Riskestimates		Comments
			No. of cases	RR (95% CI)	
(Matanoski <i>et al.</i> , 1991); New York State (USA)	Workers < 65 employed in one statewide telephone company during 1976-80	Line jobs Central office technician (personal monitoring of a sample of workers indicates central office technicians exposed to mean magnetic field of 0.25 μ T)	2	6.5 (0.79-24)	SIR Denominator is state incidence. Cases identified from New York State tumor registry
(Demers <i>et al.</i> , 1991); USA	Cases were 227 male workers in all occupations diagnosed with breast cancer 1983-87. 300 controls matched by age from random-digit dialing and Medicare records. Exposure assignment based on longest-held job reported at interview	All electrical occupations electric utility trades welders	All subjects		Risks not altered by adjustment for education, Jewish ethnicity, history of head injuries, exposure to diagnostic X-rays, or BMI
			33	1.8 (1.0-3.7)	
			13	6.0 (1.7-21)	
			4	0.8 (0.2-3.1)	
(Loomis, 1992); USA - 24 states	Death registration data from 24 states. Cases are men over age 19 who died of breast cancer 1985-88. Occupational data obtained from death record	Age at death less than 65 years All electrical occupations Telephone workers	Exposed before age 30		OR, controls randomly selected with other causes of death, matched by year of death
			and for > 30 years until diagnosis		
			22	3.3 (1.5-7.3)	
(Rosenbaum <i>et al.</i> , 1994); New York State & 8 western counties (USA)	71 male breast cancer cases reported to a cancer registry 1979-88; 256 controls who participated in a free cancer screening but were found to be disease free. Usual occupation reported in questionnaire, supplemented with city directory information	Job exposure to EMF	11	7.4 (1.6-34)	OR, adjusted for age, county, and occupational heat exposures The risks from heat exposures were significant (OR = 2.5, CI = 1.0-6.0)
			3	4.3 (0.4-43)	

Table 4.14 (continued)

Reference, country	Study population	Exposure classification	Riskestimates		Comments	
			No. of cases	RR (95% CI)		
(Stenlund & Floderus, 1997); Sweden	All male workers aged 20-60 in 1980, 56 males diagnosed with breast cancer (adenocarcinoma) 1985-91	TWA magnetic fields	All subjects		OR adjusted for age, education, and solvent exposure	
		Quartile 2, 0.16-0.19 μ T	17	1.2 (0.6-2.7)		
		Quartile 3, 0.20-0.28 μ T	17	1.3 (0.6-2.8)	EMF exposure estimate based on job titles identified from the work histories, plus the JEM from the magnetic field measurements in Floderus (Floderus <i>et al.</i> , 1993)	
		Quartile 4, > 0.29 μ T	11	0.7 (0.3-1.9)		
		90th percentile > 0.41 μ T	4	0.7 (0.2-2.3)		
			\leq 60 years			
		Quartile 2, 0.16-0.19 μ T	9	2.9 (0.7-11)		
Quartile 3, 0.20-0.28 μ T	8	2.5 (0.6-9.5)				
Quartile 4, > 0.29 μ T	5	0.9 (0.2-4.5)				
90th percentile, > 0.41 μ T	3	1.5 (0.3-8.3)				

OR, odds ratio; CI, confidence interval; SIR, standardized incidence ratio; BMI, body mass index

Table 4.15 Case-control studies of female breast cancer and occupational studies of EMF

Reference, country	Study population	Exposure classification	Riskestimates		Comments	
			No. of cases	RR (95% CI)		
(Loomis <i>et al.</i> , 1994b); 24 US states	Women who died of breast cancer 1985-89 compared with those who died of other causes. 27 814 cases and 110 750 controls	15 electrical occupations	68	1.4 (1.0-1.8)	MOR, adjusted for age, race, and class	
		other occupations				
		computer programmer	26	1.1 (0.70-1.7)		
		telephone operator	328	0.96 (0.84-1.1)		
(Cantor <i>et al.</i> , 1995a); 24 US states	Women who died of breast cancer 1984-89 (same dataset used by (Loomis <i>et al.</i> , 1994b) with an additional year of data). 29 397 white and 4112 black woman who dies from breast cancer		white women		MOR, adjusted for age and class (Cantor <i>et al.</i> , 1995b) reported a significant association with radio frequency fields in the same population	
		medium exposure	1746	1.1 (1.0-1.2)		
		high exposure	123	0.97 (0.8-1.2)		
			black women			
		medium exposure	273	1.3 (1.1-1.5)		
		high exposure	20	1.2 (0.7-2.1)		
(Coogan <i>et al.</i> , 1996); 4 US states	All female workers in state registry records with breast cancer, 6888 cases and 9529 controls	All women			OR, adjusted for age, BMI, history of breast disease, age at menarche, parity, age at first birth, education, and alcohol consumption	
		high exposure jobs	6851	1.4 (0.99-2.1)		
		test for trend	57	$p = 0.11$		
		Premenopausal women only			Potential EMF exposure classified by an industrial hygienist for the most representative occupation collected at an interview	
		high exposure jobs	1424	2.0 (1.0-3.8)		
		test for trend	20	$p = 0.49$		
	Postmenopausal women only					
high exposure jobs	5163	1.3 (0.82-2.2)				
test for trend	35	$p = 0.30$				

MOR, mortality odds ratio; CI, confidence interval; BMI, body mass index; OR, odds ratio

Table 4.16 Epidemiological studies of lung cancer with full-shift measurements of magnetic fields

Reference; type of study, country	Study population	Exposure classification	Lung cancer risks		Comments
			No. of cases	OR (95% CI)	
(Thériault <i>et al.</i> , 1994); case-control, Canada and France	Male utility workers in 3 large companies; cohort of 223292 employees; 4151 cancer cases; 6106 controls. Cumulative exposure from job history and JEM based on magnetic field measurements of 2066 workers	Cumulative TWA magnetic fields			OR, adjusted for social class
		≥ median ≥ 3.1 μT-years	450	0.92 (0.70-1.2)	
		≥ 90th percentile	93	1.0 (0.67-1.5)	
(Armstrong <i>et al.</i> , 1994); case-control, Quebec (Canada) and France	Male utility workers in 2 large companies; base population of about 192 000 workers; 508 lung cancer cases and 508 controls. Cumulative exposures from job histories and JEM of PEMF measurements on 1295 workers.	Cumulative PEMF* exposure			OR, adjusted for social class
		≥ median	308	1.3 (0.96-1.7)	
		≥ 90th percentile (≥16 μT-years)	84	3.1 (1.6-6.0)	PEMF sensor found to be sensitive to radio transmission as well as shocks from electric lines.
(Savitz <i>et al.</i> , 1997); cohort, USA	Male utility workers in 5 large companies; base population of 138 905 workers; 20 733 worker deaths. Cumulative exposures from job histories and JEMs for magnetic fields (Savitz & Loomis, 1995) and PEMF (Armstrong <i>et al.</i> , 1994)	60 Hz exposure:			SMR with US population as reference, PMR with comparison between exposure categories for more common cancers
		0.7-2.3 μT-year (2-10 year lag)	302	1.3 (1.1-1.6)	
		0.9-2.9 μT-year (10-20 year lag)	429	1.2 (1.0-1.4)	
		2-14.6 μT-year (> 20 year lag)	243	1.3 (1.0-1.5)	
		highest pulsed MF exposures			
	5.4-11.9 μT-year	401	1.3 (1.1-1.6)		
	11.9-41.2 μT-year	196	1.4 (1.1-1.7)		

RR, relative risk; CI, confidence interval; SIR, standardized incidence ratio; OR, odds ratio; TWA, time-weighted average; JEM, job-exposure matrix; PEMF, pulsed EMF; nominally 5-20 Mhz; SMR, standardized mortality ratio; PMR, proportional incidence ratio

Table 4.17 Central nervous system tumors in offspring of EMF-exposed parents

Reference, type of study, country	Study population	Exposure classification	Riskestimate		Comments	
			No. of cases	OR (95% CI)		
(Spitz & Johnson, 1985); case-control study, Texas (USA)	157 children who died of neuroblastoma (1964-78) identified from Texas State death certificate records matched with 314 controls randomly selected from birth records.	Broad definition of EMF exposure	17	2.1 (1.1-4.4)	OR, narrow definition limited to electricians, electric and electronics workers, linemen, utility workers, and welders	
		Narrow definition of EMF exposure	13	2.1 (0.95-4.8)		
		Electronics workers only	6	12 (1.4-99)		
(Nasca <i>et al.</i> , 1988); case-control, New York State (USA)	338 cases of primary CNS tumors obtained from tumor registries. Two controls per patient selected from birth certificates (676 controls total). Parental occupation from phone interview.	Narrow definition of EMF exposure (from Spitz, 1985)	15	1.7 (0.80-3.6)	OR, controlled for gender, race and year of birth. Controls with ionizing radiation exposures excluded. Diagnosis confirmed by histologic examination of pathology slides	
		Broad definition of EMF exposure	19	1.6 (0.83-3.1)		
(Johnson & Spitz, 1989); case-control, Texas (USA)	499 cases of intracranial and spinal-cord tumors obtained from death certificates. Birth certificates provided parent's occupation plus 2 controls per case (998 controls total)	All electrical occupations	28	1.4 (0.88-2.4)	OR, controlled for gender, age, and year of birth	
(Bunin <i>et al.</i> , 1990); case-control, Philadelphia, PA (USA)	181 children diagnosed with neuroblastoma identified in tumor registries. Single control per case identified through random-digit dialing. Parents of cases and controls interviewed by phone to obtain occupational history for each parent	Narrow definition of EMF exposure (Spitz & Johnson, 1985)	Preconception	9	1.3 (0.4-4.1)	OR, controlled for race, birth year, and telephone exchange
			During pregnancy	3	0.3 (0.1-1.3)	
		Broad definition of EMF exposure	Preconception	14	1.0 (0.4-2.3)	
	During pregnancy	7	0.6 (0.2-1.6)			

Table 4.17 (continued)

Reference, type of study, country	Study population	Exposure classification	Risk estimate		Comments	
			No. of cases	OR (95% CI)		
(Wilkins & Hundley, 1990); case-control, Columbus, OH (USA)	101 cases of neuroblastoma identified through the Children's Hospital Tumor Registry. Four controls per cases selected from State birth certificate roster. Paternal occupation and industry obtained from birth certificates.	Electrical occupation definitions: (Deapen & Henderson, 1986) (Lin <i>et al.</i> , 1985):	4	1.6 (0.3-9.1)	OR, controlled for year of birth, race, gender, and mother's county at time of birth	
		definite exposure (A)	1	NR		
		probable exposure (B)	5	1.2 (0.2-6.4)		
		possible exposure (C) A+B	13	0.5 (0.2-1.2)		
		(similar to narrow in Spitz & Johnson, 1985) A+B+C (similar to broad in Spitz & Johnson, 1985)	6	1.9 (0.4-9.7)		
(Wilkins & Wellage, 1996); case-control, Columbus, OH (USA)	94 cases of CNS tumors identified through hospital tumor registry. 166 cancer-free controls identified by random-digit dialing. Fathers interviewed to obtain occupation before conception, during pregnancy, and from birth to diagnosis.	Occupations with presumed EMF exposure	Preconception	11	1.3 (0.58-3.0)	OR, controlled for year of birth, race, and gender. Jobs involving welding are defined more liberally than the standardized occupational categories.
			Pregnancy	9	1.0 (0.45-2.4)	
		Occupations involving welding	Preconception	6	3.8 (0.95-16)	
			Pregnancy	5	2.5 (0.67-9.3)	
(Tornqvist, 1998); retrospective and prospective cohort studies, Sweden	Retrospective study: Fathers who had electrical occupations in the power industry selected from census over a 25-year span. Children identified from Medical Birth Registry, and cancers from the national tumor registry. Prospective study: Cohort of first-employed power industry workers had health outcomes followed over 10 years.	Retrospective study: Electric jobs in year before birth	All cancers	6	0.75 (0.24-2.3)	[Risks were calculated by Working Group from observed and expected cancers (all types) reported in the paper. Expected CNS cancers estimated from US rates For RR, the exposed are fathers who held electric jobs in the year before the birth of the child with cancer, and the unexposed were electric workers at some other time. For SIR, the childhood cancer outcome for the entire cohort of electrical workers compared with the general population]
		Electrical jobs at any time		12	SIR = 2.1 ($p = 0.02$)	
		Electric jobs in year before birth	CNS tumors (estimates)	3	0.75 (0.14-4.1)	
		Electrical jobs at any time		6	SIR = 5.4 ($p = 0.002$)	
		Prospective study: First employed power industry workers; same occupations as retrospective study	Prospective study: No cancer cases identified			

RR, relative risks; CI, confidence interval; OR, odds ratio; CNS, central nervous system; SIR, standardized incidence ratio

Table 4.18 Design of studies of leukemia and residential exposure to EMF

Study	Case selection	Control selection	Exposure metrics	Confounders analyzed
USA				
Preston-Martin <i>et al.</i> (1988)	Confirmed AML and CML cases aged 20-69, resident in LA county, alive at interview and English speaking from cancer registry (1979-85) 224 cases included in analyses	Neighborhood controls (1 per case) matched on sex, race and birth year, resident in LA county, alive at interview and English speaking 224 controls included in analyses	Electric blanket use from questionnaire (ever/never, duration, year of first and last regular use)	Sex Race Age Diagnostic X-rays Work as a welder Life on a farm
Severson <i>et al.</i> (1988)	ANLL cases aged 20-79, resident in Western Washington State, from cancer registry (1981-84) 114 cases included in analyses (91 AML)	Population-based controls from random-digit dialing, matched on geographical area and frequency matched on age and sex 133 controls included in analyses	Wertheimer and Leeper wire-coding Estimation of magnetic fields from maps and wire coding —method of Kaune (1987) One-time measurements of 60 Hz magnetic fields inside (kitchen, bedroom, family room in HPC ¹ and LPC ¹) and outside house 24-hour measurements in sample of houses Electric appliance use from questionnaire	Age Sex Cigarette smoking Family income Race
Lovely <i>et al.</i> (1994)	Same cases as Severson 67-70 cases included in analyses:, depending on appliance (missing data)	Same controls as Severson 66-69 controls included in analyses:, depending on appliance	Use of electric razors, hair dryers and massage units from questionnaire	Age Sex Smoking
Sussman & Kheifets (1996)	Same as Lovely and Severson, excluding proxy respondents 24 cases included in analyses	Same as Lovely and Severson	Same as Lovely	Sex
Sweden				
Feychting and Ahlbom (1994)	All incident cancer cases from cancer registry(1960-1985),from cohort of Swedish population aged 16 or over, living on a property located within 300 meters of any 220 or 400 kV power lines 325 cases in analyses (72 AML, 57 CML, 14 ALL and 132 CLL)	Two controls per case from same cohort Matched on age, sex, parish and residence near same power line 1 091 controls in analyses	Distance to power lines from residence In-home magnetic field spot measurements under low and high power use conditions Calculations of the magnetic fields generated by the power lines at the time spot measurements were assessed (calculated contemporary fields) and for the year closest in time to diagnosis (historical calculated fields)	Age Sex Year of diagnosis Residing or not in the county of Stockholm Type of residence SES

Table 4.18 (continued)

Study	Case selection	Control selection	Exposure metrics	Confounders analyzed
Feychting <i>et al.</i> (1997)	Same as Feychting and Ahlbom (1994)	Same as above	Same as above for residential Occupational exposure from job-exposure matrix developed from workday measurements made for a large number of occupations outside the framework of this study and information on occupation held in the year prior to the reference date	Same as above Occupational exposures to motor fuel/exhaust fumes, benzene, oil products, solvents and welding fumes
Finland				
Verkasalo <i>et al.</i> (1996)	All primary leukemia cases reported to the Finnish Cancer Registry (1974-89) from cohort of Finnish population, aged 20 or older, living within 500 m of overhead power lines of 110-400 kV in building with a calculated magnetic field of $\geq 0.01 \mu\text{T}$ for any period between the years 1970-89 203 cases identified	Cohort study: consisting of 383 700 persons (189 300 men) who contributed 2.5 million person years of follow-up after age 20	Average annual magnetic fields Cumulative exposure Estimates based on residential history, distance between center of residential buildings and each power line in 500 m corridor and calculated average annual magnetic fields for each building. Takes into account current, typical locations of phase conductors in power lines, and distance	Sex Age Socioeconomic status
Verkasalo <i>et al.</i> (1998)	Same as Verkasalo <i>et al.</i> (1996) 196 leukemia cases included (60 AML, 12 ALL, 30 CML, 73 CLL, and 21 other or unknown subtype)	10 controls per case from cohort Matched on sex, age at diagnosis and alive in the year of diagnosis of the case	Cumulative exposure: total and within 0-4, 5-9, and 10 years or more of diagnosis Annual average magnetic fields 1 through 20 years prior to diagnosis Highest annual average magnetic field ever and in time windows before diagnosis Age at first exposure to annual average magnetic field greater than a specified level Duration and time since exposure to annual averages above that level.	Sex Age Type of municipality Type of housing Occupational exposure (none/possible or probable)

Table 4.18 (continued)

Study	Case selection	Control selection	Exposure metrics	Confounders analyzed
Taiwan				
Li <i>et al.</i> (1997)	Pathologically confirmed incident cases of leukemia from northern Taiwan from cancer registry (1987-92) 870 cases included in analyses	One control per case from cancer registry, excluding leukemia, brain and breast cancers, cancers of the haematopoietic and reticulo-endothelial system, skin, ovary, fallopian tube, and broad ligament. Matched on date of birth, sex, and date of diagnosis 889 controls included in analyses	Distance from lines Average and maximum magnetic fields assessed using distance from the lines, distance between wires, height of wires above the ground, annual and maximum loads along the lines from 1987 to 1992, current phase, and geographical resistivity of earth	Age Sex Index of urbanization

AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia; LA, Los Angeles; ANLL, acute nonlymphocytic leukemia; HPC: high power configuration; LPC: low power configuration; ALL, acute lymphocyte leukemia; CLL, chronic lymphocytic leukemia

Table 4.19 (continued)

Study	Main results: OR and 95% CI (unless otherwise specified)	Additional notes
(Feychting <i>et al.</i> , 1997)	Magnetic fields closest to diagnosis <i>Subjects with only residential exposure (i.e. with occupational exposure < 0.13 μT)</i> <i>(Reference ≤ 0.2 μT) – Unmatched analyses</i> <i>All leukemia</i> ≥ 0.2 μT 0.9 (0.4-1.8) <i>AML</i> ≥ 0.2 μT 1.3 (0.4-5.0) <i>CML</i> ≥ 0.2 μT 0.5 (0.1-3.9) <i>CLL</i> ≥ 0.2 μT 0.8 (0.3-2.3)	Same as above
(Verkasalo, 1996)	Magnetic fields – highest annual average exposure <i>(Reference < 0.1 μT)</i> All leukemia (No. of exposed cases) 0.10 - 0.19 μT (ND) 1.1 (0.60-2.0) 0.20 - 0.29 μT (ND) 1.2 (0.40-3.3) ≥ 0.30 μT (ND) 0.53 (0.16-1.7) <i>CLL</i> 0.10 - 0.19 μT (5) 1.0 (0.37-2.5) 0.20 - 0.29 μT (1) 1.4 (0.16-11) ≥ 0.30 μT (2) 0.87 (0.20-3.8) Magnetic fields - cumulative exposure <i>(Reference < 0.40 μT-years)</i> <i>CLL</i> 0.40 - 0.99 μT-years (8) 0.98 (0.45-2.2) 1.00 - 1.99 μT -years (3) 1.3 (0.37-4.4) ≥ 2.00 μT -years (3) 1.7 (0.48-5.8) <i>Cumulative exposure</i> <i>CLL</i> ≥ 0.20 μT -years vs. < 0.20 μT -years < 5 years before diagnosis (12) 0.93 (0.48-1.8) 5 - 9 years (11) 1.5 (0.72-3.1) ≥ 10 years (9) 2.8 (1.1-7.4) ≥ 0.40 μT -years vs. < 0.40 < 5 years (5) 0.84 (0.32-2.2) 5 - 9 years (5) 1.4 (0.52-4.0) ≥ 10 years (6) 4.6 (1.4-15) <i>Duration of exposure to magnetic fields</i> <i>(Reference < 3 years)</i> 3 - 5 years (1) 0.54 (0.90-3.0) 6 - 8 years (1) 0.55 (0.10-3.0) 9 - 11 years (1) 0.81 (0.15-4.5) ≥ 12 years (3) 4.8 (1.5-15)	Cohort study, SIRs No information on other sources of residential EMF exposure No direct information from study subjects Cumulative exposure not treated as time dependent variable in the analyses

Table 4.19 (continued)

Study	Main results: OR and 95% CI (unless otherwise specified)	Additional notes
(Li <i>et al.</i> , 1997)	Magnetic field exposure in year of diagnosis (Reference < 0.1 μT) 0.1-0.2 μT 1.3 (0.8-1.9) > 0.2 μT 1.4 (1.0-1.9)	Limited information on confounders because of restrictions on interview
Studies using direct residential measurements		
(Severson <i>et al.</i> , 1988)	Mean exposure from one time measurements (Reference: 0-0.05 μT) Low-power configuration 0.05-0.199 μT 1.2 (0.52-2.6) $\geq 0.2 \mu T$ 1.5 (0.48-4.7) High-power configuration 0.05-0.199 μT 0.55 (0.25-1.2) $\geq 0.2 \mu T$ 1.6 (0.49-5.0) Weighted mean exposure (vs. 0-0.5 mT) Low-power configuration 0.05-0.199 μT 1.2 (0.54-2.5) $\geq 0.2 \mu T$ 1.0 (0.33-3.2) High-power configuration 0.05-0.199 μT 0.91 (0.42-2.0) $\geq 0.2 \mu T$ 1.3 (0.35-4.5)	Refusal rate for measurements much higher among controls (27%) than cases (4.9%) One-time measurements made in a limited number of houses (56%) since many subjects had moved recently
(Feychting & Ahlbom, 1994)	Spot measurements (Reference $\leq 0.09 \mu T$) – Matched analyses <i>All leukemia</i> 0.10-0.19 μT 1.1 (0.7-1.9) $\geq 0.20 \mu T$ 1.2 (0.8-1.9) <i>AML</i> 0.10-0.19 μT 0.9 (0.3-2.3) $\geq 0.20 \mu T$ 1.1 (0.4-2.4) <i>CML</i> 0.10-0.19 μT 0.6 (0.1-1.8) $\geq 0.20 \mu T$ 1.5 (0.7-3.2) <i>CLL</i> 0.10-0.19 μT 1.3 (0.7-2.6) $\geq 0.20 \mu T$ 0.9 (0.5-1.8)	Matched and unmatched analyses, adjusted or not for age and SES were carried out No information on other sources of residential EMF exposure

AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia; OLCC, ordinary low current configuration; OHCC, ordinary high current configuration; VHCC, very high current configuration; SES, socioeconomic status; CLL, chronic lymphocytic leukemia; ND, not determined; SIR, standardized incidence ratio

4.3 Epidemiological studies of carcinogenicity in children

Wertheimer and Leeper (Wertheimer & Leeper, 1979) were the first to generate the hypothesis that EMF from electrical power lines and substations are associated with childhood cancer. Since their seminal paper, a number of epidemiological studies have been undertaken to investigate that hypothesis. Interpretation of epidemiological evidence on the potential causal relationship between exposure to magnetic fields and childhood cancer is difficult because of the low incidence of the diseases involved and the rarity of high exposures. The results of several epidemiological studies have been combined to derive a single summary measure of association, and the consistency of the results across individual studies have been examined in meta-analyses by several researchers.

The Working Group decided to exclude studies in which established epidemiological methods were not used, for example those in which advertisements were used to identify subjects or in which dwellings were analyzed rather than subjects. Studies in which the methods were too crude to assess exposure to magnetic fields were not considered; thus, results based on distance alone were not included, nor were those of one study in which 0.1 μT was the highest exposure cut-point (Myers *et al.*, 1990). One study in which exposure was assessed for only 12% of the subjects was also not evaluated (Dockerty *et al.*, 1998). The Working Group also decided not to consider studies that were re-analyses of primary data. As weight is given in the evaluation to individual studies with primary data, formal meta-analyses are included but are only briefly discussed.

The characteristics of all of the studies are summarized in Table 4.20, while the results are summarized in Tables 4.21–4.24, and the meta-analyses are summarized in Tables 4.25 and 4.26.

4.3.1 Effects of power lines

In the case-control study of Wertheimer and Leeper (Wertheimer & Leeper, 1979) cancer mortality was examined from death certificates for residents of greater Denver, Colorado (USA), who died at less than 19 years of age during the years 1950–73. The population was further restricted to subjects living in the greater Denver area and born 1949–73 in Colorado. A total of 344 cases of childhood cancer were identified, and 344 population controls were selected from Denver-area birth certificates matched on birth month and county. Exposure was assessed from the wire code configurations of the homes occupied at the time of birth and the homes occupied at the time of death. Addresses at the time of birth were missing for 20% of cases and addresses at the time of death for 5%. The equivalent information for controls was not available. Wire code configurations were developed as a surrogate method of estimating long-term exposure to EMF from information on nearby distribution lines, transmission lines, and substations (see section 2.5). Two classes of wire-code configuration have been examined: high-current and low-

current configurations. These measures were developed specifically for the Denver area, considering such issues as location of transformers, placement of service drops, and age of the lines (pre-1956 or later). They noted that children who died of cancer were more likely to have lived in homes classified as high-current configuration than in homes classified as low-current configuration. The unadjusted relative risks for leukemias, lymphomas, and nervous system tumors (exposure classification conducted at the death address) were 3.0 (95% CI, 1.8–5.0), 2.1 (0.84–5.2), and 2.4 (1.2–5.0), respectively.

In this exploratory study, when wire codes were assigned, the case or control status of the homes was known to the coder. Thus, exposure assessment was not conducted in a blinded fashion. This may have introduced bias, although the investigators conducted two smaller studies to assess the possible effect of lack of blinding on the outcome (Wertheimer & Leeper, 1979). In part of that study, a separate investigator blindly coded the homes of 70 cases and 70 controls and found a 91% agreement, with about half of the disagreements favoring the association with higher wire codes and half countering the association. [This rate of agreement is similar to that observed in studies in which the process of wire coding was blinded] (Tarone *et al.*, 1998). In a second, smaller study including birth addresses in Colorado Springs and Pueblo, 32% of the cases and 18% of the controls had lived in high-wire code homes, whereas in the larger study the numbers were 37 and 20%, respectively. Furthermore, accounting for potential confounding factors and effect modifiers (e.g. socioeconomic class, urban–suburban differences, traffic density, and gender) did not change the results. None of the relative risks reported in this study was adjusted for these factors. [Death certificate-based studies are subject to differential survival bias. Children in families of higher socioeconomic class have greater access to health care and may thus have higher rates of survival from cancer. Consequently, there may be a bias toward lower socioeconomic cases in this study. If children in families of lower socioeconomic class tended to be categorized in the high-current configuration homes, such bias would inflate the risk estimates.]

Savitz *et al.* (Savitz *et al.*, 1988) conducted a case-control study of residential exposure in the same area as that of Wertheimer and Leeper (Wertheimer & Leeper, 1979). They studied Denver residents under 15 years of age and assessed the exposure in the homes occupied at the time of cancer diagnosis and two years before diagnosis. Cases were obtained from population-based cancer registries and hospital records for the years 1976–83. Controls were selected by random-digit telephone dialing after the close of the study period and were further restricted to have been living in the study area at the time their matched cases (by age \pm three years, gender, and telephone exchange at the time of cancer diagnosis of the matched case) were diagnosed. A total of 356 childhood cancer cases were eligible, and 278 population controls were identified. [It is unclear why there are fewer controls than cases despite the matched selection of controls.] Exposure in the home occupied at the time of diagnosis was assessed by the dichotomous wire coding scheme of Wertheimer and Leeper (Wertheimer & Leeper, 1979) and the five-level wire code of Wertheimer and Leeper (Wertheimer & Leeper, 1982) for 90% of cases and 93% of controls and by spot measurements of EMF taken 1–9 years after diagnosis, by the front door, in the child's and parents' bedrooms, and in all rooms occupied by the child for at

least 1 h/d; 36% of cases and 75% of controls participated. Both the electric and magnetic fields were measured with a model 111 or 113 Electric Field Meter. A weighted average of measurements in all measured rooms was computed and used as a summary exposure measure.

The relative risk for all cancers among children living in homes in the high-current classification was 1.5 (95% CI, 1.0–2.3). A detailed categorization of wiring configurations (very low, which included buried wires, ordinary low, ordinary high, and very high) was analyzed to elucidate a dose–response relationship. The estimated relative risks tend to increase in a linear fashion up to an almost tripling of risk in the highest exposure category (2.8; 0.9–8.4), representing a statistically significant linear trend. This association was not corroborated by spot field-strength measurements, regardless of low or high power use conditions. For leukemias, a relative risk of 1.5 (0.9–2.6) was reported when comparisons were made between high- and low-current classifications; the relative risk with spot measurements of $\geq 0.2 \mu\text{T}$ was 1.9 (0.7–5.6) under low-power use conditions and 1.4 (0.6–3.5) under high-power use conditions. For brain cancer, a relative risk of 2.0 (1.1–3.8) was found for the high-current configuration exposure category. For homes occupied at the time of diagnosis, the relative risk for brain cancer associated with average spot magnetic field-strengths $> 0.2 \mu\text{T}$ was 1.0 (0.2–4.8). No increase in the risk for childhood lymphoma was found in a comparison of high-current and low-current configurations. The relative risk for lymphoma with spot measurements $\geq 0.2 \mu\text{T}$ was 2.2 (0.5–10) under low and 1.8 (0.5–6.9) under high power use conditions. Approximately 20 other potential risk factors for childhood leukemia were considered, and those found to be related to the risk for leukemia, e.g., socioeconomic status, traffic density, maternal age, and smoking during pregnancy, were controlled for in the analyses. Control for confounding did not change the risk estimates.

[An important methodological issue is the selection of controls that represent a residentially stable subset of the population in which the cases occurred after the study period. Control selection bias may have been introduced if exposure was related to characteristics of residential stability. Jones *et al.* examined the effect of the differential stability in a different population and concluded that the control selection bias would lead to an exaggerated estimate of risk. Wertheimer and Leeper, however, presented additional analyses of the Savitz *et al.* study to show that the effect of the bias was to attenuate risk. The very low participation rate for spot measurements among the cases limits the validity of the results based on these measurements. Control selection through random-digit dialing is also a limitation. A strength of the study is the evaluation of a large number of potential confounding factors, including socioeconomic status and traffic density.] (Jones *et al.*, 1993; Savitz *et al.*, 1988; Wertheimer *et al.*, 1994)

London *et al.* (London *et al.*, 1991) conducted a case–control study of 232 cases and 232 population controls, focusing strictly on the incidence of childhood leukemia, and assessed exposures in selected homes during an ‘etiologic period’ defined as the period beginning at the estimated time of conception and ending on the date of diagnosis for children aged one year or less at diagnosis, six months before diagnosis for children aged

one to two years at diagnosis, and one year before diagnosis for children aged above two years at diagnosis. The population base in this study consisted of all children under 10 years of age living in Los Angeles County during the years 1980–87. The 331 eligible cases were obtained from a population-based tumor registry. Controls were friends (65 controls accrued during the period 1980–84) or obtained by random-digit telephone dialing (167 controls accrued during the period 1985–87) and were matched to the cases by age, gender, and ethnicity. [Whether friends of cases are representative of the entire population from which the cases were identified is not clear. Issues previously discussed with regard to random-digit telephone dialing are also applicable here.]

Exposure was assessed by three methods: five-level wire code configuration classifications developed by Wertheimer and Leeper (Wertheimer & Leeper, 1982); spot measurements in the center of the child's bedroom of EMF, static magnetic fields, and the harmonic content of the magnetic field; and 24-h measurements of magnetic fields under the bed in the child's bedroom. Spot measurements were made with a Deno Power Frequency Meter 120; 24-h measurements were made with an IREQ meter in the early parts of the study and with an EMDEX-100 meter for most of the study. The comparability of the data collected with the IREQ and EMDEX meters was ascertained. Harmonic content was determined during the spot measurement period with the broad-band mode of the Deno meter. The investigators also recorded the Earth's magnetic field during the spot measurements with a fluxgate magnetometer (Bartington MAG-01). The participation rates were 42% for both cases and controls for the spot measurements, 50% for cases and 56% for controls for 24-h measurements, and 66% for cases and 81% for controls for wire codes. The measurements were made 1–10 years after diagnosis. Comparisons across these various exposure metrics and between previous studies showed that the 24-h average measurements were considerably higher than the spot measurements in the same homes, and in contrast to the study of Savitz *et al.* (Savitz *et al.*, 1988), more than twice the number of control homes were classified in the high-current configuration categories (45%), but spot-measured magnetic fields were lower within five-level wiring configuration code categories (the difference was especially pronounced in the high-current categories). London *et al.* (London *et al.*, 1991) noted that this discrepancy may have been due to the differences in the electrical distribution system in the Los Angeles and Denver areas.

The relative risk for leukemia in relation to wire code configuration (high- versus low-current classification) was 1.7 (95% CI, 1.1–2.5). With a more detailed categorization of wiring configuration (very low, ordinary low, ordinary high, and very high), the estimated relative risks tended to increase in a linear fashion (statistically significant linear trend) up to more than a doubling of risk in the highest exposure category (2.2; 1.1–4.3). No associations were found with spot electric or magnetic field measurements or static magnetic fields. The results with the 24-h magnetic field measurements indicated an increased risk only for the highest cut-point used ($> 0.27 \mu\text{T}$) with a relative risk of 1.5 (0.7–3.3). The authors noted that similar results were obtained for the ALL and ANLL subtypes of leukemia, but they did not report them separately. Potential factors associated with cancer risk that were controlled for and included were age, gender,

ethnicity, paternal use of pesticides, use of cigarettes, drugs, and incense, traffic density, and socioeconomic status. [A limitation of this study is the uneven ascertainment of wire code information between cases and controls: spot and 24-h measurements of magnetic fields resulted in much lower percentages of ascertainment than wire codes.]

Feychting and Ahlbom (Feychting & Ahlbom, 1993) conducted a population-based case-control study in Sweden to examine the association between exposure to magnetic fields generated by high-voltage power lines and cancer incidence in children. The population base for this study consisted of all children who resided on a property located in a high-voltage power-line corridor, defined as a property located at least partially within 3 m of any 220 or 400 kV power lines. The subjects were children under 16 years of age who resided within a high-voltage power-line corridor during 1960–85. They were followed from the time they moved into the corridor through the end of the study period. The Swedish Cancer Registry was used to identify the 142 cancer cases occurring within high-voltage corridors during the study period. Approximately four controls per case (total, 558) were selected randomly from the study base and were matched according to age, gender, parish residence during the year of diagnosis or the last year before the case moved, and proximity to the same power line.

Exposure to magnetic fields was assessed by spot measurements, contemporary calculated fields, and historical calculated fields (see section 2.4). The spot measurements were made closely following the protocol implemented by Savitz *et al.* (Savitz *et al.*, 1988) with a meter constructed for the purpose of the study. Spot measurements were performed in the home within the power-line corridor in which the patients and corresponding controls had lived closest to the time of diagnosis and were obtained for 62% of cases and controls. The measurements were made 5–31 years after diagnosis, with a median of 16 years (Feychting *et al.*, 1995). Most of the dwellings in which measurements were not made were located in Stockholm. Contemporary calculated field strengths were estimated from information about the height of the towers, distance between the towers, distance between phases, ordering of phases, and line load. The contemporary line load was obtained during the visit to each dwelling. Both transmission and distribution lines were considered; however, less than 20% of the homes were located near distribution lines. Historical annual average line load during the study period was used in calculating historical field strengths for all but one case and four controls. In their analysis, Feychting and Ahlbom (Feychting & Ahlbom, 1993) emphasized the use of historical fields calculated from exposure metrics, due to the presumed accuracy of using historically calculated field strengths to estimate exposures several decades previously for some subjects and the fact that averaged spot measurements are not a representative measure of long-term exposure. Cut-points for the analyses of historical calculations consisted of a three-level, ordinal scale with the following categories: $< 0.1 \mu\text{T}$, $0.1 \mu\text{T}$, $\leq 0.2 \mu\text{T}$, and $\geq 0.2 \mu\text{T}$; analyses were also made for exposures of $\geq 0.3 \mu\text{T}$. Feychting *et al.* (Feychting *et al.*, 1995) examined exposures $\geq 0.5 \mu\text{T}$. With spot measurements, the highest exposure examined was $\geq 0.2 \mu\text{T}$.

The results for historically estimated field strengths showed elevated risks for childhood leukemia with increase in exposure (statistically significant linear trend), up to more than a tripling of risk in the exposure category $\geq 0.3 \mu\text{T}$ (RR, 3.8; 95% CI, 1.4–9.3). When the data on leukemia were further stratified by age and gender, a dose–response trend was observed for single-family dwellings but not multiple-family dwellings. Controlling for potential confounders (age, gender, county, dwelling type, year of diagnosis, socioeconomic status, and levels of nitrogen dioxide as an estimate of exposure to motor vehicle exhaust) did not alter this relationship. For exposure to $0.5 \mu\text{T}$, the relative risk was 4.6 (1.5–14). There was no evidence in this study of an association between historically calculated exposure to magnetic fields and all cancers combined, lymphomas, or central nervous system tumors. In analyses based on spot measurements, no increase in risk was observed for all cancers, leukemia, or central nervous system tumors.

In analyses to validate the various calculations and measurements of magnetic fields used by Feychting and Ahlbom (Feychting & Ahlbom, 1993), spot measurements showed poor agreement with calculated historical fields but good agreement with contemporary calculations. This result was interpreted by the authors as an indication that spot measurements are poor predictors of exposure many years earlier. [A strength of this study is the minimal potential for selection bias in the analyses of historical calculations. Another strength is that the historical calculations are based on established laws of physics and conditions prevailing prior to diagnosis. A limitation is the small number of exposed subjects.]

Olsen *et al.* (Olsen *et al.*, 1993) conducted a population-based case-control study to investigate whether residence before and after birth near high voltage facilities was associated with an increased risk for childhood cancer. They studied 1707 cases of leukemia, malignant lymphoma, and central nervous system tumor in Danish children aged < 15 reported to the Danish Cancer Registry during the years 1968–86. Two to five controls, selected randomly from the Danish Central Population Register among cancer-free children, were matched to each case by gender and age (\pm one year), for a total of 4788 controls. They assessed exposure from calculated average magnetic field strengths. Residences located outside the area of potential exposure to high-voltage facilities (generally > 300 m away from overhead lines or transformer substations) were assumed to have an average calculated magnetic field of zero. Estimates of relative risk were obtained for cut-points associated with low ($0.1 \mu\text{T}$), intermediate ($0.25 \mu\text{T}$), and high exposure ($0.4 \mu\text{T}$) and were adjusted for gender and age at diagnosis.

Comparisons made between exposure to $\geq 0.4 \mu\text{T}$ and to $< 0.1 \mu\text{T}$ resulted in crude relative risks of 6.0 (95% CI, 0.8–44) for leukemia, 6.0 (0.7–44) for central nervous system tumors, and 5.0 (0.3– 82) for malignant lymphoma. In analyses further adjusted for the potential confounding effects of population density, socioeconomic class, and family's mobility, no effect on the risk estimates was observed. [The current on the transmission lines was not recorded, but was estimated on an annual average basis by an expert group of utility planners. This process led to uncertainty in the calculated fields. In

addition, the methods of calculation were not confirmed by measurements. Due to the low prevalence of exposure, the risk estimates were unstable.]

Verkasalo *et al.* (Verkasalo *et al.*, 1993) conducted a population-based cohort study of 134 800 Finnish children (68 300 boys and 66 500 girls) aged < 20 who lived within 500 m of 110–400 kV overhead power lines and to magnetic fields calculated to be $\geq 0.01 \mu\text{T}$ during the period 1970–89. The 140 cases of childhood cancer were obtained from the Finnish Cancer Registry and included all primary tumors of the nervous system, leukemia, lymphoma, and all other cancers grouped. Exposure to magnetic fields was estimated from calculations of the annual average fields for all years between birth and diagnosis, based on information about typical line configurations, historical load on the lines, and distance (obtained from computerized sources). The historical load for the last third of the observation period was obtained from simulations, those for the middle third from existing records, and those for the first third from the last year with existing records. Exposure was assessed by two calculated estimates: average magnetic field and cumulative exposure. Cumulative exposure was defined as the average exposure per year multiplied by the number of years exposed (μT -years). The cut-points chosen for high exposure were $0.2 \mu\text{T}$ for average exposure and $0.4 \mu\text{T}$ -years for cumulative exposure to magnetic fields. These cut-points were selected *a priori* from the distribution of the number of exposed children and taking into account the typical residential magnetic field of $0.01 \mu\text{T}$ (referent exposure). [The calculated fields were not validated by actual measurements.] A cohort approach with person–years calculations was used to investigate the risk of cancer in children living close to power lines. The expected number of cases was calculated from Finnish national incidence rates.

Regardless of exposure metric, a four-fold increase in risk for nervous system tumors was seen among boys (SIR, 4.2; 95% CI, 1.4–9.9) for cumulative exposure, but not for girls for whom no cases were observed at high exposure. The increase in risk was largely attributable to one boy who had three primary tumors of the nervous system. If the analysis had been restricted to first primary cancers, the estimate would have been slightly elevated, with a larger confidence interval overlapping the null. The SIRs for leukemias, lymphomas, and cancers at other sites were close to unity for both average and cumulative exposure. The results for cumulative exposure of $\geq 1.0 \mu\text{T}$ -years has also been reported (Verkasalo *et al.*, 1994). The relative risk estimates were 2.3 (95% CI, 1.0–1.3) for all cancers combined, 3.5 (0.7–1.0) for leukemia, and 2.8 (0.6–8.1) for nervous system tumors. These risk estimates were not adjusted for potential confounding factors. In particular, Verkasalo *et al.* (Verkasalo *et al.*, 1993) reported that childhood cancer, other than leukemia, was commoner in urban than in rural settings. Thus, the crude risk estimates reported (excepting leukemia) are slightly higher than they would have been had the analysis been adjusted for this covariant. [Selection bias is not a concern in this study since it is population-based. The study is limited by the small number of exposed subjects. The calculated field strengths were not validated by measurements. The validity of including three brain tumors in one subject as three separate cases is questionable.]

The United States West Coast Childhood Brain Tumor Study was a multicenter, population-based case-control interview study to evaluate potential environmental and nutritional risk factors for diagnosis of brain tumor (benign or malignant tumor of the brain, cranial nerves, or cranial meninges) in children aged ≤ 19 in 1984–90. To be eligible for participation in the study, each child's biological mother had to speak English, be available for interview, and have a telephone. Mothers of children with brain tumors were asked questions about exposure and conditions thought likely to be related to risks for pediatric tumor (e.g. ionizing radiation, predisposing genetic syndromes, exposure to magnetic fields during pregnancy). Subanalyses of this multicenter trial addressed the risk for childhood brain tumor in relation to residential exposure to magnetic fields in Los Angeles, California (Preston-Martin *et al.*, 1996b), to residential power-line configurations, electric heating sources, and electric appliances in Seattle, Washington (Gurney *et al.*, 1996), and the use of electric blankets and water-bed heaters for the entire study population (Preston-Martin *et al.*, 1996a).

Preston-Martin *et al.* (Preston-Martin *et al.*, 1996b) initiated a study of magnetic fields two years after the beginning of the multicenter interview study. The parents of cases were re-contacted by telephone in order to obtain measurements of magnetic fields at their residences. Of the 304 cases in the multicenter study, 298 cases were included in the substudy. A control group of 298 children within the same range of birth years and with the same distribution by gender as the cases were identified by random-digit dialing, were matched to the cases by gender, birth date (\pm one year), and had to be the same age at the time of interview as the case had been at the time of diagnosis. Cases and controls were accrued concurrently during 1989 to the end of the study period; before 1989, the controls were accrued by random-digit dialing [but further details are not given]. Exposure to magnetic fields was assessed from spot measurements taken outside the residence and from wire code configurations. Magnetic fields could be measured for 59% of the eligible cases and 54% of the eligible controls. The exterior residential measures included the fields over water meters and water pipes, static magnetic fields, front-door fields, and STAR magnetic field profiles (see section 2.3.1), including the front wall and perimeter of the dwelling. [The STAR meter does not measure magnetic fields at harmonic frequencies.] For cases whose current residence was also the residence in which they lived at the time of diagnosis (and for their matched controls), interior home measurements were taken, consisting of 24-h EMDEX measurements in the children's bedrooms and in a second room in which the children spent most of their time.

Wire codes were obtained for three types of residences: the residence occupied at the beginning of the study (nine months before birth), the residence occupied for the longest time, and the residence occupied at the date of diagnosis. Wire codes were obtained for 80% of cases for homes two years before diagnosis. The investigators found that too few subjects were within category of the usual reference wire code, 'underground', to serve as a stable reference, and so they pooled the 114 cases and 102 controls in the 'very low' and 'ordinary low' categories and used this as the reference category. [This categorization of wire codes is unusual.]

Preston-Martin *et al.* (Preston-Martin *et al.*, 1996b) reported elevated risks for brain cancer in several exposure categories but no statistically significant trend, e.g. for all exposure metrics. When the analyses were restricted to very high exposure ($> 0.3 \mu\text{T}$), the 24-h EMDEX measure revealed a relative risk of 1.7 (95% CI, 0.6– 5.0), and spot measurements and STAR profiles both led to a relative risk of 0.9 (95% CI, 0.3– 3.2 and 0.2–4.1, respectively). These estimates are highly unstable owing to the small numbers of subjects living in residences with magnetic field strengths $> 0.3 \mu\text{T}$, i.e. 12 or fewer cases and 7 or fewer controls. [Limitations associated with random-digit dialing telephone methods to select controls are applicable to this study. Notably, the participation rates for all EMF measurements except wire codes were low. Stratified analyses based on whether controls were concurrently accrued with cases yielded inconsistent risk estimates with wire codes.]

Gurney *et al.* (Gurney *et al.*, 1996) initiated an epidemiological study to assess the relationship between childhood brain cancer and proximity to high-current power lines. The study population was derived from the Seattle, Washington, component of the multicenter United States West Coast Childhood Brain Tumor Study and comprised children < 20 years of age at diagnosis of a primary brain tumor in 1984–90, who were identified from a population-based cancer registry. Of the 179 eligible cases, 133 participated in the study (a participation rate of 74%). A control group of children stratified within the same range of birth years and county of residence as the cases was identified by random-digit dialing, which resulted in the participation of 270 controls out of 343 eligible for inclusion (a participation rate of 79%). Exposure was assessed by the five-level wire coding scheme developed by Wertheimer and Leeper (Wertheimer & Leeper, 1982).

Gurney *et al.* (Gurney *et al.*, 1996) reported no association between the occurrence of pediatric brain tumors and residential exposure to magnetic field sources, which included analyses of five-level and two-level wire code configurations. The risk for brain tumor did not increase with increasing exposure (relative to underground wiring) when the five-level Wertheimer and Leeper wire code configuration was analyzed, the relative risks being 1.3 (95% CI, 0.7–2.1) for very low current configuration, 0.7 (0.3–1.6) for low current configuration, 1.1 (0.6–2.1) for high current configuration, and 0.5 (0.2–1.6) for very high current configuration. When the wire codes were dichotomized (high vs. low), the relative risk was approximately unity. After evaluating 13 potential risk factors, the authors found no associations, and thus crude risk estimates were reported. [The limitations associated with random-digit dialing to select controls are applicable to this study. A strength is the large number of potential confounding factors evaluated.]

Linnet *et al.* (Linnet *et al.*, 1997) assessed the association between childhood ALL and residential exposure to magnetic fields for children aged < 15 who resided in Illinois, Indiana, Iowa, Michigan, Minnesota, New Jersey, Ohio, Pennsylvania, or Wisconsin and were registered with the Children's Cancer Group, in whom ALL was diagnosed during the period 1989–94. A total of 767 cases were eligible for inclusion. Random-digit telephone dialing was used to recruit the controls, who were individually matched to the

cases by the first eight digits of their telephone numbers (including area code), age, and race, resulting in 725 controls who were eligible for inclusion. The authors reported a participation rate of 78% for cases and 63% for controls.

Magnetic fields were measured at all subjects' residences with EMDEX-C meters. The standardized measurement protocol followed included 24-h measurements in the child's bedroom (with the meter placed under or adjacent to the bed), 30-s measurements in the center of the child's bedroom, the family room, the kitchen, and the room in which the mother slept during the subject's pregnancy, and a 30-s outdoor measurement made within 1 m of the front door of the residence. A single summary exposure metric for each home was calculated from a weighted average of the room measurements (see section 2.3.1). The weights were based on the typical amount of time spent in each room according to the child's age (Kleinerman *et al.*, 1997). For each child under the age of five, the investigators attempted to measure magnetic fields in all homes the subject had lived in for at least six months and required that at least 70% of the child's life had been spent in the measured homes. For children over the age of five, the investigators measured a maximum of two homes lived in during a reference period of five years immediately preceding diagnosis, and required that the child had lived for at least 70% of the reference period in the measured houses. A weighted average of all homes was used as the summary exposure metric. On the basis of the distribution of the measurements in the control homes, the following exposure categories were chosen *a priori* for the summary measurements of residential magnetic fields: 0.065 μT , 0.065–0.09 μT , 0.1–0.19 μT , and $\geq 0.2 \mu\text{T}$. Higher exposures (up to 0.5 μT) were also measured. Wire code classifications (the five-level Wertheimer-Leeper classification and the modified three-level Kaune–Savitz scheme) were assigned to the subjects' main residences for a subgroup of 408 case–control pairs in which both the case and the control had been residentially stable, i.e. lived for at least 70% of the reference period in one home, and to those in which the family had lived during the mother's pregnancy (230 matched case–control pairs). [In most cases, the fields were measured within two years of diagnosis; thus, the measurements taken are more representative of exposure during the relevant etiologic period than fields many years and sometimes decades after diagnosis. There are apparent discrepancies in the reported participation rates of all eligible subjects: we calculate participation rates of 68% for cases and 48% for controls. Another concern is that wire codes were assessed for only 43% of the eligible cases and 32% of the eligible controls. Limitations associated with the use of random-digit dialing to select controls apply to this study.]

For TWA exposure to $\geq 0.2 \mu\text{T}$, the matched and unmatched analyses give relative risks of 1.5 (95% CI, 0.91–2.6) and 1.2 (0.86–1.8), respectively. For exposure to $\geq 0.3 \mu\text{T}$, matched analyses were not reported, but the unmatched analyses gave a relative risk of 1.7 (1.0–2.9). For the *a priori* measurement categories, when exposure was evaluated as a continuous variable, the *p* value for trend was 0.09 for the matched analysis and 0.15 for the unmatched analysis. When exposure was evaluated as a categorical variable, the *p* value for trend was 0.12 for the matched analysis and 0.22 for the unmatched analysis. In the matched analyses based on wire code configurations, the risk for childhood ALL was not associated with very high wire codes in the subject's main residence: relative risk =

0.88 (95% CI, 0.48–1.6) for the Wertheimer-Leeper wire code and 1.0 (0.65–1.7) for the Kaune–Savitz wire code. The results reported for the 225 matched case–control pairs for which wire codes were assessed for the mothers’ residences during pregnancy showed a trend ($p = 0.07$) for the Wertheimer–Leeper wire code configuration.

All of the unmatched risk estimates reported by Linet *et al.* (Linet *et al.*, 1997) were adjusted for the age of the subject at the reference date, the subject’s gender, the mother’s educational level, and family income. These adjustments for potentially confounding variables had little effect on the risk estimates. The authors note that a limitation of this study is the use of random-digit dialing, which was believed to have resulted in higher family incomes of controls as compared with cases. The authors interpret their study as providing little evidence for an association between exposure to magnetic fields and childhood leukemia. [It is unclear why the criteria for matching controls to cases did not include gender, since males are at greater risk for leukemia than females.] (Robison *et al.*, 1995) [The heterogeneity of wire codes as estimates of exposure to magnetic fields across geographic areas (nine states) may also be of concern. The use of TWA measured fields in several different homes may have diluted the effect (e.g. high exposures for short times averaged with low exposures for longer times). The results based on 24-h measured fields strengthen the evidence for an association, especially in view of the pattern of trend in the estimates; however, the results for wire codes detract from this evidence.]

Tynes and Haldorsen (Tynes & Haldorsen, 1997) conducted a nested case-control study of Norwegian children < 15 years of age who had lived in a census ward crossed by power lines (voltages of 45 kV or more in urban areas and more than 100 kV in rural areas) during at least one of the years 1960, 1970, 1980, 1985, 1987, or 1989. Cases were identified from the Cancer Registry of Norway and consisted of children in whom cancer had been diagnosed during the years 1965–89. For each case, five controls were selected from the cohort who had been alive at the time of diagnosis of the case and were matched by gender, year of birth, and municipality. Calculated historical magnetic fields were the primary basis for classifying study subjects into different categories of exposure. All power lines 11 kV or greater were considered in the calculations of exposure. Underground cables were not taken into account because it was assumed that they were not a significant source of magnetic fields. Categories for the analyses of exposure were obtained for a three-level ordinal scale from average background levels in a typical Norwegian residence (< 0.05 μT) and the median TWA exposure of the controls (0.14 μT). [The calculated fields were not validated by actual measurements.]

The risk for cancers at all sites combined in relation to calculated TWA exposure to magnetic fields from birth to diagnosis was estimated to be 1.9 (1.2–3.3) for the category $0.5 \leq 0.14 \mu\text{T}$ and 0.9 (0.5–1.8) for exposure to $\geq 0.14 \text{ T}$; the corresponding risks for leukemia were 1.8 (0.7–4.2) and 0.3 (0.0–2.1), respectively. Adjustment for socioeconomic status and number of residences did not affect these results. [The results are based on a low exposure category (0.14 μT , and few subjects were exposed to magnetic field strengths of $\geq 0.14 \mu\text{T}$: approximately 2% (TWA exposure) and 4% (calculated exposure closest to time of diagnosis) of the study population.]

Michaelis *et al.* (Michaelis *et al.*, 1998; Michaelis *et al.*, 1997) performed a population-based case-control study to explore the association between childhood leukemia and exposure to EMF in Lower Saxony, Germany, and later used the same study design in Berlin; they then pooled the two sets of results. Cases were recruited from the German Childhood Cancer Registry. The eligibility criteria for the study in Lower Saxony were newly diagnosed leukemia during the years 1988–93, date of birth after 1 July 1975, < 15 years of age at diagnosis, and a resident of Lower Saxony at the date of diagnosis. For the cases in Berlin, the diagnosis had to have been made between January 1991 and September 1994, and the children had to be residents of Berlin at the time of diagnosis. A total of 283 cases were eligible. Controls (919) were selected from the respective local government offices for registration of residents and were matched to the cases by gender, date of birth, and district within the city. Questionnaires were distributed to patients and controls to ascertain their residential history and potential confounding factors, i.e. socioeconomic status and degree of urbanization. The participation rates were 62% for cases and 45% for controls. [The age ranges and observation periods differed for the two cohorts, but these were controlled for in the analysis.]

Exposure was assessed by two methods: measurements of the magnetic field over a 24-h period and indoor spot measurements with an EMDEX II meter. The 24-h measurements were collected in the subject's bedroom and in the living room of the residence where the child had lived longest before the date of diagnosis. Measurements were made 1–7 years after diagnosis. The median magnetic field strength during the 24-h period in the child's bedroom was the primary measure used in the analyses. Median values were preferred to mean values since they are less likely to be influenced by outlying values. The relative risk estimates were adjusted for gender, age, socioeconomic status, and degree of urbanization.

The exposure was dichotomized at 0.2 μT , and the risk estimate was 2.3 (95% CI, 1.2–12). The risk was higher in Lower Saxony, 3.2 (0.7–15) than in Berlin, 1.3 (0.1–12). When the analysis was restricted to the median magnetic field measured during the night, the risk estimate for the 0.2 μT cut-point was 3.8 (1.2–12). No associations were reported between the incidence of childhood leukemia and indoor spot measurements. [The main limitations of this study are the low percentage of subjects exposed to magnetic fields at strengths > 0.2 μT , the reduction in the study size due to inability to obtain permission to measure residential magnetic fields, and the lower participation rate among controls than among cases.]

4.3.2 Effects of appliances

Several epidemiological studies have been conducted to determine the association between exposure to magnetic fields attributed to the use of various electrical appliances and childhood cancer. Appliances that can result in substantial exposure were usually studied and assessed on the basis of each subject's recall of use. Electrical appliances may be a potentially important contributor to overall exposure to EMF.

Savitz *et al.* (Savitz *et al.*, 1990) examined the association between the incidence of childhood cancer and prolonged exposure to electrical appliances on the basis of information from interviews conducted during their previous case-control study (Savitz *et al.*, 1988), described in the previous section. The appliances of primary interest in this study were electric blankets, heated water-beds, electric heating pads, and bedside electric clocks, and they studied both the mother's and the child's use, i.e. prenatal and postnatal exposure, respectively. Exposure was first examined as 'ever' or 'never' use, separately for prenatal and postnatal exposures; more detailed information obtained included electric blanket and heated water-bed settings, duration of use, and timing of use. Complete information on use of appliances was obtained for 233 mothers of patients (65% of those eligible) and 206 mothers of controls (74% of those eligible) and for 244 patients (69% of those eligible) and 216 controls (78% of those eligible).

Use of none of the appliances considered in the study was associated with a notably elevated relative risk (ever vs. never use) for cancers at all sites. The estimated, unadjusted risks with prenatal exposure to electric blankets were 1.8 (95% CI, 0.9–4.0) for childhood brain cancer, 1.3 (0.7–2.6) for leukemia, and 1.1 (0.4–3.6) for lymphoma. In analyses of prenatal exposure stratified by electric blanket use during the first trimester, the estimated risks were 1.6 (0.8–3.2) for cancers at all sites, 4.0 (1.6–9.9) for brain cancer, and 2.3 (1.0–5.8) for leukemia. For postnatal use of electric blankets, the crude risk estimates were 1.5 (0.6–3.4) for cancers at all sites, 1.5 (0.5–5.1) for leukemias, 1.2 (0.3–5.7) for brain cancer, and 1.0 (0.2–8.6) for lymphoma.

[The methodological limitations of this study include those with the control selection process, described by Savitz *et al.* (Savitz, 1988) and the fact that the study size was severely limited for assessing the exposures of interest, especially in the postnatal analyses, as very few children were exposed to electric blankets or electric water-bed heaters. Parents' recollection of appliance use was the only method used to assess exposure, and their recall may be incomplete; furthermore, the parents of patients might report differently from those of controls, resulting in recall bias. The questionnaire was not validated. Most of the statistical analyses in this study were based on 'ever/never' use of appliances. An underlying assumption is that the pattern of appliance use among users was similar for cases and controls; if the patterns of use were dissimilar, the sensitivity to detect an association would be diminished.]

London *et al.* (London *et al.*, 1991) examined the association between the incidence of childhood cancer and prolonged exposure to electrical appliances on the basis of information collected at interviews during their study of residential exposure. The appliances of primary interest were those that could produce considerable magnetic fields. Children's exposure was estimated on the basis of regular use (at least once a week) of the appliance. The statistical analyses were based on regular vs. infrequent use (less than once per week). Mothers' exposure was based on use of the appliance at any time during pregnancy. Complete information on use of 15 appliances by mothers and children was obtained for 232 cases and 232 controls; the participation rates were 70% for cases and 90% for controls.

The relative risks associated with use of 11 of the appliances were greater than the null. The risks for leukemia among children who used black-and-white televisions and electric hair-dryers at least once a week were 1.5 (95% CI, 1.0–2.2) and 2.8 (1.4–6.3), respectively, as compared with nonusers and children who used these appliances less than once a week. The largest relative risks were associated with use of electric blankets and curling irons, but these estimates were unstable because of the small number of subjects. The risks associated with use by the mothers of three of the five appliances that were evaluated were greater than the null. [The limitations of this study are similar to those described for the study of Savitz *et al.*] (Savitz *et al.*, 1990).

As part of the study of Preston-Martin *et al.* (Preston-Martin *et al.*, 1996b), a questionnaire was administered to mothers and fathers about exposures and conditions thought likely to be related to the risk for pediatric brain tumors. Mothers were asked about exposure to appliances during their pregnancy and about their child's daily exposure to specific appliance-related sources of magnetic fields. The exposures were examined as 'ever' or 'never' used, separately for the mother's exposure during pregnancy and the child's exposure. Complete information on appliance use by mothers and children was obtained for 304 cases and 304 controls.

The risks associated with use by the mothers of six of the seven appliances that were evaluated were greater than the null. An approximately two-fold increase in risk for brain tumors was reported among children whose mothers had slept in electrically heated water-beds during pregnancy (2.1; 1.0–4.2). For the 12 appliances that were evaluated for children, the relative risks were greater than the null for six. As for the mothers, there was a two-fold increase in risk among children who slept in electrically heated water-beds (2.0; 0.6–6.8). [With such low percent use of these appliances, it is difficult to assess their impact with respect to cancer risk.]

Preston-Martin *et al.* (Preston-Martin *et al.*, 1996a) evaluated the effects of use of electric blankets and water-bed heaters on the risk for pediatric brain tumors. Since there were not enough cases in Los Angeles to adequately address this hypothesis, cases were included from two other regions that participated in the multicenter US West Coast Childhood Brain Tumor Study: Seattle, Washington and San Francisco, California. The cancer registry at each location was used to identify 813 cases, of which 540 children were considered to be eligible on the basis of information in the registry and the study criteria and were enlisted in the study as cases. Controls were identified and recruited from the same geographic regions in which the cases arose by a two-step random-digit telephone dialing procedure. This resulted in a comparison group that was similar to the cases with regard to gender and age and at ratios of approximately two controls per case in Seattle and San Francisco and one control per case in Los Angeles, for a total of 801 eligible controls. Of those eligible to participate, 73% of cases and 74% of controls were interviewed for the study.

Maternal use of electric blankets during pregnancy with the patient, regardless of trimester or use, was not associated with subsequent risk for brain tumor; thus, the

relative risk as compared with nonusers of these appliances was 0.9 (95% CI, 0.6-1.2). Similar results were reported for prenatal use of water-beds with electric heaters, but the risk varied substantially with geographic area. The relative risk for pediatric brain tumor associated with maternal use of heated water-beds during pregnancy was 2.1 (1.0–4.4) for Los Angeles participants and 0.7 (0.4–1.0) for participants from San Francisco and Seattle. [This study includes information about use of electric blankets and heated water-beds that was reported by Preston-Martin *et al.* and Gurney *et al.*] (Preston-Martin *et al.*, 1996b) and (Gurney *et al.*, 1996). [Although data from three study sites was pooled, exposure to electric blankets and heated water-beds was relatively uncommon, especially among children. Furthermore, reported use of these appliances from the questionnaires may not have been a sensitive enough measure to detect differences in brain cancer risk due to prolonged exposure to magnetic fields.]

Gurney *et al.* (Gurney *et al.*, 1996) assessed exposure to magnetic fields from electric blankets and heated water-beds on the basis of responses to a questionnaire administered in person to 133 patients and 270 controls, with participation rates of 74% among cases and 79% among controls. A mailed questionnaire was used subsequently to collect information on use of electric heating and electric appliances other than electric blankets and water-beds. Questionnaires were returned for 98 cases and 208 controls. The analyses of use of electric heaters (within three years before diagnosis of the cancer) and appliances were based on whether the subject had ever used the appliance in question or never used it.

Mothers' use of seven appliances and heat sources was evaluated. The only increase in relative risk was that associated with prenatal use of an electric water-bed. Of the relative risks associated with use of 19 appliances and heat sources that were evaluated for children, eight were greater than the null. [The study size was severely limited for assessing the exposures of interest. Recall may have been incomplete, and it is unclear whether the parents of the patients report differently from those of controls, resulting in recall bias. Most of the statistical analyses in this study were based on 'ever/never' use of appliances. An underlying assumption is that the pattern of appliance use among users was similar for cases and controls; if the patterns of use were dissimilar, the sensitivity to detect an association would be diminished.]

As part of a study of residential exposure to magnetic fields, Linet, *et al.* (Linet *et al.*, 1997), Hatch, *et al.* (Hatch *et al.*, 1998), evaluated the association between childhood ALL and use of electrical appliances during pregnancy and childhood. The study population is described in section 4.2.2. Personal interviews were conducted with 788 patients and 699 controls, corresponding to participation rates of 84% among cases and 54% among controls. [The authors report participation rates of 88% and 64%, but the number of eligible cases was 942 and that of eligible controls, 1232.] Of these participants, 640 matched pairs were used in the analysis. Questions were asked about the mother's use during pregnancy and the child's use of electric blankets, mattress pads, heating pads, water-beds, stereos or other sound systems, television, video machines in arcades, computers, microwave ovens, sewing machines, hair-dryers, curling irons, humidifiers,

and electric clocks. Use of stereo systems without headsets, night lights, and ceiling fans was considered unlikely to have resulted in substantial exposure to magnetic fields, but they were included as 'red herring' variables to evaluate the potential for recall bias. The interviewers asked for the child's age when starting and stopping use of a specific appliance and the frequency of use during the year before diagnosis. For three appliances associated with potentially high exposure to magnetic fields (electric blankets, water-beds, and hair-dryers), questions were asked about the frequency of use during the last year of use if the child had stopped using the appliance. The authors analyzed the use of each of the appliances separately and did not create an overall estimate of exposure to magnetic fields from appliances. Mattress pads and electric blankets were analyzed together. Matched analyses were conducted with adjustment for income and maternal education. Potential confounding from parental age, occupation, smoking, type of dwelling, urbanization, number of siblings, and breast feeding were evaluated. Age- and gender-specific analyses were done, and the mother's use was analyzed according to trimester.

The estimated risks were 1.6 (95% CI, 1.1–2.3) for mother's use of electric blankets or mattress pads and 1.5 (1.0–2.1) for their use of heating pads and humidifiers, but with no consistent dose–response pattern. When frequency of use was evaluated, a reduced risk was found for use of sewing machines (0.76; 0.59–0.98). The risk estimates for use of other appliances were close to unity.

Elevated risks were found for children's use of electric blankets (2.8; 1.5–5.0), hair-dryers (1.6; 1.2–2.1), curling irons (1.7; 0.91–3.3), video arcade machines (1.7; 1.2–2.3), sound systems with headset (1.3; 0.97–1.8), and video games connected to a television (1.9; 1.4–2.7). Consistent dose–response patterns were found for use of sound systems with a headset, video arcade machines, and video games connected to a television, but not for use of electric blankets, hair-dryers, or curling irons. The risk estimates for other appliances were close to unity, except for night-lights (0.81; 0.63–1.0). None of the 'red herring' variables was associated with an increased risk. Time spent watching television was associated with disease, and the risk increased with increasing time. Watching television at closer than 6 feet (2 m) was also associated with disease, but the highest risk was found for distances ≥ 4 to ≤ 6 feet (≥ 1.3 and ≤ 6 m; relative risk, 1.7; 1.2–2.4). For distances < 4 feet (< 1.3 m), the relative risk was 1.6 (1.1–2.4).

When the time spent watching television and the distance from the television were combined, inconsistent dose–response patterns were seen. The authors emphasized the potential for differential recall bias, especially when patterns of use changed after diagnosis, as may be the case for television viewing patterns. They also mention the possibility that mothers of children with ALL may be more prone to remember use of appliances discussed in the media as potential risk factors for leukemia, such as electric blankets. Another source of error noted by the authors is potential selection bias due to the use of random-digit dialing for control selection and the lower participation rate among controls, both being associated with socioeconomic status. The authors also mention the possibility of confounding from some factor related to the type of life-style associated with, for example, watching television for many hours per day. They found it unlikely

that the associations found reflect a causal association between exposure to magnetic fields and childhood ALL. [The inconsistent dose–response patterns may also be the result of nondifferential exposure misclassification.] Selection bias is unlikely to explain the findings for use of electric blankets. Differential recall bias may have affected the results, but a comparison between answers from an earlier telephone interview and those obtained at the later personal interview about electric blanket use did not indicate differences in the recall between cases and controls. [Questions on other appliances were not validated. Another limitation is the considerable lower participation rate among controls as compared to cases. Finally, the magnetic fields of the appliances were not measured.]

4.3.3 Meta-analyses of studies of effects of power lines

In reviewing the individual epidemiological studies, it is difficult to summarize and draw overall conclusions about a possible association between exposure to ELF EMF and the incidence of childhood cancer. These difficulties arise due to differences in study design, case selection, identification of controls, exposure assessment methods, and accounting for such factors as confounders and effect modifiers. Furthermore, a common feature of most of the studies was the lack of a large population of highly exposed children.

Meta-analysis provides a means for summarizing the results of individual studies into a single measure of effect (Fleiss, 1993). The objectives of a meta-analysis often include identification and review of all studies conducted on a specific topic; assessment of the consistency and comparability of the results of each identified study; estimation of average measures of effect, if studies are sufficiently similar; and assessment of reasons for heterogeneity (Blair *et al.*, 1995).

Four meta-analyses have been conducted of studies of the possible association between exposure to magnetic fields and the incidence of childhood cancers, in which summary effect measures were stratified by exposure metric (wire codes, distance from electrical facility, calculated magnetic fields, and measured magnetic fields) (NRPB, 1992); (Ahlbom *et al.*, 1993); (Miller *et al.*, 1995); (Meinert & Michaelis, 1996). These are summarized in Tables 4.25 and 4.26. In general, the summary risks for each of the metrics considered were elevated but less than 2.0 at all cut-points. [In general, as the number of studies included in the meta-analysis increased, the confidence intervals narrowed, indicating increasing statistical power; however, the effect estimates did not change substantially. Use of different exposure metrics, such as 24-h measures vs. spot measures, or cut-points, such as 0.2 μT vs. 0.3 μT , can result in quantitative but not qualitative differences.]

Wartenberg and colleagues (Wartenberg *et al.*, 1998) and National Academy of Sciences (NRC *et al.*, 1997) conducted a more extensive meta-analysis of the studies of the possible association between exposure to magnetic fields and the incidence of childhood

leukemia and brain tumors. In addition to calculating a summary effect measure, they conducted a limited sensitivity analysis, assessed the heterogeneity among the studies, evaluated possible dose–response relationships, evaluated the likelihood of publication bias, and assessed the robustness of results to inclusion of additional studies. They also provided a more carefully considered rationale for grouping studies.

The reported summary effect measures are similar to those reported in previous meta-analyses: generally > 1.0 but < 2.0 . The results were moderately robust to exclusion of individual studies. Substantial heterogeneity was reported for wire codes and proximity to electrical facilities for both leukemia and brain tumors. Analyses to characterize the source of the heterogeneity gave equivocal results. The relative risk estimates for dose–response relationships for spot measures were weakly elevated, those for calculated fields were slightly higher, and those for wires codes (converted to magnetic fields by using the mid-range of the wire code category) were still slightly higher. There is little evidence for publication bias. Calculations showed that inclusion of an extremely large study would be required to substantially change the reported summary estimates of effect.

[This meta-analysis included several studies that this Working Group excluded from consideration in their deliberations.]

4.3.4 Summary

Cancers at all sites

The Working Group considered that an evaluation of cancers at all sites combined would not be informative because it would be driven largely by the results for leukemia and brain cancer.

Childhood leukemia

Four studies in which wire codes were used to assess exposure to EMF were considered to be of sufficient quality to be used in the evaluation of an association between the incidence of childhood leukemia and exposure to magnetic fields. Three of the studies found an increased risk (Wertheimer & Leeper, 1979); (Savitz *et al.*, 1988); (London *et al.*, 1991), and one study found no effect on the risk for childhood leukemia (Linet *et al.*, 1997). A trend of increasing risk with increasing wire codes was found by both Savitz *et al.* and London *et al.* Wertheimer and Leeper did not assess trend. The unblinded assessment of the wire codes in the latter study may have affected the results, but it is unlikely that this potential bias can fully explain the observed increase in risk.

Selection bias introduced by the control selection technique is unlikely in the Wertheimer and Leeper study, because a birth registry was used as the population source. In the other

three studies, random-digit dialing was used to select controls, which may have introduced some bias toward higher socioeconomic status among the controls. If higher socioeconomic status is related to lower wire codes, use of random-digit dialing may have led to an overestimation of the risk. As Savitz *et al.*, London *et al.*, and Linet *et al.* all used random-digit dialing to select controls, it is unlikely that the associated bias would have affected only the risks found by Savitz *et al.* and London *et al.* The study of Savitz *et al.* has a further limitation in the way in which controls were selected, requiring them to be residentially stable; this may have introduced bias leading to an overestimation of the risk, but it is unlikely that this could entirely explain the larger risk estimate. The observed elevated risks and dose–response patterns cannot be explained by selection bias.

Confounding from other risk factors for childhood leukemia must also be considered. The etiology of this disease is largely unknown. The most frequently discussed factors that may be related to both wire codes and childhood leukemia are traffic density and socioeconomic status. Confounding from traffic density was evaluated in all three studies that showed increased relative risks and was found not to explain the observed association. It was not evaluated in the study of Linet *et al.* The potential impact of socioeconomic status was evaluated in all four studies: it did not explain the observed results. Furthermore, Savitz *et al.* evaluated a substantial number of additional potential risk factors, which were also shown to have little effect on the risk estimates.

The lack of an association with wire codes in the study by Linet *et al.* is difficult to explain, given the associations observed in the other studies. The validity of using wire codes in regions other than in Denver is not clear, but the potential shortcomings should have applied to the studies of both Linet *et al.* and London *et al.* Linet *et al.* included several regions in their study, however, and the validity of using the wire codes as estimates of exposure to magnetic fields may vary among the regions. The fact that the proportion of subjects exposed to magnetic fields $> 0.2 \mu\text{T}$ was considerably higher in the study of Savitz *et al.* than in those of Linet *et al.* or London *et al.* may explain some of the disparity in the results. Linet *et al.* included only cases of acute lymphoblastic leukemia, while the other studies included all types of leukemia. The results of the studies, when taken together, support the association between classification of exposure from wire codes and the incidence of childhood leukemia. This is further supported by the results of the formal meta-analysis, which found, on average, a 40% excess risk for leukemia (OR = 1.5; 95% CI, 1.0–2.2) (Wartenberg *et al.*, 1998).

Among the studies in which calculated fields were used to assess exposure to magnetic fields, four Nordic studies were considered to be of sufficient quality to be used in the evaluation. Three of the studies found increasing leukemia risk with increasing calculated fields (Feychting & Ahlbom, 1993; Olsen *et al.*, 1993; Verkasalo *et al.*, 1993), and a smaller study found no effect (Tynes *et al.*, 1992). All four studies were population-based, with minimal potential for selection bias both in terms of control selection and participation rates. The exposure assessment method used in these studies is based on the laws of physics and engineering design and provides estimates of the exposure for a relevant etiologic period from historical information about line loads and configurations.

Thus, the exposure estimates may be less subject to misclassification than those in the studies based on wire codes. The main limitations of all four of the studies are the small number of cases and the low prevalence of exposure. Potential confounding from traffic exhaust was controlled in the Swedish study and did not change the effect estimate. Adjustment for socioeconomic status was made in all of the studies except that in Finland, again with no effect on the observed risk estimates. The results of these studies, when taken together, support an association between exposure to calculated magnetic fields and the incidence of childhood leukemia. This conclusion is further supported by the results of the formal meta-analysis which found, on average, a 63% excess risk for leukemia (OR = 1.6; 95% CI, 0.8–3.0) (Wartenberg *et al.*, 1998).

Of the studies in which spot measurements were used to assess exposure to magnetic fields, three were considered to be of sufficient quality to be used in the evaluation (London *et al.*, 1991; Michaelis *et al.*, 1998; Savitz *et al.*, 1988). The results of these three studies are inconsistent, two being close to unity and the third (Savitz *et al.*) showing increased risks. The very low participation rate among cases in the study of Savitz *et al.* limits its validity. The study of Feychting and Ahlbom (Feychting & Ahlbom, 1993) is not included in this assessment because the spot measurements were made too long after the relevant etiologic period.

Neither selection bias nor confounding had a major impact on the reported results. The study of Michaelis *et al.* is limited by the small number of exposed subjects. Exposure misclassification is a potential limitation in all three studies. The usefulness of spot measurements for retrospective assessment of exposure to magnetic fields during the etiologically relevant period has been questioned. These studies do not provide sufficient information to evaluate the association between exposure to magnetic fields evaluated by spot measurements and the incidence of childhood leukemia. Furthermore, the formal meta-analysis did not find an appreciable excess risk for leukemia (OR = 1.2; 95% CI, 0.7–2.1) (Wartenberg *et al.*, 1998).

Three studies in which 24-h measured magnetic fields were used to assess exposure to magnetic fields were considered to be of sufficient quality to be used in an evaluation of the association between the incidence of childhood leukemia and exposure to magnetic fields (Linet *et al.*, 1997; London *et al.*, 1991; Michaelis *et al.*, 1998). The results of all three studies showed an increased risk for children in higher exposure classes. The data reported by Linet *et al.* showed an exposure–response relationship, which was not found by London *et al.* and was not assessed by Michaelis *et al.*

The studies of both Linet *et al.* and London *et al.* had potential limitations due to use of random-digit dialing to select controls. Control selection in the study of Michaelis *et al.* is unlikely to be subject to selection bias. The low participation rates in all three studies might have resulted in selection bias. Confounding due to socioeconomic status was controlled in all three studies. Confounding by traffic exhaust was addressed in previous studies in which other exposure assessment methods were used, and was found unlikely to affect the results. The study of Michaelis *et al.* is limited by the small number of

exposed subjects, and there were few highly exposed subjects in all three studies. It is not clear how well a 24-h magnetic field measurement reflects exposure during the relevant etiologic period, nor how representative it is of long-term exposure, given the weekly, seasonal, and secular patterns. This method is, however, an improvement over spot measurements of magnetic fields. The study of Linet *et al.* is an improvement over the previous studies because of the markedly shorter time between diagnosis and exposure assessment.

The results of these studies provide some support for a possible association between exposure based on 24-h measured magnetic fields and the incidence of childhood leukemia. This conclusion is further supported by the results of the formal meta-analysis, which showed, on average, a 50% excess risk (OR = 1.5; 95% CI, 1.0–2.3).

Three studies of appliance use were considered to be of sufficient quality to be used in an evaluation of the association between the incidence of childhood leukemia and exposure to magnetic fields (Hatch *et al.*, 1998; London *et al.*, 1991; Savitz *et al.*, 1990). The results do not fit a coherent pattern, but elevated risks were reported for a variety of appliances in different studies. Many increased risk estimates were found by Hatch *et al.*; however, it is interesting to note that no associations were found for the three appliances that do not involve significant exposure to magnetic fields (i.e. those that were included in the study to assess the possible role of recall bias). The possibility of recall and reporting bias in the study of Hatch *et al.* and in any of the other studies cannot, however, be ruled out. Furthermore, chance cannot be ruled out as an explanation for the observations. In addition, low participation rates and use of random-digit dialing in all three of the studies may have influenced the results in any direction. These studies provide inadequate evidence to assess an association of use of appliances and the incidence of childhood leukemia.

Childhood nervous system tumors

Four studies were considered to be of sufficient quality to be used in an evaluation of the association between the incidence of childhood brain tumors and classification of exposure based on wire codes. The two early studies found an increased risk (Savitz *et al.*, 1988; Wertheimer & Leeper, 1979), and the two later studies found no effect on the incidence of child brain tumors (Gurney *et al.*, 1996; Preston-Martin *et al.*, 1996b). Selection bias is an unlikely explanation for the observed increased risks in the earlier studies or the lack of association in the later ones. A large number of potential confounding factors were evaluated in three of the studies. The disparity of the results precludes the drawing of an inference. The formal meta-analysis bears this out, providing a relative risk estimate of 1.2 with an associated 95% confidence interval of 0.7–2.2 (Wartenberg *et al.*, 1998).

Equally inconclusive results were observed in studies of the possible association between childhood brain tumors and spot-measured magnetic fields, 24-h measured magnetic fields, and use of appliances. The data from studies on childhood brain tumors and calculated

magnetic fields provide some evidence that there is no association; however, these results are based on a very small number of cases, and chance cannot be ruled out as an explanation for the lack of association. The results of the meta-analysis results are inconclusive with regard to all exposure metrics.

Childhood lymphoma

The number of cases of lymphoma in each of the studies was too small for any reliable inferences to be drawn.

Reasoning for the evaluation of degree of evidence from studies of childhood leukemia

The results of the studies of a possible association between exposure to magnetic fields and the incidence of childhood leukemia present a complex picture. The most compelling data come from the Nordic studies, in which calculated magnetic fields were used as the metric of exposure to magnetic fields, arguably the most accurate way of reconstructing exposure during the relevant etiological periods, especially if they are very long. These data are supported by the results of studies in which 24-h magnetic field measurements and wire codes were used as the exposure metrics. The only exposure metric that did not appear to be associated with an increased leukemia risk with increased exposure was spot measurement, but this exposure metric has been criticized as being unrepresentative of long-term exposure to magnetic fields because it fails to capture the daily, weekly, seasonal, and long-term fluctuations in magnetic field strength. The studies of the possible association of use of appliances and the incidence of childhood leukemia were not viewed as contributing to this evaluation. Chance is an unlikely explanation for the observed associations, and the dose–response patterns observed strengthens this conclusion.

Confounding seems to be an unlikely explanation for the observed results. A confounder must be associated with a sufficiently large relative risk to overcome that associated with magnetic fields. Given the extensive search for possible confounders and the fact that no strong candidates have been identified, the impact of confounding appears to be minimal.

Selection bias cannot be ruled out in several of the studies; however, increased risk estimates and consistent dose–response patterns were found also in the Nordic studies, in which selection bias is unlikely.

As research on EMF evolved, both exposure assessment and study designs have improved. The results of studies would thus have been expected to become more consistent. In fact, this has not occurred, which raises questions about whether the ‘improvements’ in exposure assessment have more accurately captured the relevant EMF exposure.

In sum, although the exposure metrics used as surrogates for exposure to magnetic fields are of varying precision, it is difficult to find an explanation other than exposure to

magnetic fields for the consistency of the reported excess risks for childhood leukemia in studies conducted in different countries under different conditions, with different study designs. Overall, the Working Group gave preference to the Nordic studies in which bias in the selection of study subjects can be ruled out and in which the most sophisticated exposure assessment methods were used. The Working Group considers, with some minor reservations, that the strengths and consistency of these study results are suggestive in spite of their limitations.

Evaluation

There is limited evidence that residential exposure to ELF magnetic fields is carcinogenic to children.

[This conclusion was supported by 20 Working Group members; there were 6 votes for 'inadequate' evidence, 2 abstentions, and 1 absent.]

There is inadequate evidence with respect to childhood nervous system tumors.

[This conclusion was supported by 25 Working Group members; there were 2 abstentions and 2 absent.]

There is inadequate evidence with respect to childhood lymphoma.

[This conclusion was supported by 25 Working Group members; there were 2 abstentions and 2 absent.]

Table 4.20 Summary of epidemiological studies on childhood cancers

Study*	Case selection	Control selection	Exposure metrics	Confounders analyzed	Additional notes
Wertheimer and Leeper (1979)	Cancer mortality records (1950-1973) of persons less than 19 years of age, that were born in Colorado and resided in Denver Largest number of cases used in the analysis: 328	Denver-area birth certificates Total number of controls enrolled: 344	2-level wire code (HCC vs. LCC) Non-blinded wire code assessment	Cancer onset age Urban/suburban Socioeconomic status Birth order Maternal age Traffic congestion Gender	Crude relative risk estimates cited Potential confounders were individually analyzed
Savitz <i>et al.</i> (1988)	All cancer incidence cases reported in Denver, Colorado during the years 1976-1983 of persons less than 15 years of age 356 cases identified 320 cases had 5-level wire codes assessed 252 cases were interviewed 128 cases had magnetic field measurement data	Controls selected via random digit telephone dialing methods Matched to cases by age, gender, and telephone exchange area 278 controls identified 259 cases had 5-level wire codes assessed 222 cases were interviewed 207 cases had magnetic field measurement data	5-level wire code In-home electric and magnetic field spot measurements under low and high power use conditions	Gender, age Type of housing Socioeconomic status Smoking during pregnancy Traffic density Parental age Race and education Income Family cancer history, <i>In utero</i> exposure to Alcohol use X-rays, influenza, and medications Birth defects Birth order Birth weight Illness Residential stability Medication x-rays	Control selection procedures resulted in the controls being more residentially stable than the cases Matched analysis not performed Adjusted relative risk estimates were described but not presented in a table and did not change the results.

Table 4.20 (continued)

Study*	Case selection	Control selection	Exposure metrics	Confounders analyzed	Additional notes
London <i>et al.</i> (1991)	All leukemia incidence cases reported to the Los Angeles County Cancer Surveillance Program (1980-1987) of persons less than 10 years of age 331 cases identified and 232 interviewed 169 cases had 24-hour magnetic field measurements recorded 140 cases had spot measurements recorded 219 cases had 5-level wire codes assessed	Controls were obtained through friends of cases (1980-1984) and via random digit telephone dialing methods (1980-1987) Matched to cases by age, gender, and ethnicity 257 controls identified and 232 interviewed 149 controls had 24-hour magnetic field measurements recorded 109 controls had spot measurements recorded 207 controls had 5-level wire codes assessed	5-level wire code Outdoor and in-home electric and magnetic field spot measurements under low and normal power use conditions 24-hour magnetic field measurements underneath the bed in the child's bedroom Self-report of appliance use	Various factors associated with cancer that were reported in previous studies Appliance use Socioeconomic status	Exposures assessed in homes during an "etiologic period" defined as the period beginning at the estimated time of conception and ending on the date of diagnosis inset "for children aged 1 year or less at time of diagnosis date minus 6 months" for children aged 1-2 years at diagnosis; and one year prior to diagnosis for children diagnosed at ages greater than 2 years Matched and unmatched analyses were carried out since the mean 24-hour magnetic field exposure was lower among matched controls as compared to unmatched
Olsen <i>et al.</i> (1993)	All leukemia, tumor of the central nervous system, or malignant lymphoma incidence cases reported to the Danish Cancer Registry (during the period from April 1, 1968 to December 31, 1986) of persons less than 15 years of age 1707 cases identified	Two to five controls were selected at random from among people who had survived without cancer until the date of diagnosis of the case Controls matched to the case by gender and date of birth 4788 eligible controls identified	Distance from transformer substations, overhead lines, and underground cables Average calculated magnetic field exposure averaged over residence period Cumulative calculated magnetic field exposure = (number of months exposed) multiplied by (average calculated level of magnetic field at the residence)	Gender Age at diagnosis Socioeconomic status Population density at place of residence Number of changes of address	Analyses controlled for gender and age at diagnosis for each cancer grouping At cut-point 0.4 μ T and greater the numbers of exposed cases and controls is too small to indicate significant increases in cancer incidence for individual cancer types.

Table 4.20 (continued)

Study*	Case selection	Control selection	Exposure metrics	Confounders analyzed	Additional notes
Feychting and Ahlbom (1993)	All cancer incidence cases reported to the Swedish Cancer Registry of persons under 16 years of age living on a property located within 300 meters of any 220 or 400 kV power lines in Sweden (1960-1985) 142 cases identified 141 cases had calculated fields assessed 89 cases had spot measurements recorded	Controls per case were randomly selected from all persons under 16 years of age living on a property located within 300 meters of any 220 or 400 kV power lines in Sweden (1960-1985) Controls matched to cases by birth year, gender, residence in the same parish during the year of diagnosis or the last year before the case moved, lived near the same power line as the case 558 controls identified 554 controls had calculated fields assessed 344 controls had spot measurements recorded	Distance to power lines from residence In-home magnetic field spot measurements under low and high power use conditions Calculations of the magnetic fields generated by the power lines at the time spot measurements were assessed (calculated contemporary fields) and for the year closest in time to diagnosis (historical calculated fields)	Age Gender Year of diagnosis Whether or not the subject lived in the county of Stockholm Type of residence (single-family home or apartment) Nitrogen dioxide content as an index of air pollution from road traffic Socio-economic status	Matched analysis was conducted Magnetic field spot measurements taken 5-31 years after diagnosis. Median 16 years
Verkasalo <i>et al.</i> (1993)	All primary cancer cases reported to the Finnish Cancer Registry (1970-1989) of persons less than 20 years of age living within 500 m of overhead power lines of 110-400 kV in magnetic fields calculated to be 0.01 μ T and greater 140 cases identified	Entire cohort consisted of 68,300 boys and 66,500 girls less than 20 years of age living during 1970-1989 within 500 m of overhead power lines of 110-400 kV in magnetic fields calculated to be 0.01 μ T and greater	Calculated magnetic field exposure average exposure cumulative exposure	Gender Age	Analysis based upon cohort approach (standardized incidence ratios) with person years at risk stratified by gender, age (grouped in 5-year age categories), and exposure category Analysis included all primary cancers rather than first primary cancers, which resulted in multiple cancers per person being counted

Table 4.20 (continued)

Study*	Case selection	Control selection	Exposure metrics	Confounders analyzed	Additional notes
Preston-Martin <i>et al.</i> (1996a)	Patients under 20 years of age who were residents of Los Angeles County and had a benign or malignant primary tumor of the brain, cranial nerves, or cranial meninges of any histologic type diagnosed during the period January 1, 1984-June 30, 1991 437 eligible cases were obtained 304 cases had complete interview data 292 cases had wiring maps assessed for at least one residence 255 cases had spot measurement data 236 cases had at least one STAR magnetic field profile 110 cases had 24-hour measurements assessed in at least one room	Controls were obtained via random digit telephone dialing methods Matched to cases by birth date, age at time of diagnosis 433 eligible controls were obtained 304 controls had complete interview data 269 controls had wiring maps assessed for at least one residence 206 controls had spot measurement data 181 controls had at least one STAR magnetic field profile 101 controls had 24-hour measurements assessed in at least one room	Wire coding according to the 5-level Wertheimer-Leeper classification Spot measurements inside and outside the residence STAR magnetic field profiles 24-hour magnetic field measurements taken in the child's bedroom and other rooms Self-report of appliance use	Demographic variables Parental occupation Exposures during gestation Building type Appliance use Maternal occupational exposure to high magnetic fields during pregnancy	Matched and unmatched analyses performed Compared to parents of cases, a higher proportion of control mothers and fathers were Latino Compared to cases, a higher proportion of controls were in the highest social class
Gurney <i>et al.</i> (1996)	Patients under 20 years of age who were diagnosed with a benign or malignant primary tumor of the brain, cranial nerves, or cranial meninges of any histologic type diagnosed during the period 1984-1990 195 cases were eligible Largest number of cases used in the analysis: 120	Controls were obtained via random digit telephone dialing methods Approximately two cases per control were stratified by age, gender, and area of residence 270 eligible controls were identified Largest number of controls used in the analysis: 240	Wire coding according to the 5-level and 2-level Wertheimer-Leeper classifications Self-report of heating sources and appliance use	Age, gender, race County at reference date Reference year Mother's education Family history of brain tumors Passive tobacco smoke exposure in the home Whether the child lived on a farm Whether or not the child had a history of head injury, x-ray to the head or neck, epilepsy, or fits from severe fever	A small percentage of cases were classified in the very high current classification (3%)

Table 4.20 (continued)

Study*	Case selection	Control selection	Exposure metrics	Confounders analyzed	Additional notes
Linet <i>et al.</i> (1997)	All acute lymphoblastic leukemia incidence cases registered with the Children's Cancer Group (1989-1994) of persons less than 15 years of age 942 cases were eligible for the study 629 unmatched cases had magnetic field measurements recorded (463 case-control pairs included in the analysis) 408 matched cases had wire codes assessed in their main residence 225 matched cases had wire codes assessed in the residence of pregnancy	Controls were obtained via random digit telephone dialing methods Matched to cases by the first eight digits of the telephone number, age, and race 1292 controls were eligible for the study 619 unmatched controls had magnetic field measurements recorded (463 case-control pairs included in the analysis) 408 matched controls had wire codes assessed in their main residence 225 matched controls had wire codes assessed in the residence of pregnancy	24-h magnetic fields measurements in the child's bedroom 30-s measurements in the center of the child's bedroom, family room, kitchen, the room in which the mother slept during the index pregnancy, and near the front door of the residence Wire coding according to the 5-level Wertheimer-Leeper classification and the modified 3-category Kaune-Savitz scheme 24-h measurement 1-bedroom	Age Gender Race Socioeconomic status Temporal factors Urbanization Type of residence Gender Race Mathew's educational level	Magnetic field measurements generally measured within two years of leukemia diagnosis Single summary exposure for magnetic field measurements was calculated based upon a weighted average of the room measurements with weights based upon estimated time spent in each room according to the child's age. Matched and unmatched analyses cited. Measurements summarized as time-weighted-average over five years preceding diagnosis.

Table 4.20 (continued)

Study*	Case selection	Control selection	Exposure metrics	Confounders analyzed	Additional notes
Tynes and Haldorsen (1997)	All cancer incidence cases reported to the Cancer Registry of Norway (1965-1989) of persons less than 15 years of age who had lived in a census ward crossed by high-voltage power lines (45 kV or more in urban areas and more than 100 kV in rural areas) during at least one of the years 1960, 1970, 1980, 1985, 1987, or 1989 532 cases identified Largest number of cases used in the analysis: 500	5 controls per case were selected at random from among Norwegian children living in a census ward crossed by high-voltage power lines (45 kV or more in urban areas and more than 100 kV in rural areas) during at least one of the years 1960, 1970, 1980, 1985, 1987, or 1989 that were alive at the time of diagnosis of the case Matched to cases by gender, birth year, and municipality 2122 controls identified Largest number of controls used in the analysis: 2004	Distance to power line from residence Calculated magnetic field exposure estimate Time-weighted average calculated magnetic field exposure Time-weighted average cumulative exposure Average maximal exposure Mother's exposure at the time of conception Child's exposure in the year closest in time to diagnosis Average exposure during the first year of the child's life Average exposure during the first 4 years of the child's life	Socioeconomic status Type of building Number of dwellings	Few subjects were exposed to calculated, magnetic fields greater than 0.14 μ T The narrow distribution of exposures resulted in limited discrimination of the effects of different exposure indices
Michaelis <i>et al.</i> (1997)	All leukemia incidence cases reported to the German Childhood Cancer Registry (1988-1993) of persons less than 15 years of age and a resident of Lower Saxony at the date of diagnosis 219 cases were identified 129 cases had 24-h magnetic field measurements recorded	Controls were obtained from the files of local government offices for registration of residents Two controls per case were selected one control from the same registration office as the case one control selected from a randomly chosen registration office in Lower Saxony 328 controls had 24-h magnetic field measurements recorded	24-h magnetic field measurements in the child's bedroom 24-h magnetic field measurements in the living room Spot measurement at the residence where the child lived the longest Non-blinded magnetic field assessment	Gender Age Age at diagnosis Socioeconomic status Urbanization	Matched analysis conducted A prior cut-point of μ T G was chosen Low percentage of subjects exposed to measured magnetic field strengths greater than 2 μ T (1.5% of the entire study population)

* All studies are case-control with the exceptions of Verkasalo *et al.* (1993), Lin and Lee (1994), and Li *et al.* (1998), which are cohort studies

¹Analysis results based upon dwelling counts of cases and controls

Table 4.21 Childhood leukemia

Studies wire codes	Exposure classification	Leukemia no. cases	RR (95% CI)	Acute lymphoblastic no. of cases	RR (95% CI)
Wertheimer & Leeper (1979)	Birth address:				
	LCC	84	reference		
	HCC	52	2.28 (1.34-3.91)		
	Death address:				
	LCC	92	reference		
	HCC	63	2.98 (1.78-4.98)		
Savitz <i>et al.</i> (1988)	HCC/LCC	27 / 70	1.54 (0.90-2.63)	19 / 59	1.28 (0.70-2.34)
	VHCC/Buried	7 / 28	2.75 (0.94-8.04)	6 / 24	2.75 (0.90-8.44)
London <i>et al.</i> (1991)	UG+VL	31	references		
	OLCC	58	0.95 (0.53-1.69)		
	OHCC	80	1.44 (0.81-2.56)		
	VHCC	42	2.15 (1.08-4.26)		
Linnet <i>et al.</i> (1997)	UG+VLCC			175	references
	OLCC			116	1.07 (0.74-1.54)
	OHCC			87	0.99 (0.67-1.48)
	VHCC			24	0.88 (0.48-1.63)
Calculated fields					
Feychting & Ahlbom (1993)	Unmatched analyses				
	(μ T)				
	< 0.1	27	reference		
	0.1-0.19	4	2.1 (0.6-6.1)		
	\geq 0.2	7	2.7 (1.0-6.3)		
	\geq 0.3	7	3.8 (1.4-9.3)		
Matched analyses:(μ T)					
	0.1-0.19		4.3 (1.0-8.9)		
	\geq 0.2		3.5 (0.9-13.6)		
Olsen <i>et al.</i> (1993)	(μ T)				
	< 0.1	829	reference		
	0.1-0.24	1	0.5 (0.1-4.3)		
	\geq 0.25	3	1.5 (0.3-6.7)		
	\geq 0.40	3	6.0 (0.8-44)		

Table 4.21 (continued)

Studies wire codes	Exposure classification	Leukemia no. cases	RR (95% CI)	Acute lymphoblastic no. cases	RR (95% CI)
Verkasalo <i>et al.</i> (1993, 1994)	Cumulative exposure (μ T-years)				
	0.01-0.39	32	0.90 (0.62-1.3)		
	≥ 0.40	3	1.2 (0.26-3.6)		
	≥ 1.0	3	3.5 (0.7-10)		
	Average exposure (μ T)				
	0.01-0.19	32	0.89 (0.61-1.3)		
	≥ 0.2	3	1.6 (0.32-4.5)		
Tynes & Hulderson (1997)	Average exposure (μ T)				
	< 0.05	139	reference		
	0.05-0.13	8	1.8 (0.7-4.2)		
	≥ 0.14	1	0.3 (0.0-2.1)		
	Closest to diagnosis (μ T)				
	<0.05	134	reference		
	0.05-0.13	10	1.5 (0.7-3.3)		
	≥ 0.14	4	0.8 (0.3-2.4)		
	≥ 0.2	2	0.5 (0.1-2.2)		
Spot measurements					
Savitz <i>et al.</i> (1988)	Low Power conditions (μ T)				
	< 0.2	31	reference	23	reference
	≥ 0.2	5	1.93 (0.67-5.56)	3	1.56 (0.42-5.75)
	High power conditions (μ T)				
	< 0.2	30	reference	23	reference
	≥ 0.2	7	1.41 (0.57-3.50)	4	1.05 (0.34-3.26)
	Electric fields (μ T)				
	< 12 V/m	31	reference	23	reference
≥ 12 V/m	6	0.75 (0.29-1.91)	4	0.67 (0.22-2.04)	
London <i>et al.</i> (1991)	Low power conditions (μ T)				
	< 0.032	67	reference		
	0.032-0.067	34	1.01 (0.61-1.69)		
	0.068-0.124	23	1.37 (0.65-2.91)		
	≥ 0.125	16	1.22 (0.52-2.82)		

Table 4.21 (continued)

Studies wire codes	Exposure classification	Leukemia no. cases	RR (95% CI)	Acute lymphoblastic no. cases	RR (95% CI)
Michaelis (1997b)	Short-term measurement (μT)				
	< 0.2	170	reference		
	≥ 0.2	6	0.7 (0.3-1.8)		
London, <i>et al.</i> (1991)	24 hour measurements (μT)				
	0-0.067	85	reference		
	0.068-0.118	35	0.68 (0.39-1.17)		
	0.119-0.267	24	0.89 (0.46-1.71)		
	≥ 0.268	20	1.48 (0.66-3.29)		
Michaelis, <i>et al.</i> (1997a)	Median of measurements (μT)				
	< 0.2	125	reference		
	≥ 0.2	4	3.2 (0.7-14.9)		
	Mean of measurements (μT)				
	< 0.2	125	reference		
	≥ 0.2	4	1.5 (0.4-5.5)		
Michaelis <i>et al.</i> (1997b)	Median during the night (μT)				
	< 0.2	124	reference		
	≥ 0.2	5	3.9 (0.9-16.9)		
Michaelis <i>et al.</i> (1997b)	Median of measurements (μT)				
	< 0.2	167	reference		
	≥ 0.2	9	2.3 (0.8-6.7)		
	Median during the night (μT)				
< 0.2	167	reference			
≥ 0.2	9	3.8 (1.2-11.9)			

Table 4.21 (continued)

Studies wire codes	Exposure classification	Leukemia no. cases	RR (95% CI)	Acute lymphoblastic no. cases	RR (95% CI)	
Linnet <i>et al.</i> (1997)	Unmatch Analysis (μ T)					
	< 0.065			267	reference	
	0.065-0.099			123	1.1 (0.81-1.50)	
	0.1-0.199			151	1.1 (0.83-1.48)	
	0.2-0.299			38	0.92 (0.57-1.48)	
	0.3-0.399			22	1.39 (0.72-2.72)	
	0.4-0.499			14	3.28 (1.15-9.39)	
	≥ 0.5			9	1.41 (0.49-4.09)	
	≥ 0.2			83	1.24 (0.86-1.79)	
	≥ 0.3			45	1.7 (1.0-2.9)	
	Matched Analysis (μ T)					
	< 0.065			206	reference	
	0.065-0.099			92	0.96 (0.65-1.40)	
	0.1-0.199			107	1.15 (0.79-1.65)	
	0.2-0.299			29	1.31 (0.68-2.51)	
	0.3-0.399			14	1.46 (0.61-3.50)	
	0.4-0.499			10	6.41 (1.30-31.73)	
≥ 0.5			5	1.01 (0.26-3.99)		
≥ 0.2			58	1.53 (0.91-2.56)		

Table 4.22 Results for childhood nervous system tumors

Studies	Exposure classification	No. of cases	RR (95% CI)	
Wire codes				
Wertheimer and Leeper (1979)	Birth address HCC/LCC	22 / 35	2.36 (1.03-5.41)	
	Death address HCC/LCC	30 / 36	2.40 (1.15-5.01)	
Savitz <i>et al.</i> (1988)	HCC/LCC	20 / 39	2.04 (1.11-3.76)	
	VHCC/Buried	3 / 17	1.94 (0.47-7.95)	
Preston-Martin <i>et al.</i> (1996a)	UG	39	2.3 (1.2-4.3)	
	VLCC/OLCC	114	reference	
	OHCC	97	0.8 (0.6-1.2)	
	VHCC	31	1.2 (0.6-2.2)	
Gurney <i>et al.</i> (1996)	High/low	23 / 97	0.9 (0.5,1.5)	
	UG	47	reference	
	VLCC	39	1.3 (0.7-2.1)	
	OLCC	11	0.7 (0.3-1.6)	
	OHCC	19	1.1 (0.6-2.1)	
	VHCC	4	0.5 (0.2-1.6)	
Calculated fields				
Feychting & Ahlbom (1993)	Unmatched analyses (μT)			
	< 0.1	29	reference	
	0.1-0.19	2	1.0 (0.2-3.8)	
	≥ 0.2	2	0.7 (0.1-2.7)	
	≥ 0.3	2	1.0 (0.2-3.9)	
	Matched analyses			
	0.1-0.19		0.8 (0.1-4.9)	
≥ 0.2		0.7 (0.1-3.2)		
Olsen <i>et al.</i> (1993)	< 0.1	621	reference	
	0.1-0.24	1	1.0 (0.1-9.6)	
	≥ 0.25	2	1.0 (0.2-5.0)	
	≥ 0.4	2	6.0 (0.7-44)	
Verkasalo <i>et al.</i> (1993)	Cumulative exposure (μT -years)		(SIR)	
	0.01-0.39	32	0.82 (0.56-1.2)	
	≥ 0.40	7	2.3 (0.94,4.8)	
	≥ 1.0	3	2.8 (0.6-8.1)	
	Average exposure (μT)			
	0.01-0.19	34	0.85 (0.59-1.2)	
≥ 0.2	5	2.3 (0.75-5.4)		
Tynes & Haldorsen (1997)	Average exposure (μT)			
	< 0.05	144	reference	
	0.05-0.13	8	1.9 (0.8-4.6)	
	≥ 0.14	4	0.7 (0.2-2.1)	
	Closest to diagnosis (μT)			
	< 0.05	142	reference	
	0.05-0.13	5	0.9 (0.3-2.5)	
≥ 0.14	9	1.1 (0.5-2.5)		

Table 4.22 (continued)

Studies	Exposure classification	No. of cases	RR (95% CI)
Measurements			
Savitz <i>et al.</i> (1988)	Spot measurements		
	Low power conditions (μT)		
	< 0.2	23	reference
	≥ 0.2	2	1.04 (0.22-4.81)
	High power conditions		
	< 0.2	22	reference
	≥ 0.2	3	0.82 (0.23-2.93)
	Electric fields (V/m)		
	< 12	22	reference
≥ 12	3	0.53 (0.15-1.81)	
Preston-Martin <i>et al.</i> (1996)	Spot measurements (μT)		
	> 0.2	13	0.7 (0.3-1.5)
	> 0.25	11	0.9 (0.3-2.3)
	> 0.3	7	0.9 (0.3-3.2)
	<i>p</i> for trend		0.29
	24-h measurements (μT)		
	> 0.2	16	1.2 (0.5-2.8)
	> 0.25	13	1.4 (0.5-3.8)
	> 0.3	12	1.7 (0.6-5.0)
	<i>p</i> for trend		0.79
	STAR profiles (μT)		
	> 0.2	13	1.2 (0.5-3.3)
> 0.25	10	1.5 (0.5-5.1)	
> 0.3	5	0.9 (0.2-4.1)	
<i>p</i> for trend		0.82	

Table 4.23 Results for childhood lymphoma

Studies	Exposure classification	No. of cases	RR (95% CI)
Wire codes			
Wertheimer and Leeper (1979)	Birth address HCC/LCC	10 / 21	2.48 (0.73-8.37)
	Death address HCC/LCC	18 / 26	2.08 (0.84-5.16)
Savitz <i>et al.</i> (1988)	HCC/LCC	5	0.80 (0.29-2.18)
	VHCC/Buried	3	3.30 (0.80-13.65)
Calculated fields			
Feychting & Ahlbom (1993)	Unmatched analyses (μT)		
	< 0.1	16	reference
	0.1-0.19	1	0.9 (0.0-5.2)
	≥ 0.2	2	1.3 (0.2-5.1)
	≥ 0.3	1	0.9 (0.0-5.4)
	Matched analyses		
0.1-0.19		0.8 (0.1-7.8)	
≥ 0.2		0.9 (0.2-5.0)	
Olsen <i>et al.</i> (1993)	< 0.1	247	reference
	0.1-0.24	2	5.0 (0.7-36)
	≥ 0.25	1	5.0 (0.3-82)
	≥ 0.4	1	5.0 (0.3-82)
Verkasalo <i>et al.</i> (1993)	Cumulative exposure (μT -years)		(SIR)
	0.01-0.39	14	0.88 (0.48-1.5)
	≥ 0.40	1	0.64 (0.02-3.6)
	Average exposure (μT)		
	0.01-0.19	15	0.91 (0.51-1.5)
	≥ 0.2	0	0.0 (0.0-4.2)
Tynes & Haldorsen (1997)	Average exposure (μT)		
	< 0.05	27	reference
	0.05-0.13	1	1.0 (0.1-8.7)
	≥ 0.14	2	2.5 (0.4-15.5)
	Closest to diagnosis (μT)		
	< 0.05	27	reference
0.05-0.13	1	0.8 (0.1-6.7)	
≥ 0.14	2	1.2 (0.2-6.4)	
Measurements			
Savitz <i>et al.</i> (1988)	Spot measurements		
	Low power conditions (μT)		
	< 0.2	11	reference
	≥ 0.2	2	2.17 (0.46-10.31)
	High power conditions		
	< 0.2	10	reference
≥ 0.2	3	1.81 (0.48-6.88)	
Electric fields (V/m)			
< 12	11	reference	
≥ 12	2	0.70 (0.15-3.27)	

Table 4.24 Summary of appliance studies

Studies	Appliances	Leukemias		Lymphoma		Nervous system tumors	
		Prenatal	Postnatal	Prenatal	Postnatal	Prenatal	Postnatal
Savitz <i>et al.</i> (1990) ¹	Electric blanket	1.3 (0.7-2.6)	1.5 (0.5-5.1)	1.1 (0.4-3.6)	1.0 (0.2-8.6)	1.8 (0.9-4.0)	1.2 (0.3-5.7)
	Electric water bed	0.3 (0.1-1.2)	0.7 (0.2-2.5)	-	-	0.5 (0.2-2.0)	0.3 (0.1-2.7)
	Bedside electric clock	0.9 (0.5-1.6)	1.4 (0.7-2.9)	0.5 (0.2-1.2)	1.5 (0.6-4.5)	0.8 (0.4-1.7)	1.1 (0.5-2.8)
	Heating pad	0.9 (0.4-2.2)	-	2.0 (0.7-5.9)	-	0.9 (0.4-2.7)	-
	Hair dryer	-	0.5 (0.2-1.3)	-	0.7 (0.2-2.5)	-	0.6 (0.3-1.7)
London <i>et al.</i> (1991) ²	Bedroom. air conditioner.	0.91 (0.51-1.66)	0.54 (0.21-1.25)				
	Electric blanket	1.21 (0.66-2.29)	7.0 (0.86-121.8)				
	Electric fan	1.16 (0.77-1.75)	1.20 (0.81-1.80)				
	Electric space heater	1.18 (0.62-2.32)	1.45 (0.82-2.66)				
	Electric water bed	0.67 (0.34-1.28)	1.00 (0.45-2.29)				
	B&W television	-	1.49 (1.01-2.23)				
	Electric clock (all)	-	1.33 (0.90-1.97)				
	Electric clock-dial	-	1.86 (0.97-3.83)				
	Electric clock-digital	-	1.10 (0.71-1.72)				
	Color television	-	1.06 (0.66-1.74)				
	Curling iron	-	6.0 (0.72-104.8)				
	Electric clippers	-	1.0 (0.06-19.60)				
	Electric hair dryer	-	2.82 (1.42-6.32)				
Microwave oven	-	0.81 (0.48-1.36)					
Video game	-	1.57 (0.80-3.27)					
Preston-Martin <i>et al.</i> (1996a) ¹	Electric blanket					1.2 (0.6-2.2)	1.2 (0.5-3.0)
	Electric water bed					2.1 (1.0-4.2)	2.0 (0.6-6.8)
	Electric clock (all)					1.0 (0.8-1.3)	0.7 (0.4-1.0)
	Electric clock-dial					1.1 (0.7-1.8)	0.6 (0.3-1.4)
	Electric heat					1.6 (0.8-3.0)	1.3 (0.7-2.4)
	Electric heat-radiant					1.3 (0.2-8.3)	1.4 (0.4-5.0)
	Microwave					1.4 (0.9-2.3)	1.0 (0.6-1.5)
	Ham radio					-	2.1 (0.2-23.7)
	Hair dryer					-	1.2 (0.7-2.1)
	Curling iron					-	1.0 (0.4-2.5)
Preston-Martin <i>et al.</i> (1996b) ¹	Electric blanket					0.9 (0.6-1.2)	1.0 (0.6-1.7)
	Electric water bed					0.9 (0.6-1.3)	1.2 (0.7-2.0)

Table 4.24 (continued)

Studies	Appliances	Leukemias		Lymphoma		Nervous system tumors	
		Prenatal	Postnatal	Prenatal	Postnatal	Prenatal	Postnatal
Hatch <i>et al.</i> (1998)	Electric blanket Ever used	1.59 (1.11-2.29)	2.75 (1.52-4.98)				
	Electric water bed Ever used	0.9 (0.67-1.21)	1.19 (0.87-1.62)				
	Hair dryer Ever used	1.14 (0.8-1.61)	1.55 (1.18-2.05)				
	Curling iron Ever used	1.06 (0.83-1.36)	1.74 (0.91-3.31)				
		Reference: Never used or not within 3 feet	Reference: Not used during reference year				
	Electric clock Digital display	0.98 (0.73-1.31)	1.20 (0.83-1.76)				
	Dial display	0.81 (0.52-1.28)	1.69 (0.61-4.65)				
	TV video game Ever used		1.91 (1.36-2.68)				

¹Odds ratios (ever use versus never use)

²Matched analysis. Odds ratios (prenatal use: anytime during pregnancy versus never use, postnatal use: at least once a week versus less than once a week)

Table 4.25 Summary of meta-analysis results

Meta-analyses	Studies included	All childhood cancers	Leukemias	Lymphomas	Central nervous system tumors
NRPB (1992) ¹	Wertheimer and Leeper (1979) Fulton <i>et al.</i> (1980) Tomenius (1986) Savitz <i>et al.</i> (1988) Coleman <i>et al.</i> (1989) Lin and Lu (1989) Myers <i>et al.</i> (1990) London <i>et al.</i> (1991)	Measured EMFs: 1.82 (1.09-3.04) Distance from EMF source: 1.11 (0.71-1.73) Wire codes (HCC vs. LCC): 1.53 (1.04-2.25)	Measured EMFs: 1.16 (0.65-2.08) Distance from EMF source: 1.31 (0.72-2.21) Wire codes (HCC vs. LCC): 1.39 (1.08- 1.78)		Measured EMFs: 1.85 (0.91-3.77) Distance from EMF source: 1.09 (0.50-2.37) Wire codes (HCC vs LCC): 2.04 (1.11-3.76)
Ahlbom <i>et al.</i> (1993)	Feychting and Ahlbom (1993) Olsen <i>et al.</i> (1993) Verkasalo <i>et al.</i> (1993)	Calculated EMFs: 1.3 (0.9-2.1)	Calculated EMFs: 2.1 (1.1-4.1)	Calculated EMFs: 1.0 (0.3- 3.7)	Calculated EMFs: 1.5 (0.7-3.2)
Washburn <i>et al.</i> (1994) ^{2,3}	Wertheimer and Leeper (1979) Fulton <i>et al.</i> (1980) Tomenius (1986) Savitz <i>et al.</i> (1988) Coleman <i>et al.</i> (1989) Myers <i>et al.</i> (1990) London <i>et al.</i> (1991) Lowenthal <i>et al.</i> (1991) Fajardo-Gutierrez (1993) Feychting and Ahlbom (1993) Olsen <i>et al.</i> (1993) Petridou <i>et al.</i> (1993) Verkasalo <i>et al.</i> (1993)		Distance from EMF source: 1.49 (1.11-2.00)	Distance from EMF source: 1.58 (0.91- 2.76)	Distance from EMF source: 1.89 (1.34-2.67)

Table 4.25 (continued)

Meta-analyses	Studies included	All childhood cancers	Leukemias	Lymphomas	Central nervous system tumors
NAS Report (1994) ^{2,4}	Wertheimer and Leeper (1979) Fulton <i>et al.</i> (1980) Tomenius (1986) Savitz <i>et al.</i> (1988) Coleman <i>et al.</i> (1989) London <i>et al.</i> (1991) Fajardo-Gutierrez (1993) Feychting and Ahlbom (1993) Olsen <i>et al.</i> (1993) Petridou <i>et al.</i> (1993) Verkasalo <i>et al.</i> (1993)		Wire codes (HCC vs. LCC): 1.48 (1.18-1.85) - fixed 1.52 (1.08-2.14) - random Wire codes and distances less than 100 m: 1.36 (1.13-1.63) - fixed 1.38 (1.08-1.76) - random Spot measurements (2 mg exposures and greater): 0.92 (0.57-1.49) - fixed 0.89 (0.51-1.57) - random		
Feychting <i>et al.</i> (1995) ⁵	Feychting and Ahlbom (1993) Olsen <i>et al.</i> (1993)	0.1 - 0.19 μ T: 1.4 (0.6-2.9) \geq 0.2: 1.5 (0.9-2.7) \geq 0.5: 3.5 (1.7-7.3)	0.1 - 0.19 μ T: 2.0 (0.7-5.3) \geq 0.2: 2.0 (1.0-4.1) \geq 0.5: 5.1 (2.1-12.6)	0.1 - 0.19 μ T: 0.7 (0.1-5.6) \geq 0.2: 2.1 (0.8-5.5) \geq 0.5: 3.3 (0.7-15.0)	1.0 - 1.9 μ T: 1.1 (0.3-3.6) \geq .2: 0.8 (0.3-2.4) \geq .5: 2.3 (0.6-8.0)
Meinert and Michaelis (1996) ^{2,6}	Wertheimer and Leeper (1979) Fulton <i>et al.</i> (1980) Tomenius (1986) Savitz <i>et al.</i> (1988) Coleman <i>et al.</i> (1989) Myers <i>et al.</i> (1990) London <i>et al.</i> (1991) Fajardo-Gutierrez (1993) Feychting and Ahlbom (1993) Olsen <i>et al.</i> (1993) Petridou <i>et al.</i> (1993) Verkasalo <i>et al.</i> (1993) Preston-Martin <i>et al.</i> (1994)	Wire code (HCC vs. LCC): 1.37 (0.94-2.00) Distance: < 100 m: 1.09 (0.89-1.35) < 50 m: 1.10 (0.86-1.40) < 25 m: 1.42 (0.88-2.29) EMF measures: > 0.1 μ T: 0.97 (0.82-1.15) > 0.2 μ T: 1.23 (0.96-1.57) > 0.3 μ T: 1.62 (1.10-2.39)	Wire code (HCC vs. LCC): 1.66 (1.11-2.49) Distance: < 100 m: 1.13 (0.79-1.62) < 50 m: 1.31 (0.92-1.87) < 25 m: 1.85 (0.98-3.49) EMF measures: > 0.1 μ T: 1.55 (0.88-2.73) > 0.2 μ T: 1.89 (1.10-3.26) > 0.3 μ T: 1.27 (0.28-5.76)	Wire code (HCC vs. LCC): 1.32 (0.52-3.37) EMF measures: > 0.1 μ T: 2.18 (0.51-9.34) > 0.2 μ T: 2.21 (0.72-6.80) > 0.3 μ T: 1.69 (0.43-6.59)	Wire code (HCC vs. LCC): 1.50 (0.69-3.26) Distance: < 50 m: 1.53 (0.19-12.0) EMF measures: > 0.1 μ T: 0.89 (0.39-2.05) > 0.2 μ T: 1.30 (0.78-2.19) > 0.3 μ T: 1.89 (0.80-4.43)

¹Relative risk estimates do not incorporate the results from the Wertheimer and Leeper (1979) study²Relative risk estimates do incorporate the results from the Wertheimer and Leeper (1979) study³Relative risk estimates in relation to distances 50 meters and greater⁴Relative risk estimates based upon fixed and random effects statistical models⁵Relative risk estimates in relation to calculated historical magnetic field exposures less than 0.1 μ T (1 mG, adjusted for age, gender, and country)⁶Relative risk estimates in relation to dichotomous cut-points

Table 4.26 Summary of NIEHS meta-analysis

Leukemia: meta-analysis	No. of studies	No. of exposed cases	Random effects odds ratio (95% CI)	Fail-safe N	Sample size needed	P-Value for heterogeneity	Range of odds ratios from sensitivity analysis
Calculated Fields	5	20	1.6 (1.0-2.7)	—	3268	0.4	1.3-1.8
Measured Fields	6	125	1.3 (0.8-2.0)	—	2454	0.1	1.1-1.4
Wire Codes	5	336	1.4 (1.0-2.0)	13	1898	0.03	1.3-1.6
Proximity to electrical facilities	11	375	1.4 (1.1-1.8)	31	3433	0.06	1.3-1.5

Leukemia: dose-response analysis	No. of studies		Random effects relative risk (95% CI) per 0.1 μT	Regression slope	Standard error	P-Value for heterogeneity test
Spot measurements	4		1.1 (0.9-1.3)	0.08	0.10	0.3
Calculated fields						
0.2 or 0.25 μ T	4		1.2 (0.9-1.5)	0.16	0.13	0.2
0.3 or 0.4 μ T	4		1.2 (1.0-1.5)	0.20	0.11	0.2
Wire codes						
Scored by spot measurements	2		2.7 (0.8-8.7)	0.99	0.60	0.1
Scored by 24-hour Bedroom measurements	2		1.6 (0.5-4.6)	0.45	0.55	0.02

Brain cancer: meta analysis	No. of studies	No. of exposed cases	Random effects odds ratio (95% CI)	Fail-safe N	Sample size needed	P-value for heterogeneity	Range of odds ratios from sensitivity analysis
Calculated fields	4	13	1.2 (0.6-2.4)	—	2699	0.2	0.8-1.5
Measured fields	4	36	1.4 (0.8-2.4)	—	612	0.4	1.1-1.6
Wire codes	4	193	1.2 (0.7-2.2)	—	1106	0.01	1.0-1.5
Proximity to electrical facilities	6	208	1.1 (0.7-1.7)	—	1790	0.03	0.9-1.3
Spot measurements	3		1.1 (0.7-1.6)		0.05	0.20	
Calculated fields							
0.2 or 0.25 μ T	4		1.1 (0.9-1.3)		0.08	0.08	
0.3 or 0.4 μ T	4		1.1 (1.0-1.3)		0.10	0.07	

Table 4.26 (continued)

Brain cancer: dose response analysis	No. of studies	Random effects relative risk (95% CI) per 0.1 μT	Regression slope	Standard error	P-Value for heterogeneity test
Wire codes					
Scored by spot measurement					
Flat model	2	1.2 (0.8-2.0)	0.22	0.23	0.3
Linear model	2	1.2 (0.7-2.0)	0.18	0.25	0.2

4.4 Non-cancer health effects in experimental animals

4.4.1 Immunological effects

Experimental evaluation of the response of the immune system to antigenic challenge is difficult because the immune system is highly redundant. An extensive range of assay systems has therefore been developed to measure the effects of adverse insults. These assay systems are targeted at acquired (humoral or cellular) and innate immunity; they include measurements to determine an animal's ability both *in vivo* and *in vitro* to respond to invaders including bacteria, intracellular parasites, viruses, and tumor cells (host resistance) and immunoassays that are correlated with activities associated with humoral, cellular, and innate immunity.

In general, the experimental models used to study interactions with EMF have been guided by methods and end-points developed to assess the effects of drugs, chemicals, and ionizing radiation on the immune system. Specific assays have been developed to measure suppression and/or stimulation (immunopotential) of a specific immune organ (thymus, spleen, lymph nodes), cell (helper and suppressor T cells, antibody-producing cells, natural killer cells, and macrophages), or function (antibody synthesis, cytokine production, cytotoxic activity, host resistance to infectious and/or malignant disease) (Luster *et al.*, 1990; Luster *et al.*, 1992a; Luster *et al.*, 1994; Luster *et al.*, 1993; Luster *et al.*, 1992b). Changes in the results of these assays have been correlated with host resistance. Alterations in antibody-producing cells, NK cell activity, and delayed hypersensitivity are significantly related to altered disease resistance (Luster *et al.*, 1993). Multiple end-points must be examined in order to clearly establish an interaction between an outside influence and the multiple-faceted immune system.

The exposure, biological end-points, and responses observed in a number of studies are summarized below and in Table 4.27.

4.4.1.1 Magnetic and electric fields

Exposure of adult male baboons *in vivo* to EMF has yielded contradictory information (Murthy *et al.*, 1995). In a pilot study, a social group of six baboons was followed for six weeks before exposure, for six weeks of exposure, and for six weeks after exposure. The animals were exposed to a 6 kV/m electric field and a 50 μ T magnetic field. Blood samples were taken in the fifth week of each period, and the distribution of helper and suppressor T cells, expression of interleukin-2 receptors, and NK cells were determined. Total lymphocyte count (cells/mm³) and stimulation of isolated peripheral blood lymphocytes by concanavalin A, phytohemagglutinin, and pokeweed mitogen were measured. Comparison of results obtained before exposure indicated a significant decrease ($p < 0.05$)

in the numbers of lymphocytes, helper, and suppressor T cells, interleukin-2 receptors, and response to phytohemagglutinin and pokeweed mitogen.

In a second study, eight baboons were field exposed (30 kV/m, 100 μ T) and eight were sham exposed, and the responses in mitogen stimulation assays and the distribution of cell types as identified by surface markers and interleukin-2 receptor activity were compared. The decreases seen in the pilot study were not seen in this follow-up study.

4.4.1.2 Magnetic fields

Groups of nine female Sprague-Dawley rats (52–54 days old) were exposed continuously (24 h/d) on 7 d per week for 2, 4, 8, or 13 weeks to a 50 Hz, 100 μ T magnetic field with concurrent sham-exposed controls (Mevissen *et al.*, 1998b). The biological end-points were body weight, splenic cellularity, and immune parameters (stimulation of spleen cells by concanavalin A and pokeweed mitogen and assessment of interleukin-1 production in pokeweed mitogen-stimulated cells). At 2, 4, 8, and 13 weeks after the start of the study, a significant reduction in viable lymphocytes from exposed rats was observed when compared with sham-exposed controls ($p < 0.05$). Splenic T cells showed an increased ($p < 0.05$) proliferative response to concanavalin A at 2 and 4 weeks of exposure, followed by a decrease ($p < 0.05$) at 13 weeks. No significant effects were observed on body weight, splenic T-cell response to pokeweed mitogen, or the production of interleukin-1 by pokeweed mitogen-stimulated cells. [Given the method by which the spleen cells were handled and the 20–25% reduction in control spleen-cell viability between weeks 2 and 4, the meaning of these results is unclear.]

Two separate studies (Tremblay *et al.*, 1996) were conducted in which Fischer 344/N pregnant rats were exposed to 60 Hz, sinusoidal magnetic fields of 2, 20, 200, or 2000 μ T for six weeks with sham-exposed controls, beginning on gestational day 20. At weaning, pups were separated from their mothers and held under the same field intensity for the duration of exposure of six weeks. In both studies, a cage control was included. Duplicate treatment groups of eight animals per group per study were included. The biological end-points were innate immunity (NK cell and peritoneal macrophage activities) and T and B cell counts in spleen based on specific surface markers (CD5⁺, CD4⁺, CD8⁺, and Ig⁺). The distribution of CD5⁺ cells (all T cells) was reduced in rats exposed to 200 ($p < 0.25$) or 2000 μ T ($p < 0.05$), and the numbers of CD4⁺ cells (T helper cells) and CD8⁺ cells (T cytotoxic/suppressor cells) were decreased significantly in rats exposed to 2000 μ T ($p < 0.005$). A significant reduction in all B cells was observed in rats exposed to 20 or 200 μ T ($p < 0.05$). An enhanced response of NK cells was observed in rats exposed to 2000 μ T when compared with cage controls ($p < 0.05$). Regression analysis of the data indicated a significant positive relationship between NK activity and magnetic field intensity ($p < 0.05$). The authors concluded that 60 Hz magnetic fields have significant effects on the immune responses of exposed animals. [The significant effects were found in comparisons with cage controls; no effects were seen when comparisons were made with sham-exposed animals.]

An extensive series of studies in mice and rats (House *et al.*, 1996) was conducted to measure body and tissue weights, cellularity and lymphocyte subtypes in spleen, and functional activity, delayed hypersensitivity, and host resistance of the immune system *in vivo*. Mice and rats received actual or sham exposure to 2, 200, or 1000 μT continuously or 1000 μT intermittently and to a 60 Hz magnetic field. No significant difference in the distribution of lymphocyte subsets in the spleens of exposed mice was observed when compared with controls.

NK cell activity was measured by ^{51}Cr release in female mice exposed to 1000 μT magnetic fields continuously or 1000 μT intermittently. A positive control was included to validate the responsiveness and repeatability of the assay system. Significantly ($p < 0.05$), consistently enhanced responses were seen in spleen-cell preparations from mice four weeks after exposure to 1000 μT magnetic fields continuously or intermittently, but the response was suppressed after 13 weeks of exposure to 200 or 1000 μT continuously or 1000 μT intermittently ($p < 0.05$). The studies were repeated three times for six weeks of exposure; the results were inconsistent.

The authors also conducted a series of exposures in Fischer 344 rats exposed for six weeks to sham, 2, 200, or 1000 μT continuous magnetic fields or an intermittent 1000 μT intensity. No consistent differences were observed in comparison with sham-exposed controls. Studies of cellular immunity (delayed hypersensitivity to oxazolone) in male and female mice exposed or sham-exposed for 4 or 13 weeks did not show a clear pattern or trend. No significant differences in mortality or survival time were observed in exposed mice administered *Listeria monocytogenes* when compared with appropriate sham-exposed controls.

House *et al.* (House *et al.*, 1996) concluded that continuous exposure of male and female mice to linearly polarized, pure sinusoidal 60 Hz magnetic fields at field strengths up to 1000 μT for up to 90 days did not significantly affect a broad range of immune effector functions. Moreover, this exposure regimen had no observable effect on the ability of mice to resist infection to a bacterial infection. [The results provide little support for the hypothesis that magnetic fields can alter immune responses.]

4.4.1.3 Magnetic fields and 7,12-dimethylbenz[a]anthracene

Female Sprague-Dawley rats, 52 days of age, received actual or sham exposure to 50 Hz, 50 μT magnetic fields for 13 weeks (Mevisen *et al.*, 1996b). Half of the controls and half of the exposed rats also received DMBA at 5 mg per week for four weeks by gavage. At the end of the 13 weeks, the mitogenic response of spleen cells to concanavalin A and pokeweed mitogen and splenic cellularity were measured. In rats exposed to the fields and not treated with DMBA, a significant reduction in concanavalin A stimulation was observed in spleen cells when compared with sham-exposed controls ($p < 0.05$). The response of rats treated with DMBA and exposed to magnetic fields was not significantly different from that of rats that were sham-exposed and DMBA-treated. The authors

concluded that immunoprotection may be compromised by exposure to magnetic fields. [Given the method by which the spleen cells were handled and the 20–25% reduction in control spleen-cell viability between weeks 2 and 4, the meaning of these results is unclear.]

4.4.1.4 Summary

The effects of EMF on the immune system have been investigated in baboons, rats, and mice. The studies varied in quality. Because of experimental difficulties, the studies of splenocytes are inadequate; three of the five studies were adequate to determine function, while two studies were inadequate.

There is no evidence in experimental animals for effects of ELF EMF on the immune system.

[This conclusion was supported by 13 members of the Working Group; there were 6 votes for ‘weak’ evidence, 1 abstention, and 9 absent.]

Table 4.27 Summary of immunological studies of exposure to EMF in experimental animals

Reference	Animals	Age and gender	Field characteristics	Exposure	Time of day	Light/dark cycle	Comments	Immunological and biological endpoints
				No. of Days	h/d			
Magnetic fields								
(House <i>et al.</i> , 1996)	mice BALB/C, B6C3F1	Male and female	60 Hz, Sham, 0, 2, and 200 μ T, 1 mT, 1 mT intermittent	28 or 90 d	18.5 h/d 7 d/week	12:12	Body and organ weights, < 0.1 μ T stray field to sham positive controls ($p < 0.05$)	Splenic subsets (flow) (CD-3, 4, 8, and B cells) not effected by exposure. Host resistance not affected by exposure Cellularity of spleen not effected by exposures aby (PFC/spleen) not effected by exposure. Body, spleen and thymus weights - not effected by exposures DTH - oxazolone - no consistent effect on contact hypersensitivity NK -spleen-males- no consistent pattern of effect (4 or 13 weeks) NK -females- 10G/10G intermittent - enhanced response at 4 weeks ($p < 0.05$) (200 μ T, 10 mT, and 10 mT, intermittent), suppressed response 13 weeks. ($p < 0.05$)
	B6C3F1, 3 confirmatory studies		Sham, 0, 2, and 200 μ T, 10 mT, 10mT intermittent	6 week				NK activity changes were observed but mixed: study 1 - one assay () value was decreased study 2 - reduction of NK function (200 μ T, 10 mT, and 10 mT intermittent, $p < 0.05$) study 3 - enhanced NK function (200 μ T, 10 mT, and 10 mT intermittent, $p < 0.05$)
	F344 rats	Male and female	Sham, 0, 2, and 200 μ T, 10 mT, 10mT intermittent	6 and 13 week				NK - spleen - varied effect with various target to effector ratios exhibiting effect ($p < 0.05$) in males or females
(Tremblay <i>et al.</i> , 1996)	F344 rats Studies repeated twice (8 rats/group n= 15-16 for end-points	Rats/group; final n= 15-16 for end points	60 Hz, sham (<0.02 μ T), 2, 20, 200, 2000 μ T	42 d	20	1300 to 900	2 separate experiments - rats born/raised in field pregnant females (d 20) building = $\sim 0.024 \mu$ T	Macrophage activity: H ₂ O ₂ -no effect on spontaneous production, PMA-stimulated enhanced at 20 and 2000 μ T; TNF activity - no effect correlated with exposure NO ₂ - no effect correlated with exposure CD5, 4, 8 and B cells - decrease CD5 (200 & 2000 μ T, $p < 0.05$)

Table 4.27 (continued)

Reference	Animals	Age and gender	Field characteristics	Exposure		Time of day	Light/dark cycle	Comments	Immunological and biological endpoints
				No. of Days	h/d				
								Pregnant females placed in exposure for 20 d	Decrease CD4 and 5 (2000 μ T, $p < 0.05$), decrease B cells (20 and 200 μ T, $p < 0.05$), regression analysis (MF intensities negative dose-response for CD5, CD4, CD8, $p < 0.05$) NK activity = LU - 50 % increased NK (2000 μ T, $p < 0.05$) LU = number of cell for 20% lysis - linear regression of MF vs. response ($p < 0.05$)
(Mevisen <i>et al.</i> , 1998b)	Sprague-Dawley rats 9/group	52-54 d Female	50 Hz, 100 μ T	91 d, 2, 4, 8, and 13 weeks	24, 7 d/week		12 h/12 h red light (approx. 1 lux)	Body weight Randomized (weight) Building = 0.03-.04 μ T	Cellularity - viable lymphocytes reduced for 2, 4, 8, and 13 weeks, $p < 0.05$ Con-A response enhanced at 2 and 4 weeks, $p < 0.05$ PWM - no change No effect on IL-1 production after 13 weeks
Magnetic and electric fields									
(Murthy <i>et al.</i> , 1995)	Baboons 6/group	adult, male	60 Hz - horizontal magnetic field and vertical electric field Exp III - 6 kV/m and 50 μ T, one group	6 weeks. Pre-exp. - 5 week Exp. - 6 week Post-exp. - 6 week	12	during light	12:12	CD 3, 4, 8 & NK(flow studies), IL-2R, WBC mitogen (PHA, PWM), <i>in vivo</i> exposure, ANOVA Building $\leq 0.1 \mu$ T	Decrease of CD4 cells IL2-R, $p < 0.05$

Table 4.27 (continued)

Reference	Animals	Age and gender	Field characteristics	Exposure No. of Days	h/d	Time of day	Light/dark cycle	Comments	Immunological and biological endpoints
	8/group		Exp. IV - 30 kV/m and 100 μ T, experimental and sham groups	Pre-exp. - 5 week Exp. - 6 week, Post-exp. - 6 week				Building \leq 0.2 μ T	Essentially did not replicate Exp. III
Magnetic fields and DMBA									
(Mevisse <i>et al.</i> , 1996b)	Sprague-Dawley rats	52 d Female	50 Hz, 500 μ T	91, 13 week	24, 7 d/week		12:12, off at 5 PM, red light (approximately 1 lux)	Mitogen responses (spleen), cellularity, body weight, spleen and liver weights, randomized (weight), building = 0.03-0.04 μ T, DMBA	Cellularity - spleen in DMBA-treated rats decreased ($p < 0.04$) Spleen and liver weights not affected Con-A response suppressed (no DMBA) in exposed rats ($p < 0.05$) Con-A response suppressed (with DMBA) in exposed rats (not significant) PWM - no change

4.4.2 Hematological effects

Hematological studies include measurement of the distribution of erythrocytic indices (red blood cells, hemoglobin concentration, packed red cell volume, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, hematocrit, and number of reticulocytes), platelets, total counts of nucleated leukocytes and red blood cells, and total and differential leukocyte counts (lymphocytes, neutrophils, basophils, monocytes, and eosinophils). Assessments of bone-marrow cellularity and the impression of bone-marrow smears complete the picture of the distribution of these cell types in peripheral blood.

4.4.2.1 Magnetic and electric fields

In a preliminary study (Picazo *et al.*, 1994), six female OF1 mice were exposed to a 50 Hz 0.1 mT sinusoidal magnetic field for three months. Six control mice were available. The biological end-points were hematocrit, leukocyte count, and differential leukocyte count. No difference was found in the hematocrit, and the red blood cells were similar in size in exposed mice and cage controls; however, there was a significant ($p < 0.05$) reduction in leukocyte count and changes in the distribution of some differential counts (monocyte and lymphocyte size subsets). [The groups were small, and there were no sham-exposed controls.]

In a follow-up study (Picazo *et al.*, 1995b), OF1 mice were exposed for two generations to a 50 Hz 15 μ T sinusoidal magnetic field. The first generation (mothers: 12 control and 12 exposed) was exposed for 17 weeks, and the second generation (daughters: 30 control and 30 exposed) was born and exposed for 14 weeks. Comparisons of hemological parameters in exposed and control mice showed no statistically significant change. [This study involved only females.]

Three groups of 18 mice were used to assess peripheral blood characteristics after exposure to a 20 mT magnetic field for 24 h/d for seven days (Lorimore *et al.*, 1990). The leukocytes were counted 0, 2, 4, 7, 10, and 18 days after exposure in three mice at each time. The authors stated that there were no significant differences between the field-exposed and sham-exposed groups. [The groups were extremely small.]

Margonato *et al.* (Margonato *et al.*, 1993) examined numerous hematological and serum chemical parameters in groups of 20 adult male Sprague-Dawley albino rats sham-exposed or field-exposed to 25 or 100 kV/m 50 Hz electric fields for 8 h/d for 280, 440, or 1240 h. No statistically significant effects were observed.

Margonato *et al.* (Margonato *et al.*, 1995) assigned 512 adult male Sprague-Dawley albino rats to sham or field exposure to a 50 Hz, 5 μ T magnetic field for 22 h/d for a total of 32 weeks. Hematological and serum chemical variables were measured at weeks 0, 12, 24, and 32. No statistically significant differences were detected.

Groups of 10 male and 10 female Fischer 344/N rats were sham-exposed or exposed to 60 Hz magnetic fields at 20, 200, or 1000 μ T continuously or 1000 μ T intermittently for 18.5 h/d for seven days per week (Boorman *et al.*, 1997). After eight weeks, the animals were anesthetized with CO₂, and blood was collected. Hematological and clinical chemical parameters did not differ between sham-exposed and field-exposed animals.

Zecca *et al.* (Zecca *et al.*, 1998) used three groups of 64 adult male Sprague-Dawley rats; one group was sham exposed; a second group was exposed to a 50 Hz, 5 μ T, 1 kV/m field; and a third group was exposed to a 100 μ T, 5 kV/m field. Blood samples were collected before exposure and after 12 weeks. No statistically significant difference was observed in numerous hematological and serum variables.

[The seven studies reviewed provide no evidence that exposure to power-frequency EMF affects the hematological or clinical chemical picture of rodents. These studies were generally short and some included a limited number of animals.]

4.4.2.2 Summary

There is no evidence that exposure to power-line frequency EMF affects the hematological parameters of rodents.

[This conclusion was supported by 17 members of the Working Group; there was 1 abstention and 11 absent.]

4.4.3 Effects on the nervous system

4.4.3.1 Field detection

(a) Electric fields

There is no doubt that animals can perceive electric fields, as previously reviewed by the National Research Council (NRC *et al.*, 1997). Briefly, Graves *et al.* (Graves *et al.*, 1978), Cooper *et al.* (Cooper *et al.*, 1981), and Graves (Graves, 1981) used conditioned response suppression techniques to assess perception. The data suggest that pigeons can detect 50 kV/m and chickens, 32 kV/m fields. Stern *et al.* (Stern *et al.*, 1983) and Stern and Laties (Stern & Laties, 1985) reported electric field detection thresholds of 3–10 kV/m in psychophysical experiments with rats, but the authors tended to emphasize the best performance of the animals. Sagan *et al.* (Sagan *et al.*, 1987) observed mean thresholds of 8 and 13 kV/m, depending on the psychophysical method used.

Stell *et al.* (Stell *et al.*, 1993) reported that the mean electric field detection threshold in rats was 8 kV/m (Table 4.28). In a series of experiments with six baboons, Rogers *et al.* (Rogers *et al.*,

1995c) demonstrated that electric fields of 22–64 kV/m can serve as a discriminative stimulus and a secondary reinforcer, implying detection. Orr *et al.* (Orr *et al.*, 1995) used psychophysical methods to measure electric field detection by six baboons: the mean threshold was 12 kV/m; however, one animal with an estimated threshold of 5 kV/m was able to detect electric fields of less than 4 kV/m, the lowest intensity achievable.

Weigel *et al.* (Weigel *et al.*, 1987) recorded single-unit activity in the sensory nerves of a cat's forearm; exposure to 600 kV/m (60 Hz) increased the firing rate, and shaving and application of mineral oil reduced it. Weigel and Lundstrom (Weigel & Lundstrom, 1987) showed that relative humidity affected vibration of the whiskers of anesthetized rats in a 50 kV/m electric field, suggesting that charges trapped on the hair led to vibration at 60 Hz. In dry air, there was less vibration. Stell *et al.* (Stell *et al.*, 1993) suggested, however, that hair vibration does not play a critical role in the detection of electric fields (0–25 kV/m, 50 Hz) by rats, and Graves (Graves, 1981) argued that electric field (50 kV/m, 60 Hz) detection by pigeons did not involve vibration of feathers. Hair vibration is thus probably sufficient but not necessary for detection of electric fields.

[Detection of electric fields is a well-established phenomenon, and the detection thresholds for mammals appear to be similar. Differences within species appear to be about as large as differences between species.]

(b) Magnetic fields

Smith *et al.* (Smith *et al.*, 1994) reported that a very strong magnetic field could serve as a cue for five Long-Evans female rats in a conditioned suppression paradigm (Table 4.29). Five frequency- and flux-dependent pairs of stimuli, ranging between 1900 μ T at 7 Hz and 200 μ T at 65 Hz, were used. The effect did not vary with different magnetic field intensity or frequency combinations. Stern (Stern & Justesen, 1995) suggested that the design of this study was inadequate to support the conclusion reached; no sham-field tests were completed, and temporal contingencies might have supported responses. [There is no experimental evidence that mammals can perceive magnetic fields at an environmentally relevant flux density.]

4.4.3.2 Avoidance and aversion

(a) Electric fields

It was reported in some early studies that exposure of rodents to electric fields was 'stressful' (see section 4.4.3.4 for a discussion of the endocrine effects of exposure to electric fields). Stimuli detectable at low intensities become aversive when present at high levels. The microshocks that animals can receive when exposed to high-voltage electric fields could elicit adverse behavioral or physiological responses. Thus, perception and/or aversion might be an 'indirect' causative mechanism in experiments using supra-threshold electric fields. These possibilities were not carefully considered in the early studies of exposure to electric fields, in which very high electric field strengths were used in an effort to address the problem of scaling

between rodents and humans (see section 3.4 for a discussion of electric field scaling factors; size, shape, and orientation are all important).

Hjeresen *et al.* (Hjeresen *et al.*, 1980; Hjeresen *et al.*, 1982) reported that exposure to electric fields (60 to 105 kV/m, 60 Hz) induced avoidance of the exposure area ($p < 0.05$) during the inactive portion of the day–night cycle: eight sham-exposed and 32 exposed rats showed avoidance during the day, and 15 sham-exposed and seven exposed pigs (30 kV/m, 60 Hz) showed avoidance at night. Rosenberg *et al.* (Rosenberg *et al.*, 1981) demonstrated that deer mice (21–34 per group) responded to strong electric fields (100 kV/m) with a transitory increase in activity. Rosenberg *et al.* (Rosenberg *et al.*, 1983) indicated that the increase in activity appeared at about 50 kV/m, and Blackwell and Reed (Blackwell & Reed, 1985) reported that 20 sham-exposed and 20 mice exposed to 400 V/m (50 Hz) or less did not show changes in activity. Easley *et al.* (Easley *et al.*, 1991) demonstrated that social stress was induced in baboons (eight per group) exposed to 60 kV/m (60 Hz) electric fields. These results, in several species, implied that exposure to electric fields might be aversive; however, Creim (Creim *et al.*, 1984) reported that exposure to as much as 133 kV/m electric fields did not induce taste aversion in male rats (three per group), and Stern and Laties (Stern & Laties, 1989) established that five male rats would not turn off a 100 kV/m (60 Hz) electric field but would turn off a light. [These results suggest that exposure to electric fields up to 133 kV/m is not highly aversive.]

Coelho *et al.* (Coelho *et al.*, 1991) reported that exposure to electric fields at 30 kV/m (60 Hz) increased the frequency of occurrence ($p < 0.05$) of three of ten categories of social behavior of baboons (eight per group) during a six-week exposure, in comparison with the equivalent rates observed in six-week pre- and post-exposure periods (Table 4.29). The effects on passive affinity, tension, and stereotypy were of the same magnitude with exposure to 30 or 60 kV/m (Easley *et al.*, 1991).

Easley *et al.* (Easley *et al.*, 1992) reported a replication of the behavioral effect at 30 kV/m. The means for the entire exposure period differed ($p < 0.05$) from those for the pre- and post-exposure periods, which were equivalent; analyses of weekly means indicated that the effect occurred almost exclusively during the first week of exposure ($p < 0.05$). The effect also occurred during the first week in the experiments reported by Easley *et al.* (Easley *et al.*, 1991) and Coelho *et al.* (Coelho *et al.*, 1991).

Rogers *et al.* (Rogers *et al.*, 1995c) found that six male baboons would not turn off an electric field above their detection thresholds, suggesting that exposure to electric fields is not aversive. [This outcome is generally similar to those of several studies in rats.]

Rogers *et al.* (Rogers *et al.*, 1995b) examined the effects of exposing two groups of six male baboons to 30 kV/m (60 Hz) electric fields. The baboons had been trained, under signal control, to respond on either FR30 (fixed ratio 30) or DRL 20 (differential reinforcement of low rate, 20 s) schedules. They were assigned randomly to field-exposed and sham-exposed groups and entered into a six-week pre-exposure, exposure, and post-exposure schedule. On the first day

of exposure, the field-exposed baboons showed 'work stoppage' ($p < 0.05$) or did not respond. Most began responding on the second day of exposure; once responding began, performance was normal. In a cross-over experiment, the effect was examined a second time. When the former controls received their first 30-kV/m exposure, they showed work stoppage. The original experiment was repeated at 60 kV/m with a new set of baboons, and the same work stoppage effect was observed ($p < 0.05$). Because exposure to a novel stimulus usually interrupts operant response, the authors did not regard this as an adverse effect.

[Introduction of a perceptible electric field can change the behavior of mice, rats, and nonhuman primates; however, the changes are transitory, appear to be secondary to detection of a novel stimulus, and do not suggest acute adverse effects.]

(b) Magnetic fields

Smith and Justesen (Smith & Justesen, 1977) reported that exposure to magnetic fields (1.7 mT, 60 Hz) increased activity in mice. Rudolph *et al.* (Rudolph *et al.*, 1985) reported that exposure to 40 μ T (50 Hz) increased activity in male Wistar rats (24 per group) but only at the beginning of tests conducted in the presence of illumination. Lovely *et al.* (Lovely *et al.*, 1992) reported that a 60 Hz magnetic field of 3.03 mT did not induce place avoidance in adult male rats (eight sham- and 24 field-exposed). [Too few experiments are available to reach a conclusion on the effect of magnetic fields on avoidance and aversion reactions.]

(c) Electric and magnetic fields

Groups of eight field-exposed (6 kV/m, 50 μ T, 60 Hz) and eight sham-exposed baboons were tested by the approach described previously (Coelho *et al.*, 1991). When the same animals were subsequently exposed for six weeks to 30 kV/m, 100 μ T, 30 kV/m electric fields did not elicit the initial increases in the frequency of passive affinity, tension, and stereotype. The authors speculated that the presence of the magnetic field might have blocked the response normally elicited by strong exposure to electric fields.

Orr *et al.* (Orr *et al.*, 1995) examined the effects of exposure to EMF in two groups of five male baboons trained to perform a match-to-sample operant task. In the first experiment, initial exposure to 6 kV/m and 50 μ T did not induce work stoppage. When the same animals were exposed to a perceptible 30 kV/m field accompanied by 100 μ T, no work stoppage occurred. A short cross-over experiment was completed in which the unexposed controls were exposed to 30 kV/m and 100 μ T for the first time; once again, exposure to EMF did not induce work stoppage. Inclusion of the 100 μ T field prevented the occurrence of work stoppage seen with 30 kV/m alone.

[The available evidence, including that from the series of experiments conducted with nonhuman primates in a well-controlled exposure facility suggests that exposure to EMF is not aversive] (Rogers *et al.*, 1995a; Rogers *et al.*, 1995b). [This series of experiments also suggests

that addition of a magnetic field can modulate the acute behavioral response of animals to exposure to perceptible electric fields.]

4.4.3.3 Learning and performance

(a) *Electric fields*

Several investigators have examined the ability of power-frequency, sinusoidal electric fields to affect learning and/or performance. Gavalas *et al.* (Gavalas *et al.*, 1970) and Gavalas-Medici and Day-Magdelano (Gavalas-Medici & Day-Magdaleno, 1976) reported that exposure to very weak electric fields (7-100 V/m) at 4–10 Hz (in the range of electroencephalogram (EEG) frequencies) disrupted the ‘timing’ behaviors of macaques (3-5 animals) performing a DRL-like operant schedule. Frey and Wesler (Frey & Wesler, 1984) reported that exposure to a relatively weak electric field (3.5 kV/m) induced a reduction response in suppression (Table 4.30). [This brief report is lacking many important details.]

Eight measures of the operant behavior of baboons on a FR30/DRL20 schedule were studied at 30 kV/m and at 60 kV/m (Rogers *et al.*, 1995b) and analyzed by analysis of variance. Other than the initial work stoppage, no effect on operant performance was seen. In a series of seven experiments with a set of six baboons, Rogers *et al.* (Rogers *et al.*, 1995c) observed that exposure to electric fields had no effect on response rate, number of errors, or extinction of a simple, appetitively motivated operant task.

[There is relatively little information on the possibility that exposure to power-frequency electric fields can affect performance of learned behavior. The available evidence does not suggest major, persistent effects.]

(b) *Magnetic fields*

As reviewed by the National Research Council (NRC *et al.*, 1997), Davis *et al.* (Davis *et al.*, 1984) reported that exposure to a 1.65 mT (60 Hz) magnetic field did not affect passive avoidance learning by male mice. Thomas *et al.* (Thomas *et al.*, 1986) reported that a 30-min treatment with a combined horizontal 60 Hz magnetic field (26 μ T) and static magnetic field adversely affected performance of five male rats on a DRL schedule, increasing DRL response. Fixed ratio performance was unaffected. The DC field was used to ‘cancel’ the Earth’s geomagnetic field. The key behavioral observation was that fixed ratio response was unaffected but DRL performance was adversely affected ($p < 0.05$), suggesting an effect on cognitive function. The key physical concept is that the Earth’s geomagnetic field can interact with a power-frequency magnetic field to produce an effect. The authors reported that neither DC exposure nor sinusoidal exposure to magnetic fields alone produced the effect. Liboff *et al.* (Liboff *et al.*, 1989) reported further studies in the same animals, which showed a threshold at 27 μ T. A step-function ‘threshold’, rather than a monotonically increasing function over a range of values, was observed. [These reports by themselves are not convincing; they were

based on data from only five rats and a few sessions conducted at the end of a series of experiments.]

Details of the following studies on learning and behavioral are presented in Table 4.30.

Trzeciak *et al.* (Trzeciak *et al.*, 1993) reported that exposure to magnetic fields (50 Hz, 18 mT) had no effect on locomotor activity or on open-field behavior of groups of 10–12 adult male and female Wistar rats; however, ‘irritability’, defined as response to blowing air on the back, touching the whiskers and back with a glass rod, and holding the animal in the hand was reduced. [The behavioral testing and scoring methods were not adequately explained.]

Sienkiewicz *et al.* (Sienkiewicz *et al.*, 1994) exposed CD1 mice to 20 mT (50 Hz) fields nearly continuously throughout pregnancy; dams and pups were removed from the magnetic field less than 18 h after birth. Many behavioral indices were examined at multiple times in 168 sham-exposed pups from 21 litters and 184 pups from 23 litters as the pups developed. Three significant effects ($p < 0.05$) were detected: exposed animals acquired the righting reflex earlier; exposed males (but not females) were lighter, only at 30 days of age; and exposed animals performed less well on the rotarod, only at days 30 and 45 of age. The authors concluded that no major effects occurred.

Kavaliers *et al.* (Kavaliers *et al.*, 1996) reported that exposure of groups of five male and five female deer mice to 100 μ T, 60 Hz for 5 min during acquisition and retention of a learned task (Morris water maze task) improved performance and acquisition. Similar results were found with meadow voles (Kavaliers *et al.*, 1993). Lai *et al.* (Lai & Singh, 1997b) presented data suggesting that exposure to a magnetic field (1 mT, 60 Hz) for 1 h immediately before testing adversely affected some aspects of the performance of male Sprague-Dawley rats in a Morris water-maze (five cage controls, 10 sham-exposed, 9 field-exposed). The motor component of this task was not affected by exposure; however, spatial reference memory was diminished. The authors also noted that the deficit was related to a decrease in motivation rather than to a deficit in learning ability.

Sienkiewicz *et al.* (Sienkiewicz *et al.*, 1996b) field-exposed (5 mT, 50 Hz) or sham-exposed CD-1 pregnant mice until just before parturition. The offspring were allowed to develop without further exposure to magnetic fields. Beginning at 83 days of age, 10 males per group began training on an eight-arm radial maze. No differences in performance were observed. Sienkiewicz *et al.* (Sienkiewicz *et al.*, 1996a) studied the effects of exposure to a 50 Hz magnetic field at intensities of 5–5000 μ T on acquisition of an eight-arm radial arm maze task by adult male CD-1 mice (10 per group). Exposure occurred only while the animals were in the maze. The authors concluded that concurrent exposure to magnetic fields had no effect on spatial learning.

Groups of 4–8 male Sprague-Dawley rats exposed for 45 min to a 0.75 mT 60 Hz magnetic field immediately before training on a 12-arm radial maze made more errors than did the sham-exposed controls ($p < 0.05$) (Lai, 1996). The running speeds of the two groups did not differ.

Pretreatment with the cholinergic agonist physostigmine blocked the effect but had no effect on animals not exposed to magnetic fields.

Sienkiewicz *et al.* (Sienkiewicz *et al.*, 1998) present data from four experiments showing that exposure to 0.75 mT (60 Hz) for 45 min before training in an eight-arm radial maze slowed acquisition of the task by male C57Bl/6J mice (six animals per group). The results of all four experiments were similar. Inter-group differences were most apparent in sessions 2–4 and were gone by session 6 or 7. These results confirm the observation of Lai (Lai, 1996) that exposure to magnetic fields just prior to training sessions slows acquisition but not final performance of the task.

[One interpretative difficulty with these studies is that changes in performance can be due to a variety of causes, including level of arousal. Thus, in the absence of additional experiments, the conclusion of an effect on spatial reference memory is only a testable hypothesis for additional experiments.]

Stern *et al.* (Stern *et al.*, 1996) conducted two experiments in an effort to replicate the findings of Thomas *et al.* (Thomas *et al.*, 1986) and Liboff *et al.* (Liboff *et al.*, 1989), who suggested that cyclotron resonance could affect the operant behavior of rats. None of the several exposure conditions tested had an effect on the operant behavior of the 13 rats examined. [No obvious reasons are apparent for the differing results of the two groups.]

[Ten experiments indicate that exposure to power-frequency magnetic fields can affect acquisition or performance of learned behavior. The effects are either adverse, beneficial, or absent, depending on the task and the timing of exposure to magnetic fields.]

(c) Electric and magnetic fields

Few investigators have examined the effects of combined EMF. Wolpaw *et al.* (Wolpaw *et al.*, 1989) exposed six macaques to electric fields of 3–30 kV/m in combination with magnetic fields of 10–90 μ T for 18 h/d for three weeks. The performance of a simple food-motivated operant task was not affected as compared with sham-exposed controls. Salzinger *et al.* (Salzinger *et al.*, 1990) exposed rats to 60 Hz 30 kV/m and 100 μ T. In a complex operant experiment with multiple extinctions and testing at various times during the diurnal cycle, there was some evidence ($p < 0.05$) for a slower response at the mid-point of the light portion of the light–dark cycle.

de Lorge and Grissett (de Lorge & Grissett, 1977) studied the effects of EMF on the operant behavior of 10 male and female monkeys (Table 4.30) but detected no effects on match-to-sample, fixed interval, or reaction time response. [This brief publication summarizes a complicated series of experiments performed with various exposure paradigms and dependent behavioral variables; the information provided is insufficient for detailed review of this work.]

Orr *et al.* (Orr *et al.*, 1995) studied the effects of exposure to EMF on a match-to-sample operant task with two groups of six male baboons. As in the studies of social behavior, described previously (Coelho *et al.*, 1995) imperceptible 6 kV/m 50 μ T fields had no effect on any aspect of operant performance. When the same animals were exposed to 30 kV/m and 100 μ T, no effects on operant performance were observed.

[All of the experiments in which nonhuman primates were used to examine the effects of combined exposure to electric and magnetic fields did not detect effects on operant performance. The single experiment in rats showed a subtle effect. Overall, no major adverse effects on operant performance have been reported as a result of exposure to power-frequency EMF.]

4.4.3.4 Neurophysiology

(a) Endocrinology

Some of the early studies of the effects of exposure to electric fields on growth and development (Burack *et al.*, 1984; Marino *et al.*, 1977; Marino *et al.*, 1976; Marino *et al.*, 1980) suggested that it was 'stressful'. Thus, investigators have sought endocrine changes that are the *sine qua non* of stress.

As reviewed by the National Research Council (NRC *et al.*, 1997), Marino *et al.* (Marino *et al.*, 1977) measured blood corticosterone concentrations in rats exposed to a 15 kV/m, 60 Hz electric field for 10 months; they reported reductions in six of the ten experiments. Hackman and Graves (Hackman & Graves, 1981) reported that adult mice (5–15 per group) exposed to electric fields of up to 50 kV/m, 60 Hz showed reductions in plasma corticosterone concentrations, but only at the onset (15 min) of exposure. Free *et al.* (Free *et al.*, 1981) no increase in corticosterone concentration was found at 30 or 120 days. Quinlan *et al.* (Quinlan *et al.*, 1985) exposed four Long-Evans hooded rats to 100 kV/m (60 Hz) for 1 or 3 h. Plasma corticosterone concentrations were not elevated in the four field-exposed rats relative to four sham-exposed controls. Portet and Cabanes (Portet & Cabanes, 1988) reported that rabbits (seven per group), but not rats (25 per group) exposed to 50 kV/m (50 Hz) showed reduced adrenal gland cortisol content. Changes were not observed in blood corticosterone concentrations.

Rommereim *et al.* (Rommereim *et al.*, 1990) observed chromodacryorrhea in female rats (68 per group) exposed continuously to 130 kV/m (60 Hz) and interpreted this as a stress response. Leung *et al.* (Leung *et al.*, 1990) quantified the chromodacryorrhea effect, reporting that it was increased in incidence and severity at 65 and 130 kV/m; the group at 10 kV/m did not differ from the sham-exposed control group.

Margonato *et al.* (Margonato *et al.*, 1993) exposed groups of 20 rats to 50 Hz electric fields of either 25 or 100 kV/m for 8 h/d for 280, 440, or 1240 h. The plasma concentrations of lutenizing hormone, follicle-stimulating hormone, and testosterone differed widely among

animals within groups, and no differences between field-exposed and sham-exposed groups could be detected. No effects on testis were reported. (see Table 4.31)

In three experiments, Kato *et al.* (Kato *et al.*, 1994a) measured plasma testosterone concentrations in adult male Wistar king rats (10–12 per group) after 42 days of exposure to a 50 Hz circularly polarized magnetic field of 0.02, 0.1, 1, 5, or 50 μT . There was no effect. Picazzo *et al.* (Picazo *et al.*, 1995a) report that groups of 30 male mice continuously exposed to a 15 μT 50 Hz magnetic field had a 27% increase ($p < 0.05$) in serum testosterone concentration, accompanied by a 7% increase ($p < 0.05$) in testis weight with a 12% increase in the area of the interstitium.

de Bruyn and de Jager (de Bruyn & de Jager, 1994) suggested that continuous exposure of mice to electric fields (50 Hz, 10 kV/m) acts as a stressor (Table 4.31). Their conclusion is based on two positive observations (out of a larger set) in the offspring of breeding pairs exposed to 10 kV/m, 22 h/d during gestation until either 35 days, 6 months, or 18 months of age. Mice of each sex and three ages were examined in daytime or night-time for several different variables. In one study, the serum corticosterone concentration was determined both day or night. In the exposed adult males (5–13 per group), the mean daytime corticosterone concentration was higher than in the controls ($p < 0.02$). Lipid staining of the adrenal cortex in the zona glomerulosa but not in the zona fasciculata or zona reticularis was elevated ($p < 0.05$) only in adult males.

Picazo *et al.* (Picazo *et al.*, 1996) report that the second generation of OF-1 mice (30 exposed and 30 controls) continuously exposed to a 15 μT 50 Hz magnetic field showed significant changes ($p < 0.05$) indicative of adrenocortical effects: the normal diurnal rhythms in plasma cortisol rhythms and adrenal cortex thickness were lost. The authors indicated that 15–20% of the exposed animals showed changes associated with adrenocortical hyperplasia; however, extensive histopathological examination did not reveal statistically significant differences. [The controls were not sham exposed, and the pathology assessments were not conducted in a blind fashion.]

Thompson *et al.* (Thompson *et al.*, 1995) exposed 10 sheep beneath a 500 kV (60 Hz) transmission line; the 10 controls were housed away from the line. The average field strengths were 6 kV/m and 4 μT . Blood samples were obtained at intervals of 0.5–3 h over a 48-h periods on eight occasions over eight months. After the pre-exposure sampling, blood was sampled two weeks after initiation of exposure. No change in plasma cortisol concentration was detected. Burchard *et al.* (Burchard *et al.*, 1996) studied numerous aspects of the physiology of 16 lactating, pregnant Holstein cows during periods with and without exposure to EMF. Cortisol was sampled twice a week and showed no changes, while progesterone was measured weekly and was increased by 11% ($p < 0.05$).

[Some of these studies present evidence that exposure to electric fields can be stressful, but the available evidence does not clearly establish that such an effect occurs.]

(b) Effects on opioid action

Ossenkopp and Kavaliers (Ossenkopp & Kavaliers, 1987b) examined the effects of 60 Hz magnetic fields of 2, 100, and 150 μT intensity; 30-min exposure of groups of 10–16 CF-1 mice produced a field intensity-dependent reduction ($p < 0.05$) in the analgesic effect of morphine. Ossenkopp and Kavaliers (Ossenkopp & Kavaliers, 1987a) also described a field intensity-dependent reduction ($p < 0.05$) in morphine analgesia in two experiments conducted at 50–150 μT (Table 4.31). Morphine was given at the mid-point of a 60-min exposure and testing was done at the end of exposure to magnetic fields. In the hot-plate analgesia test, the latency to forepaw lick was 56% of the control time in mice at 50 μT , 45% at 100 μT , and 23% at 150 μT . [The latency cut-off of 150 s was excessive for studies of morphine analgesia and raises concern about the method, especially with regard to determining a relationship with the endogenous opioid system. It limits interpretation of the effects on analgesia.]

Lai and Carino (Lai & Carino, 1998) exposed 6–10 male Sprague-Dawley rats to a 2 mT, 60 Hz magnetic field for 1 h and repeated their earlier observation of decreased ($p < 0.05$) cholinergic activity in the frontal cortex and hippocampus. They also showed that pretreatment of rats with the μ -opiate receptor agonist 3-funaltrexamine or the δ -opiate receptor agonist naltrindole through an intracerebroventricular cannula 24 h before exposure to magnetic fields blocks the induced decrease in sodium-dependent, high-affinity choline uptake in the frontal cortex and hippocampus. Zecca *et al.* (Zecca *et al.*, 1998) exposed groups of 64 male Sprague-Dawley rats to 5 μT and 1 kV/m or 100 μT and 5 kV/m for eight months and measured μ -opiod receptors in the frontal and parietal cortex and hippocampus in subgroups of 10–21 rats; no change in μ -opiod receptor concentration was found in the hypothalamus, striatum, or cerebellum.

(c) Neurotransmitters

Vasquez *et al.* (Vasquez *et al.*, 1988) measured monoamines in the hypothalamus and striatum of groups of six male Sprague-Dawley rats after exposure to 39 kV/m (60 Hz) for 20 h/d for 30 days; measurements were made every 4 h throughout the light–dark cycle. Changes in phase, rather than amplitude, were reported for norepinephrine, dopamine, and the serotonin metabolite 5-hydroxindole acetic acid in the hypothalamus and for 3,4-dihydroxyphenyl acetic acid in the striatum. Seegal *et al.* (Seegal *et al.*, 1989) measured monoamine concentrations in the cerebrospinal fluid of macaques after exposure to 60 Hz 10 μT , 3 kV/m or 30 μT , 10 kV/m or 90 μT , 30 kV/m for 20 days. The concentrations of the dopamine metabolite homovanillic acid and 5-hydroxindole acetic acid were reduced in field-exposed animals.

Zecca *et al.* (Zecca *et al.*, 1991) measured norepinephrine, serotonin, 5-hydroxindole acetic acid, dopamine, and its metabolites homovanillic acid and 3-4-dihydroxyphenyl acetic acid in striatum of animals exposed to electric fields of 25 and 100 kV/m (50 Hz) for various times. The amino acid neurotransmitters taurine, glutamine, aspartic acid, glutamic acid, glycine, alanine, and γ -aminobutyric acid were also measured. Numerous *t* tests were performed, and some small (10% or less) differences ($p < 0.05$) were observed (Table 4.31).

Lai *et al.* (Lai *et al.*, 1993) examined the effects of 45 min exposures to a 60 Hz magnetic field of 500, 750, and 1000 μT intensity on sodium-dependent, high-affinity choline uptake in the brains of six male rats. Brains were collected immediately after exposure. Decreased ($p < 0.05$) sodium-dependent high-affinity choline uptake was demonstrated; dose-dependent reductions were observed in frontal cortex and hippocampus. The authors also showed that the opioid antagonist naltrexone, administered just before exposure to magnetic fields, blocked these effects, but naloxone did not. [Concern was raised by the differential effects of these two narcotic antagonists, since both inhibit central opioid receptors.]

Sakamoto *et al.* (Sakamoto *et al.*, 1993) exposed Sprague-Dawley dams and sires to 60 Hz, 50 μT circularly polarized magnetic fields before mating and dams during gestation. Six to 12 embryos per group were harvested at days 12, 14, 16, 18, and 20 of gestation and choline transferase activity in brain was measured. In an additional experiment, groups of six animals were exposed for three months before mating. The brains of offspring were analyzed 10 days after birth. In both studies, normal age-related changes were found but no effects of exposure.

Margonato *et al.* (Margonato *et al.*, 1995) measured the brain neurotransmitter concentrations in 256 male Sprague-Dawley rats (groups of 15) after 5000 h of exposure to a 50 Hz, 5 μT field for 20 h/d. Striatum, hypothalamus, hippocampus, and cerebellum were analyzed for norepinephrine, dopamine, 3,4-dihydroxyphenyl acetic acid, homovanillic acid, serotonin, and 5-hydroxyindole acetic acid. No group differences were detected. Zecca *et al.* (Zecca *et al.*, 1998) determined norepinephrine, dopamine, 3,4-dihydroxyphenyl acetic acid, homovanillic acid, serotonin, and 5-hydroxyindole acetic acid in the frontal cortex, parietal cortex, striatum, hypothalamus, and cerebellum; D2 receptor concentrations were measured in striatum and frontal cortex. No effects of an eight-month exposure to 5 μT and 1 kV/m or to 100 μT and 5 kV/m were found. [In both experiments, neurotransmitter concentrations were assessed at the end of long-term exposure, and any acute temporal trends would not have been determined.]

[Although a few studies have shown effects of magnetic fields on neurotransmitters, the results are mixed and the effects noted are relatively small. The design of many of these studies included terminal sampling at the end of long-term exposure, and limited end-points were evaluated to assess the functioning of the neurotransmitter system. The inherent difficulty in associating changes in regional neurotransmitter concentrations with functional or behavioral alterations makes interpretation of the biological significance of these findings difficult.]

4.4.3.5 Electrophysiology

(a) Electric fields

Jaffe *et al.* (Jaffe *et al.*, 1983) indicated that exposure of groups of 2-9 rats exposed *in vivo* to electric fields (60 Hz, 65 kV/m) increased the synaptic excitability, measured *ex vitro*, of the excised superior cervical ganglion. Jaffe *et al.* (Jaffe *et al.*, 1981) reported that exposure to electric fields (65 kV/m, multiple frequencies) increased the fatiguability at the rat neuromuscular junction (13-22 animals per group). Jaffe *et al.* (Jaffe *et al.*, 1980) measured

visual evoked potentials repeatedly in developing rats exposed to 60 kV/m; exposure to electric fields had no effect. Blackwell (Blackwell, 1986) measured the firing rates of 51 single units in rat cortex. Electric fields of 100 V/m had no effect on the overall firing rate; at 15 or 30 Hz, some synchrony with the applied waveform was observed, but the effect was not observed at 50 Hz.

Gavalas *et al.* (Gavalas *et al.*, 1970) and Gavalas-Medici and Day-Magdelano (Gavalas-Medici & Day-Magdelano, 1976) suggested that exposure of macaques to electric fields within the range of normal EEG frequencies, typically 30 Hz or less, affected neuronal activity. ELF-modulated VHF fields appear to be a particularly effective stimulus for such effects (Bawin *et al.*, 1973).

(b) Magnetic fields

As reported by the National Research Council (NRC *et al.*, 1997) Ossenkopp and Cain (Ossenkopp & Cain, 1988) found that groups of 17 adult male rats field-exposed or sham-exposed to a 100 μ T magnetic field at 60 Hz showed attenuation of seizure discharges in a kindling model. Ossenkopp and Cain (Ossenkopp & Cain, 1991) presented data from six experiments with group sizes of 11–20 rats in which a 60 Hz magnetic field of 50–185 μ T was applied for 1 h before induction of seizures with pentylenetetrazol (Table 4.32). In only two of six studies was seizure duration decreased ($p < 0.05$), and fewer seizures ($p < 0.05$) were observed in only one experiment. Mortality due to seizures was diminished by exposure but not in relation to field intensity. [Overall, exposure to 60 Hz magnetic fields does not aggravate seizures; however, this paper does not convincingly demonstrate that exposure to electric fields diminishes their number.]

Lyskov *et al.* (Lyskov *et al.*, 1993a) exposed 12 female Sprague-Dawley rats to magnetic fields of 126 μ T or 1.26 mT for 24 h (multiple frequencies) and then recorded an EEG. An average response (based on measurements taken immediately and 15 and 30 min after exposure) of four statistically significant effects was observed after sham exposure. The observation of 4-fold (1.26 mT) and 8.5-fold (126 μ T) increases in the number of statistically significant ($p < 0.05$) changes in EEG variables was taken by the authors as evidence of an effect of exposure to magnetic fields on the EEG. Numerous other comparisons led the authors to the generalizations that power in the delta (1–4 Hz) and theta (4–8 Hz) bands was decreased and power in the beta (12–20 Hz) and high frequency (30–60 Hz) bands was increased. [They analyzed 31 EEG parameters for four electrode combinations and three times, so that many statistical comparisons were made, and the probability that one or more of the results would be significant by chance alone (Type I errors) was high. The study is statistically invalid and has other methodological shortcomings. Use of pre-implanted metallic screws as EEG electrodes might be an issue.]

(c) Electric and magnetic fields

Dowman *et al.* (Dowman *et al.*, 1989) measured auditory, visual, and somatosensory evoked potentials twice a week during three-week exposures in six adult macaques exposed to EMF combinations of 3 kV/m and 10 μ T, 10 kV/m and 20 μ T, and 30 kV/m and 30 μ T; there were four sham-exposed controls. Evoked potentials were measured during the daily 6-h periods without exposure to EMF. There were some signs that the amplitudes of the later components of somatosensory evoked potentials were reduced in the two groups exposed to higher field intensities.

[A few papers indicate that exposure to power-frequency electric and/or magnetic fields can change the characteristics of EEGs or evoked potential activity in animals. The effects on the EEG are more prominent at frequencies less than 30 Hz, where the imposed field is in the same frequency range as endogenous neural activity; however, none of the results suggests that such effects are hazardous. The available data suggest that exposure to magnetic fields inhibits, rather than stimulates, epileptic activity.]

4.4.3.6 Summary

There is strong evidence that electric fields can be perceived.

[This conclusion was supported by 18 members of the Working Group; there were 2 abstentions and 9 absent.]

There is weak evidence for the neurobehavioral, neuropharmacological, neurophysiological, and neurochemical effects of electromagnetic fields.

[This conclusion was supported by 9 members of the Working Group; there were 8 votes for 'moderate' evidence, 3 abstentions, and 9 absent.]

Table 4.28 Perception in experimental animals exposed to EMF

Reference	Animals	Groups	Exposure conditions	Outcome
Electric fields				
(Stell <i>et al.</i> , 1993)	Sprague-Dawley rats, six adult male	Within-subject design standard in psychophysics	Vertical, 60 Hz, 0 – 25 kV/m; brief daily exposures during training trials	Moving air did not change mean detection threshold of 7.5 kV/m, implies detection not mediated by hair movement
(Rogers <i>et al.</i> , 1995c)	Baboon, <i>Papio c.</i> , six young adult male	Within-subject design common in operant experiments	Vertical, 60 Hz, 22-65 kV/m; brief daily exposures during training trials in seven experiments distributed over a 1 year	Stimuli can serve as discriminative stimulus and as a secondary reinforcer on a simple operant task, implying detection
(Orr <i>et al.</i> , 1995)	Baboon, <i>Papio c.</i> , six young adult male	Within-subject design standard in psychophysics	Vertical, 60 Hz from 4 to 41 kV/m; brief daily exposures during training trials over 16 weeks	Average detection threshold 12 kV/m; effect not mediated by sound and under stimulus control
Magnetic fields				
(Smith <i>et al.</i> , 1994)	Long-Evans rat, five young adult female	Within-subject design standard in psychophysics	200 – 1900 μ T at 7, 16, 30, 60 and 65 Hz; 1 h/d for 5 d per week for 5 weeks	MF presence served as cue for conditioned suppression of operant responding

Table 4.29 Summary of experiments assessing aversion in experimental animals fields

Reference	Animals	Groups	Exposure conditions	Outcome
Electric fields				
(Coelho <i>et al.</i> , 1991)	Baboon, <i>Papio c.</i> , young adult male	8 field-exposed and 8 sham-exposed	30 kV/m, 60 Hz, vertical; 12 h/d, 7 d/week for 6-week pre-exposure, exposure, and post-exposure periods	Rates of occurrence of Passive Affinity, Tension and Stereotypy were increased in Exposure compared to Pre- and Post-exposure
(Easley <i>et al.</i> , 1991)	Baboon, <i>Papio c.</i> , young adult male	8 field-exposed and 8 sham-exposed	60 kV/m, 60 Hz, vertical; 12 h/d, 7 d/ week for 6-week pre-exposure, exposure, and post-exposure periods	Rates of occurrence of passive affinity, tension and stereotypy were increased in exposure compared to pre- and post-exposure periods
(Easley <i>et al.</i> , 1992)	Replication of Easley <i>et al.</i> , 1991	8 field-exposed and 8 sham-exposed; cross-over from previous experiment	30 kV/m, 60 Hz, vertical; 12 h/d, 7 d/week for 3-week pre-exposure, and exposure periods	Rates of occurrence of passive affinity, tension and stereotypy were increased only in first week of exposure; true for two previous experiments as well
(Rogers <i>et al.</i> , 1995c)	Baboon, <i>Papio c.</i> , six young adult male	Within-subject design, common in operant experiments	Vertical, 60 Hz, 0-65 kV/m; brief daily exposures during training trials conducted over 1 year period	Subjects would not turn off electric fields, indicating exposure was not aversive; subjects responded readily for food rewards
(Rogers <i>et al.</i> , 1995b)	Baboon, <i>Papio c.</i> , young adult males	Six field- and six sham-exposed	Vertical, 60 Hz, 30 kV/m; 12 h/d, during 6-week pre-exposure, exposure and post-exposure periods	Initial day of exposure produced work stoppage on FR30/DRL20 operant task
		6 field and 6 sham-exposed, cross-over design	Vertical, 60 Hz, 60 kV/m; 12 h/d, during 6-week pre-exposure and exposure periods	
Electric and magnetic fields				
(Coelho <i>et al.</i> , 1995)	Baboon, <i>Papio c.</i> , young adult male	8 field-exposed and 8 sham-exposed	60 Hz ,vertical electric field (6 kV/m) and horizontal magnetic field (50 μ T); 12 h/d during 6-week pre-exposure, exposure and post-exposure periods	Based on 12 kV/m detection threshold, observed absence of changes in social behavior at onset of 6 kV/m “expected” and at onset of 30 kV/m exposure “unexpected”; magnetic field interaction?
(Orr <i>et al.</i> , 1995)	Baboon, <i>Papio c.</i> , young adult male	5 field- and 5 sham-exposed	60 Hz ,vertical electric field (6 kV/m) and horizontal magnetic field (50 μ T); 12 h/d during 6-week pre-exposure, exposure and post-exposure periods	Based on 12 kV/m detection threshold, observed absence of changes in operant behavior at onset of 6 kV/m “expected” and at onset of 30 kV/m exposure “unexpected”; MF interaction?

Table 4.30 Learning and performance in experimental animals exposed to EMF

Reference	Animal	Groups	Exposure conditions	Outcome
Electric fields				
(Frey & Wesler, 1984)	Sprague Dawley rat, adult male	Two groups of seven, field-exposed and sham-exposed	3.5 kV/m, 60 Hz, 22 h/d; testing continued for 8 d	Exposed rats made twice as many responses during conditioned emotional response testing
(Rogers <i>et al.</i> , 1995c)	Baboon, <i>Papio c.</i> , six young adult male	Within-subject design, common in operant experiments	Vertical, 60 Hz, 22-65 kV/m; brief daily exposures during training trials in 7 experiments distributed over a 1 year	Exposure had no effect on response rate or extinction of operant responding on a simple appetitive task
(Rogers <i>et al.</i> , 1995b)	Baboon, <i>Papio c.</i> , young adult male	Six field- and six sham-exposed	Vertical, 60 Hz, 30 kV/m; 12 h/d for 6-week pre-exposure, exposure, and post-exposure periods	No effect on performance on FR30/DRL20 operant task
Magnetic fields				
(Kavaliers <i>et al.</i> , 1993)	Meadow vole, <i>Microtus p.</i> , adult	Male and female, MF on and MF off; 8 - 12 per group	60 Hz, linear, 0.1 mT for c. 5 minutes per day (during testing) for 10 days	Exposure improved acquisition and retention of Morris water maze task, especially in females
(Trzeciak <i>et al.</i> , 1993)	Wistar rat, adult male and female (pregnant and non-pregnant)	Three groups of 10 – 12 animals	50 Hz, 18 mT; 2 hours per day for 20 days; test at days 0, 4, 10 and 17	Decrease in irritability score; no effects on open field behavior or locomotion
(Sienkiewicz <i>et al.</i> , 1994)	CD1 mouse, pregnant	Field-exposed (184) or sham-exposed (168)	50 Hz, 20 mT for duration of gestation; dams removed from MF shortly before parturition; offspring were tested at days 7, 14, 21, 30, 60 and 90, without further MF exposure	Numerous variables from a behavioral teratology test battery were measured; three effects were detected, none regarded as important
(Kavaliers <i>et al.</i> , 1996)	Deer mice, <i>Pero-myscus m.</i> , adult	Field-exposed and sham-exposed, male and female, five subjects per cell	100 T, 50 Hz, brief exposure (< 5 minutes) during 10 daily training sessions	Males perform better in Morris water maze than females, MF exposure improves performance of females
(Lai, 1996)	Sprague Dawley rat, young adult male	2 groups of 8 field-exposed and sham-exposed 4 groups of 4 or 5 field-exposed and sham-exposed, drug-treated and non-treated	45 minutes of exposure to 0.75 mT immediately before each of ten daily training sessions	Increase in errors in 12-arm radial maze acquisition, final performance matches controls Exposure increased errors in acquisition of 12-arm radial maze, but pre-treatment with physostigmine prevented the increase in errors
(Stern <i>et al.</i> , 1996)	Long-Evans rat, adult male	Groups of 5, 2 experiments by 3 conditions	Horizontal, 60 Hz, 50-72 μ T magnetic fields plus DC field to reduce geomagnetic field; brief daily exposures during training trials	No effects on performance on FR30/DRL20 schedule

Table 4.30 (continued)

Reference	Animal	Groups	Exposure conditions	Outcome
(Sienkiewicz <i>et al.</i> , 1996a)	CD1 mouse, adult male	Field-exposed and sham-exposed groups of 10, 4 experiments	Vertical, 50 Hz at 5, 50, 500 or 5,000 μ T; exposure during ten daily test sessions	Acquisition of radial arm maze performance not affected by exposure during testing
		Field- and sham-exposed groups of 10	Vertical, 50 Hz; experimental groups exposed to 5 mT only <i>in utero</i>	Acquisition of radial arm maze performance as adult not affected by <i>in utero</i> exposure
(Sienkiewicz <i>et al.</i> , 1998)	C57BL/6J mouse, adult male	4 experiments, field-exposed and sham-exposed groups of 6	Vertical, 50 Hz, magnetic fields at 0.75 mT for 45 min immediately before testing	Acquisition of radial arm maze performance slowed, but final performance was equal to that of controls
(Lai <i>et al.</i> , 1998)	Sprague Dawley rat, adult male	Cage controls (5), sham-exposed (10), and field-exposed (9)	60 Hz, 1 mT, 1 h; test immediately after exposure	Exposed rats swam more slowly in Morris water maze but performed as well as controls during training; in a probe trial, exposed rats performed less well
Combined electric and magnetic fields				
(de Lorge & Grisset, 1977)	Squirrel monkey, <i>Saimiri s.</i> (6), and rhesus monkey, <i>Macaca m.</i>	10 adult (males and females) animals used in multiple experiments, within-subject comparisons	14 experiments with 7-60 Hz, 1-29 V/m and 0.3 or 1.0 mT; exposures were 1 - 24 h/d for 5 - 1008 h	No effects on match-to-sample, fixed interval or reaction time responding
(Orr <i>et al.</i> , 1995)	Baboon, <i>Papio c.</i> , young adult	5 field-exposed and 5 sham-exposed	60 Hz; vertical electrical fields and horizontal magnetic fields; 6 kV/m with 50 μ T, 12 h/d during 6-week pre-exposure, exposure and post-exposure periods	No effects on match-to-sample performance, normal time-delay accuracy curves
		5 field-exposed and 5 sham-exposed	60 Hz; vertical electric fields and horizontal magnetic fields; 30 kV/m with 100 μ T; 12 h/d during 6-week pre-exposure, exposure and post-exposure periods	No effects on match-to-sample performance, normal time-delay accuracy curves
		5 field-exposed and 5 sham-exposed, cross-over design	60 Hz; vertical electric fields and horizontal magnetic fields; 30 kV/m with 100 μ T; 12h/d during 1 week pre-exposure and exposure periods	No effects on match-to-sample performance, normal time-delay accuracy curves

Table 4.31 Neurophysiological effects of EMF in experimental animals

References	Animals	Groups	Exposure conditions	Outcome
Effects on the endocrine system				
(Margonato <i>et al.</i> , 1993)	Sprague Dawley rat, young adult male	280 subjects, in groups of 20	50 Hz vertical EF for 8 h/d for 280, 440 or 1240 h at 25 kV/m or 100 kV/m	No significant changes in LH, FSH or testosterone
(Kato <i>et al.</i> , 1994a)	Wistar-King rat, adult male	5 groups of 20 - 24 animals	0.02, 0.1, 1, 5 and 50 μ T for 6 weeks (near continuous); circularly polarized	No effects on plasma testosterone concentrations
(de Bruyn & de Jager, 1994)	Balb/c mouse, males and females, 6 and 18 months	Exposed and controls (non-sham exposed), day and night, 5 - 13 per group	10 kV/m, vertical, 50 Hz; 22 h/d from conception to death, for up to 6 generations	Median daytime serum corticosterone elevated 2.5-fold for adult males only; no other differences
	Balb/c mouse, males and females; 1, 6 and 18 months	Exposed and controls (non-sham exposed); 12 - 21 per group	10 kV/m, 50 Hz; 22 h/d from conception to sampling	Lipid content of one zone of adrenal cortex reduced by one third, only in 6-month-old males
(Picazo <i>et al.</i> , 1995a)	OF1 mouse, male; second exposed generation; exposed <i>in utero</i> and to 10 weeks of age	Litters from 24 females; 30 exposed and 30 controls used for testes studies	15 μ T at 50 Hz, horizontal, near-continuous exposure; dams exposed for 14 weeks prior to mating, exposure continued until offspring were 10 weeks of age	Increases in serum testosterone and testis weight occurred in exposed animals
(Thompson <i>et al.</i> , 1995)	Suffolk lamb, female, pre-pubertal	Field-exposed and sham-exposed	6 kV/m and 4 μ T at 60 Hz, exposed from 2 to 10 months of age	Diurnal pattern of cortisol secretion was unaffected
(Burchard <i>et al.</i> , 1996)	Holstein cow, multiparous	One group of 16 studied in 28-d periods with or without exposure	30 μ T horizontal and 10 kV/m vertical; presumably 60 Hz, apparently 23 h/d	Progesterone was elevated 11% during exposure, cortisol was unchanged
(Picazo <i>et al.</i> , 1996)	OF1 mouse, male and female, second generation, 10 weeks of age	30 control and 30 exposed, divided into day and night groups	Horizontal, 15 μ T, 50 Hz; continuous exposure	Exposed rats did not show normal diurnal differences in cortisol concentration and adrenal cortex thickness
Effects on analgesic and opioid action				
(Ossenkopp & Kavaliers, 1987b)	CF-1 mouse, adult male	Cage control, field-exposed and sham-exposed, groups of 10-16 animals	Linear, 60 Hz 50, 100 or 150 μ T for 1 h	Analgesia was reduced in a dose-dependent manner
(Lai & Carino, 1998)	Sprague Dawley rat, adult male	Field-exposed and sham-exposed; sets of 6 - 8 subjects	2 mT, 60 Hz, 1 h	MF exposure reduced high affinity choline uptake in frontal cortex and hippocampus
		Field-exposed and sham-exposed, vehicle or one of two drugs, groups of 6 - 8	2 mT, 60 Hz, 1 hour	Administration of opiate antagonists blocked the effect

Table 4.31(continued)

References	Animals	Groups	Exposure conditions	Outcome
(Zecca <i>et al.</i> , 1998)	Sprague Dawley rat, adult male	3 groups of 64, 1 sham-exposed and 2 field-exposed	Horizontal magnetic fields and vertical electric fields, 5 μ T and 1 kV/m or 100 μ T and 5 kV/m, 22 h/d for 8 months	Decreased opioid receptors in frontal and parietal cortex and in hippocampus
Effects on neurotransmitters				
(Zecca <i>et al.</i> , 1991)	Sprague-Dawley rat, adult male	4 experiments, field- or sham-exposed; numbers not given, but standard errors very small	Vertical, 50 Hz, 25 and 100 kV/m; 8 – 22 h/d for 5-7 d per week, 320-1408 hours total	Short exposures reduced most of the amino acids; moderate duration exposures reduced only tau, and long exposures again reduced most of them; temporal effects not depending on electric field strength
(Lai <i>et al.</i> , 1993)	Sprague-Dawley rat, adult male	10 groups of 6-10, sham- and field-exposed, saline and 2 drugs	Horizontal, 60 Hz; 0.5, 0.75 or 1 mT; 45 min	High affinity choline uptake reduced at 0.75 and 1 mT, effect blocked by central cholinergic antagonist but not by peripheral antagonist
(Sakamoto <i>et al.</i> , 1993)	Sprague-Dawley rat	Field-exposed and sham-exposed neonates examined at days 5 and 10	60 Hz, circular, 50 μ T; apparently continuously exposed <i>in utero</i> and to time of analysis	No effects on brain choline transferase activity, normal developmental changes
		11 groups of 6 – 12 embryos measured at days 12, 14, 16, 18 and 20	60 Hz circular, 50 μ T apparently continuous; exposed <i>in utero</i> and to time of analysis	No effects on brain choline transferase activity, normal developmental changes
(Margonato <i>et al.</i> , 1995)	Sprague-Dawley rat, young adult male	A total of 30 subjects, field- and sham-exposed, two replicate experiments	5 μ T, 50 Hz, horizontal; 22 hours per day for 32 weeks	No changes in six neurotransmitters or metabolites in four brain regions
(Zecca <i>et al.</i> , 1998)	Sprague-Dawley rat, adult male	3 groups of 10, 1 sham-exposed and 2 field-exposed	Horizontal magnetic field and vertical electric field; 5 μ T and 1 kV/m or 100 μ T and 5 kV/m; 22 h/d for 8 months	At 100 T and 5 kV/m, increased pineal gland norepinephrine content; no changes in serotonin or 5-HIAA*

LH, luteinizing hormone; FSH, follicle-stimulating hormone; 5-HIAA, 5-hydroxyindole acetic acid

Table 4.32 Electrophysiological effects of EMF in experimental animals

References	Animal	Groups	Exposure conditions	Outcome
Effects on electrophysiology				
(Ossenkopp & Cain, 1991)	Long-Evans rat, adult male	18 groups of 11 – 20; sham- or field-exposed	60 Hz, horizontal magnetic field of up to 185 μ T for 1 h; drug injected after exposure	Exposure modestly decreased seizure mortality
(Lyskov <i>et al.</i> , 1993a)	Wistar rat, adult female	One group, measured in baseline and 0, 15 and 30 min after exposure	45 Hz, vertical; 126 μ T and 1.26 mT; 2 24-h exposures (24 h apart); 1 s on and 1 s off	4 “hits” after sham, 34 after 126 μ T and 16 after 1.26 mT
(Ossenkopp & Kavaliers, 1987b)	CF-1 mouse, adult male	Cage control, field-exposed and sham-exposed, groups of 10 – 16	Linear, 60 Hz, 50, 100 or 150 μ T for 1 h	Analgesia was reduced in a dose-dependent manner

4.4.4 Reproductive and developmental effects

Assessments of the effects of magnetic fields on reproduction and development have included a wide spectrum of biological end-points, including gametogenesis, fertilization, implantation, embryogenesis, and pre- and postnatal development. A series of reviews (Brent *et al.*, 1993; Chernoff *et al.*, 1992; Huuskonen *et al.*, 1998; Juutilainen, 1991; Juutilainen & Lang, 1997) have been published on the reproductive and developmental toxicity of EMF. This section addresses studies of the effects of magnetic fields on reproduction and development in avian and mammalian systems; these are summarized in Table 4.33. Studies of avian systems involving pulsed magnetic fields are not considered in this section.

4.4.4.1 Birds

Juutilainen and Saali (Juutilainen & Saali, 1986a) exposed 10 chicken embryos during the first 48 h of development to 50 Hz magnetic fields at field strengths of 0.1–10 μT ; there were 10 controls. The embryos were scored for developmental stage and categorized as normal or abnormal. No change in developmental stage due to exposure was observed. The number of abnormal embryos was increased ($p < 0.05$) at 10 and 100 A/m.

Pafkova *et al.* (Pafkova *et al.*, 1994) reported the effects of 50 Hz magnetic fields at field intensities of 6 μT or 10 mT on avian embryonic development at 2, 6, 16, 20, and 40 h. No effects were observed on mortality or structural malformations evaluated on the ninth day.

In a related study, Pafkova and Jerabek (Pafkova & Jerabek, 1994) combined magnetic fields with ionizing radiation (X-ray). Chick embryos were pre-exposed to a 50 Hz, 10 mT magnetic field from the second to fortieth hour of incubation and exposed to X-rays (4 or 5 Gy) on the third or fourth day of embryonic age. In a second series, chicks were exposed to magnetic fields before or after X-ray treatment on day 3 or 4. The authors found a statistically significant reduction in teratogenic development in embryos exposed to magnetic fields before ionizing radiation ($p < 0.003$) when the results of all studies were combined. Exposing the embryos to magnetic fields after ionizing radiation resulted in a potentiation of adverse developmental effects ($p < 0.02$).

Pafkova *et al.* (Pafkova *et al.*, 1996) conducted a series of studies in which chick embryos were pre-exposed to magnetic fields (50 Hz, 10 mT) for eight 2-h sessions for the first 48 h of incubation. After two or three days of incubation, the eggs were injected through a window in the shell with 10 μl of insulin (0.00–0.05 μg) or tetracycline (10–30 μg). Controls were injected with 10 μl of water. Exposure of eggs to magnetic fields before treatment with insulin reduced the embryotoxic effects ($p < 0.01$). Exposure to magnetic fields and tetracycline conclusion inconsistent with paper.

The effects of an intermittent horizontal sinusoidal 50 Hz magnetic field was reported by Veicsteinas *et al.* (Veicsteinas *et al.*, 1996). In these studies, eggs were exposed to an intermittent (2 h on/ 22 h off) magnetic field of 200 μT . The eggs were exposed or sham-exposed for 48 h to magnetic fields and incubation was continued in an artificial brooder. The embryos were examined for developmental anomalies and maturity at the end of the 48 h. Other end-points included extracellular membrane components on day 7 and histological malformations in the brain, liver, and heart on days 2, 7, 12 and 18 of incubation. Egg fertility and weight was examined on days 2, 7, 12, and 18. Additionally, eggs from each treatment group were allowed to hatch and the chicks were followed, being weighed at intervals, for 90 days, when the organs were examined histologically. No effects were seen on any of the end-points of embryo development, body weight, or organs.

Farrell *et al.* (Farrell *et al.*, 1997) reported the effects of 60 Hz, 4 μT sinusoidal magnetic fields on 545 developing chick embryos. A significant increase ($p < 0.01$) in morphological abnormalities was observed in eggs exposed to the sinusoidal magnetic field.

[Development abnormalities were observed in three of five studies in which chick embryos were exposed to sinusoidal 50 or 60 Hz magnetic fields, but the relevance of these results to mammalian growth and development is unclear.]

4.4.4.2 Mice

Juutilainen *et al.* (Juutilainen *et al.*, 1997) reported their investigations of resorptions in groups of 30–50 CBA/Ca mice exposed to low-frequency magnetic fields. Mice from 34–56 litters per group were exposed on days 0–18 of pregnancy for 24 h/d to a 50 Hz sinusoidal magnetic field of 13 or 130 μT . No differences were observed in resorption rates between exposed and sham-exposed mice.

In studies with CD-1 mice, Kowalczyk *et al.* (Kowalczyk *et al.*, 1994) exposed or sham-exposed pregnant mice on days 0–17 of gestation to a 50 Hz sinusoidal magnetic field at 20 mT. Pre- and postimplantation survival was recorded, and fetuses were examined for the presence of gross external, internal, and skeletal abnormalities. There were 90 exposed and 86 sham-exposed mice, and 2167 fetuses were examined. The study was conducted over a two-year period. No association was found between exposure to magnetic fields and these end-points, but an association was found between exposure and longer, heavier fetuses at term.

Spermatogenesis was evaluated in groups of five male hybrid (C57Bl/Cne x C3H/Cne) F1 mice (de Vita *et al.*, 1995), 8–10 weeks of age, which were exposed to 50 Hz magnetic fields (1.7 mT) for 2 or 4 h and analyzed 7, 14, 21, 28, 35, and 42 days after exposure. Flow cytometric DNA histograms were prepared on testicular cell suspensions to determine the relative frequencies of the various spermatogenetic cell subpopulations. In

groups exposed for 2 h, no effects were observed at any time. In the groups exposed for 4 h, a statistically significant effect ($p < 0.001$) was observed only on day 28.

[Exposure to EMF at power frequencies has not been found to have teratogenic effects in mice.]

4.4.4.3 Rats

Huuskonen *et al.* (Huuskonen *et al.*, 1993) exposed groups of 72 pregnant Han:Wistar rats to 50 Hz sinusoidal magnetic fields (12.6 μ T) on days 0–20 of pregnancy for 24 h/d. Minor skeletal malformations were observed in the offspring of the exposed group. The mean numbers of implantations and living fetuses were statistically significantly increased. The incidence of major malformations or resorption was not increased under the exposure conditions used in this study.

Mevisen *et al.* (Mevisen *et al.*, 1994) exposed female Wistar rats on days 1–20 of gestation to a 50 Hz sinusoidal magnetic field (30 mT). Three sets of exposures were conducted in which 12 rats per group were exposed or sham-exposed. On gestational day 20, the dams were sacrificed for reproductive and teratological assessment. No major malformations were seen in any groups but a number of fetuses had minor skeletal malformations.

In a study by Rommereim *et al.* (Rommereim *et al.*, 1996), pregnant Sprague-Dawley rats were weighed and randomly assigned to field- or sham-exposed groups. The rats were exposed to a 1 or 0.61 mT 60 Hz horizontal magnetic field, on days 1–20 of gestation, 20 h/d, 7 d per week. The studies were conducted as two replicate, with 96 rats per treatment group. On day 20 of gestation, the dams were sacrificed for assessment of reproductive and teratogenic end-points. The litters were evaluated for the numbers of implantations, fetal deaths, and resorptions and for gross external, visceral, and skeletal malformations and fetal weights. A total of 7903 fetuses from 519 litters were examined. In the first replicate study, the number of fetuses per litter was decreased in the group exposed to 1 mT ($p < 0.05$). This decrease was not observed in the replicate study. No major malformations were correlated with exposure to magnetic fields.

Ryan *et al.* (Ryan *et al.*, 1996) exposed groups of 46-55 timed-pregnant Sprague-Dawley rats to linearly polarized, 60 Hz magnetic fields on gestational days 6–19. The field strengths were 2 μ T, 200 μ T, and 1 mT with concurrent sham-exposed controls. A positive control group of 15 rats treated with ethylenethiourea was included. The animals were exposed or sham-exposed for 18.5 h/d, 7 d per week. On gestation day 20, the dams were sacrificed for reproductive and teratological assessments. No evidence of maternal toxicity was observed as a result of exposure. A battery of fetal examinations did not demonstrate any significant difference in the incidence of fetal malformations or anomalies between field-exposed and sham-exposed rats. The positive control caused malformations

and body-weight reductions in 100% of treated animals. [No malformations were seen in rats exposed to 50 or 60 Hz magnetic fields.]

In a study of similar design, Ryan *et al.* (Ryan *et al.*, 1998) failed to show any effect of exposure to magnetic fields in multigeneration studies of reproductive toxicity in groups of 40 male and female Sprague-Dawley rats.

4.4.4.4 Hamsters

Niehaus *et al.* (Niehaus *et al.*, 1997) exposed or sham-exposed groups of 45 Djungarian hamsters to a sinusoidal 50 Hz magnetic field (450 μ T) for 56 days. Flow cytometric DNA histograms were prepared on testicular-cell suspensions to determine the relative frequencies of the various spermatogenetic cell subpopulations on the basis of their DNA contents. Significant differences (p at least < 0.05) in spermatogenetic cell populations were observed.

4.4.4.5 Summary

A few laboratories have reported alterations in the development of chick embryos exposed to sinusoidal magnetic fields. The results of studies of teratogenic and reproductive effects in mammalian systems have generally been negative; no studies were available on other developmental end-points.

There is no evidence for the reproductive or developmental effects of exposure to sinusoidal magnetic fields.

[This conclusion was supported by 17 Working Group members; there were 3 votes for 'weak' evidence, 8 abstentions, and 1 absent.]

Table 4.33 Studies on EMF exposures and reproductive and developmental effects of EMF in experimental animals and birds

Reference	Species	Exposure				Reproductive effects analyzed	Comments
		Time	Waveform	Frequency	Intensity		
(Juutilainen & Saali, 1986a)	Chick embryos Total embryos = 800	0-52 h pc	Sinusoidal	1 Hz - 100 kHz	13-125.7 μ T	Malformations at 48 h (pc)	Effects observed: increase in abnormal embryos
(Pafkova <i>et al.</i> , 1994)	Chick embryos	0-40 h pc		50 Hz	6 μ T or 10 mT	Malformations at day 9 (pc)	No effects observed on mortality or structural malformations
(Pafkova & Jerabek, 1994)	Chick embryos	0-48 h pc		50 Hz	10 mT X-rays 4 or 5 Gy	Malformations at day 9 (pc)	Combination of exposure (magnetic fields and X-rays) No effects beyond effect observed for X-rays
(Pafkova <i>et al.</i> , 1996)	Chick embryos	0-52 h pc		50 Hz	6 μ T or 10 mT	Malformations at day 9 (pc)	Combination of exposures (magnetic fields and X-rays or chemicals) Pre-exposure reduces some effects of insulin or tetracycline and radiation
(Veicsteinas <i>et al.</i> , 1996)	Chick embryos Total embryos = 420	0-48 h pc	Sinusoidal	50 Hz	200 μ T	Anomalies Staging, fertility Group followed for 90 days post-hatching	No effects
(Farrell <i>et al.</i> , 1997)	Chick embryos Total embryos = 2500	0-48 h pc	Rectangular 0.5 ms pulse Sinusoidal	100 Hz 60 Hz	1 μ T 4 μ T	Structural abnormalities Development	Effects on abnormality rates ($p < 0.01$ to 0.001) No effect in 60 Hz study
Mice							
(Juutilainen <i>et al.</i> , 1997)	CBA/S CBA/Ca	0-18 dG	Sawtooth 45 μ s rise and 5 μ s fall time Sinusoidal	20 kHz 50 Hz	15 μ T 12.6 μ T	Gestational day 19 Total implantations Viability of fetuses	Non-significant increase in resorption in sawtooth
(Kowalczyk <i>et al.</i> , 1994)	C3H Total fetuses = 2167	0-17 dG	Sinusoidal	50 Hz	20 mT (rms)	Gestational day 17 Total implantations Viability of fetuses Fetal weight Malformations	No effects

Table 4.33 (continued)

Reference	Species	Exposure				Reproductive effects analyzed	Comments
		Time	Waveform	Frequency	Intensity		
(de Vita <i>et al.</i> , 1995)	F1 hybrids 8-10 weeks	2 or 4 h	Sinusoidal	50 Hz	1.7 mT (rms)	Relative frequency of spermatogenic cell subpopulations Testicular cell suspensions analyzed at 7, 14, 21, 28, 35, and 42 days after exposure	Effects seen at 28 days after 4 h exposure of male mice ($p < 0.001$)
Rats							
(Huuskonen <i>et al.</i> , 1993)	Han:Wistar 72 females	0-20 dG	Sawtooth 5 μ s rise and 45 μ s fall times Sinusoidal	20-k pulses per s (pps) 50 Hz	15 μ T 12.6 μ T	Gestational day 20 Total implantations Viability of fetuses Fetal weight Malformations	Increase in implants and living fetuses/litter at 50 Hz group Increase in minor skeletal anomalies at 20 k-pps
(Mevisen <i>et al.</i> , 1994)	Wistar 72 dams	0-20 dG	Static Sinusoidal	50 Hz	30 mT	Gestational day 19 Total implantations Viability of fetuses Malformations	No major malformation seen in any group Minor skeletal ossification found in both exposures Decrease in living fetuses/litter ($p < 0.05$) Enhanced postnatal growth and development
(Rommereim <i>et al.</i> , 1996)	Sprague-Dawley 7903 fetuses 519 litters Study conducted as two replicates	0-20 dG	Sinusoidal	60 Hz	0.61, 1 mT	Gestational day 20 Total implantation Viability of fetuses Fetal weight Malformations	Decrease in number of fetuses/litter (replicate 1, $p < 0.05$) Effect not seen in replicate 2
(Ryan <i>et al.</i> , 1996)	Sprague-Dawley 55 dams/treatment group Study included positive control, n=15 dams treated with ethylenethiourea	0-19 dG	Sinusoidal	60 Hz	0, 2, and 200 μ T, and 1 mT, or 1 mT intermittent (1 h on/ 1 h off)	Gestational day 19 Total implantations Viability of fetuses Fetal weight Malformations	No biologically significant difference observed in exposed groups Positive control: 100% demonstrated malformations

Table 4.33 (continued)

Reference	Species	Exposure				Reproductive effects analyzed	Comments
		Time	Waveform	Frequency	Intensity		
(Ryan <i>et al.</i> , 1998)	40 male and female Sprague-Dawley rats F ₁ , F ₂ generations	18.5 h/d	Linearly polarized	60 Hz	0, 2, 200 μ T, 10 mT and 10 mT intermittent (1 h on/ 1 h off)	Reproductive performance Fetal viability Body weight	No effects on reproductive performance or developmental toxicity
Hamsters							
Niehaus <i>et al.</i> , 1995	Djungarian hamsters n=45/group	56 d	Sinusoidal Rectangular	50 Hz	450 μ T 360 μ T	Testicular cell suspensions analyzed at 7, 14, 21, 28, 35, and 42 d after exposure Relative frequency of spermatogenic cell subpopulations	Testicular cell numbers increased at 28 d after 4 h exposure of male hamsters ($p < 0.001$)

pc, post-gestational; dG, days gestation

4.4.5 Effects on melatonin

The hypothesis that modification of melatonin production and release is a possible mechanism for some of the effects of exposure to EMF has been proposed and discussed by many authors (Baldwin & Barrett, 1998; Stevens, 1987). A useful introduction to pineal melatonin production can be found in the report of the National Academy of Sciences (NRC *et al.*, 1997, pp. 95–96). Since then, a number of studies have been done to elucidate the role of melatonin and the mechanism of its physiological activity. Reviews of these studies are available (Dubocovich, 1995; Reiter, 1997).

The studies discussed in this section are summarized in Table 4.34. Laboratory experiments on suppression of nocturnal melatonin in human volunteers are described in section 4.6.4.1.

4.4.5.1 Electric fields

Groups of five adult male Sprague-Dawley rats, eight weeks old, with long day cycles (14 h light, 10 h dark) were sham-exposed or exposed to 1.7–1.9 kV/m linearly polarized 60 Hz electric fields continuously for 30 days (Wilson *et al.*, 1981; Wilson *et al.*, 1986). Exposure was given with a parallel-plate system, in which the rats were in electrical contact with the reference ground electrode. Sham-exposed rats were housed identically except for the electric field. [The fields were not verified independently.] At the end of exposure, pineal melatonin, 5-methoxytryptophol, and serotonin-*N*-acetyltransferase activity were measured at 08:00 and 14:00 (light phase) and 22:00 and 02:00 h (dark phase). Significant decreases in nocturnal pineal melatonin ($p < 0.05$, *t* test) and *N*-acetyltransferase activity ($p < 0.002$) were found.

Groups of 20 adult male Sprague-Dawley rats, eight weeks old, with long day cycles (14 h light, 10 h dark) were sham-exposed or exposed to 39 kV/m linearly polarized 60 Hz electric fields continuously for four weeks (Wilson *et al.*, 1986), as described above. After each week of exposure, 10 field-exposed and 10 sham-exposed rats were sacrificed immediately after field termination (dark phase), and pineal melatonin and *N*-acetyltransferase activity were measured. Additional sacrifices and measurements were made three and 14 days after exposure. Significant decreases in nocturnal pineal melatonin and *N*-acetyltransferase activity were found after three or four weeks of exposure [no *p* value given]. The levels returned to normal within 3 d after exposure.

Groups of six to eight pregnant rats with long day cycles (14 h light, 10 h dark) were exposed throughout gestation, and their pups were exposed from birth to day 23 to 0, 10, 65, or 130 kV/m linearly polarized 60 Hz electric fields for 19 h/d (Reiter *et al.*, 1988) by a parallel-plate system, with the rats in electrical contact with the reference ground electrode. Sham-exposed rats were housed identically except for the electric field. At the end of exposure, male pups from six to eight litters per time were sacrificed at 22:00,

02:00 (2 h after lights off), 04:00, 06:00, and 10:00 (lights on), and their pineal melatonin levels were measured. Significant decreases in pineal melatonin were found at 02:00 ($p < 0.001$), when the concentration of melatonin would be expected to be highest.

Groups of 7–16 eight-week-old male Sprague-Dawley rats with long day cycles (14 h light, 10 h dark) were sham-exposed or exposed to 65 kV/m linearly polarized 60 Hz electric fields for 20 h/d for 30 d (Grota *et al.*, 1994). The exposure apparatus consisted of three parallel plates: a top electrified plate and grounded intermediate and bottom plates. The animals between the top two plates were exposed to a 60 Hz electric field, and the animals between the bottom two grounded plates were sham exposed. Harmonics were not detected, and the spillover to the sham condition between the lower plates was 1% or less. The effective field strength was estimated to be 82% in clean cages, which was reduced to 43% in cages in which rats had lived for more than four days. Clean cages were provided twice a week, and husbandry was done during the daily field-off period. Immediately after exposure, at 04:00 (light) or 16:00 (dark), groups of field-exposed and sham-exposed rats were sacrificed, and the plasma and pineal melatonin concentrations and pineal *N*-acetyltransferase and hydroxyindole-*O*-methyltransferase activities were measured. Significant decreases were found in nocturnal plasma melatonin ($p < 0.05$) but not in pineal melatonin or in *N*-acetyltransferase or hydroxyindole-*O*-methyltransferase activity.

[In all of these studies except that of Grota *et al.* exposure to electric fields had a statistically significant effect on at least one observation of pineal melatonin concentration. They speculated that the difference in the results of their study and others may be due to the sensitivity of the measurements to time. In particular, they considered that the dark phase was not the most sensitive for measurements of pineal function. In some experiments, the pineal and blood melatonin concentrations decreased in rats exposed to linearly polarized 60 Hz electric fields.]

4.4.5.2 Exposure to magnetic fields for < 1 h

Adult male and female Djungarian hamsters with long day cycles (16 h light, 8 h dark) were exposed to a 100 μ T 60 Hz linearly polarized magnetic field for 15 min starting 2 h before lights off (Yellon, 1994). The exposure system consisted of two Merritt coils modified to produce highly uniform fields across two perpendicular axes. The field strength was monitored and was found to be uniform to within $\pm 10\%$. Sham-exposed controls were placed in an adjacent exposure system in which no current was applied; the field was found to be 0.04 μ T. Groups of four to six animals were sacrificed at 0.5–2-h intervals from 1 h before lights off to 1 h after lights on, and their sera were harvested and pineal glands obtained for radioimmunoassay for melatonin. In controls, the pineal melatonin concentration increased significantly from an average daytime baseline of less than 0.3 ng per gland to 3 ng per gland by 3 h after lights off ($p < 0.05$). This increase was sustained for the duration of the night and returned to baseline within 1 h after lights on. A similar melatonin rhythm was found in plasma; the concentrations ranged from 30 to 50 pg/ml at night and returned to a baseline of 12 pg/ml or less by 1 h before lights on. The

single exposure to magnetic fields reduced the duration and blunted the rise in the nocturnal melatonin rhythm ($p < 0.05$). When the study was repeated in its entirety six months later, the same exposure did not significantly suppress the pineal melatonin content 5 h after lights off or reduce the plasma melatonin concentrations 3 or 5 h after the onset of dark in comparison with sham-exposed controls.

Adult Djungarian hamsters with long day cycles (16 h light, 8 h dark) were exposed once to a 10 or 100 μT linearly polarized 60 Hz magnetic field for 15 min beginning 4 h before or 4 h after lights off (Truong & Yellon, 1997). Other hamsters were exposed to a 100 μT linearly polarized 60 Hz intermittent (1 min on, 1 min off) magnetic field for 15 or 60 min between 1 and 2 h before lights off. The exposure system consisted of two Merritt coils modified to produce highly uniform fields across two perpendicular axes. Six hamsters per time per group were sacrificed 1, 1.75, 2.5, 3, and 4 h after lights off, and their sera were harvested and pineal glands obtained for radioimmunoassay of melatonin. In sham-exposed controls, i.e. hamsters placed in an adjacent coil system but without current ($< 0.6 \mu\text{T}$), the pineal and plasma melatonin concentrations increased from a low baseline (1 h after lights off) to concentrations that were typical of the night-time peak by 3 h after darkness. Exposure to the continuous magnetic field for 15 min either 4 h before or 4 h after lights off did not disrupt the nocturnal rise in pineal or plasma melatonin concentration. Similarly, the onset of the melatonin rhythm was not suppressed in comparison with that in sham controls by intermittent exposure to magnetic fields. Thus, several paradigms of exposure to magnetic fields failed to alter the rising phase of the melatonin rhythm in pineal gland content or in the circulation. The authors conclude that the biological clock mechanism that mediates photoperiodic time measurement in this seasonally breeding rodent is resistant to a variety of continuous or intermittent exposures to magnetic fields.

Adult Siberian hamsters in constant darkness were exposed to a 100 μT linearly polarized 60 Hz magnetic field for 15 min (Yellon & Truong, 1998). Sham-exposed hamsters were simultaneously placed in an adjacent coil system but without current ($< 0.6 \mu\text{T}$). Groups of five to seven animals per group were sacrificed 0, 0.75, 1.5, 2.25, and 3 h after lights off, and their sera were harvested and pineal glands obtained for radioimmunoassay of melatonin. The increase in the pineal and the circulatory content of melatonin during subjective night was not affected by exposure to magnetic fields; regression of the testes occurred in both sham-exposed controls and in hamsters in constant darkness exposed daily to magnetic fields. The authors concluded that magnetic fields are unlikely to serve as a *zeitgeber* for the circadian changes in the melatonin rhythm; rather, the photoperiod is a predominant cue for the rising phase of melatonin production in the pineal gland and concentration in circulation.

In juvenile hamsters exposed to a 100 μT magnetic field for 15 min daily for nine days, statistically significant reductions in nocturnal melatonin concentrations were observed at some times, but pubertal development was normal. A replicate study showed no reduction in nocturnal melatonin (Truong *et al.*, 1996).

Adult Djungarian hamsters were exposed to a 100 μ T 60 Hz magnetic field for 15 min 2 h before dark daily for three or six weeks. The night-time rise in melatonin concentration was delayed, and the duration was reduced in the animals exposed for six weeks but not in those exposed for three weeks (Yellon, 1996).

Groups of male Siberian hamsters, four to six months of age, were exposed to a 100 μ T 60 Hz linear magnetic field. Exposure depressed the pineal melatonin concentration at 4 h but not 2 h after the onset of darkness in male but not female hamsters. The hamsters with a short photoperiod were more sensitive to the magnetic field-induced response than those with a long photoperiod. The depression in melatonin was not seen after 42 days of exposure to magnetic fields (Wilson *et al.*, 1998).

[The apparent contradiction between the effects seen in the Yellon's 1994 study and the lack of effects in the 1997 and 1998 studies from his laboratory may be due to diurnal cycling (long days in 1994 and 1997, constant darkness in 1998), time of exposure (2 h before darkness in 1994, 4 h before or after darkness in 1997), or continuity of exposure (continuous in 1994 and 1998, continuous or intermittent in 1997). The effect of a magnetic field may be influenced by the length of the day of the exposed animals. Truong *et al.* found that the 1994 exposure schedule resulted in changes in melatonin but not to the expected downstream effects in reproductive development. Additionally, Yellon was unable to reproduce the effects that he obtained in 1994. A single continuous exposure to a 100 μ T linearly polarized 60 Hz magnetic field does not reproducibly shorten or blunt night-time plasma melatonin concentrations in Djungarian hamsters.]

4.4.5.3 Exposure to magnetic fields for 1–24 h

Groups of six nine-week-old male Wistar rats with standard day cycles (12 h light, 12 h dark) were exposed through rectangular coils to 1, 10, or 100 μ T linearly polarized 50 Hz magnetic fields for 12 h (Selmaoui & Touitou, 1995). Sham-exposed animals were kept in a similar environment. The animals were sacrificed under dim red light at the end of exposure, during the dark phase. Decreased nocturnal plasma melatonin concentration (by 30%; $p < 0.05$) and pineal *N*-acetyltransferase activity (23%; $p < 0.05$) were seen but only at the highest intensity (100 μ T). No significant differences from control were seen at the other intensities or in hydroxyindole-*O*-methyltransferase activity.

Groups of eight male Sprague-Dawley rats, 12 weeks old, with standard day cycles (12 h light, 12 h dim red light) were exposed through Helmholtz coils to 1 mT intermittent (1 min on, 1 min off cycles) linearly polarized 60 Hz magnetic fields for 1 h, starting 2 h before darkness (John *et al.*, 1998). Sham-exposed rats were simultaneously placed in an adjacent coil system but without current ($< 0.17 \mu$ T). Urine was collected at 2-h intervals. The circadian profile of urinary 6-sulfatoxymelatonin was examined before, during, and after exposure; no significant effect on excretion was observed.

Groups of 10 male and 10 female adult Wistar rats with short day cycles (9 h light, 15 h dark) were exposed to either 5 or 500 μT linearly polarized 50 Hz magnetic fields through a pair of double-wound coils embedded in epoxy resin for 24 h (Bakos *et al.*, 1995). Sham-exposed rats were simultaneously placed outside the coil system (5 μT stray fields). The fields were homogeneous to within 1%. The animals were all housed in metabolic cages. The urine of the animals was collected twice per day for five consecutive days, and the concentration of 6-sulfatoxymelatonin was measured by ^{125}I -radioimmunoassay. The urinary excretion of 6-sulfatoxymelatonin did not change significantly from baseline during or after exposure.

Groups of five adult male Wistar rats with short day cycles (9 h light, 15 h dark) were exposed to either 1 or 100 μT linearly polarized 50 Hz magnetic fields for 24 h (Bakos *et al.*, 1997). Sham-exposed rats were simultaneously placed outside the coil system (1 μT stray fields). The animals were all housed in metabolic cages. The urinary excretion of 6-sulfatoxymelatonin was not statistically significantly decreased during or after exposure to either flux density. Excretion of rats at 100 μT was significantly increased the day after exposure ($p < 0.02$) in comparison with the value during exposure, but was not significantly different from the baseline value before exposure.

[These studies neither directly support nor contradict each other because of confounding effects of strain (Wistar vs. Sprague-Dawley), field characteristics (50 Hz continuously vs. 60 Hz intermittently), and effects measured (plasma melatonin, pineal *N*-acetyltransferase activity, or urinary 6-sulfatoxymelatonin excretion). The difference between the two studies by Bakos, one indicating a potential for increased 6-sulfatoxymelatonin excretion, is confusing. The results of Selmaoui remain suggestive, although the study suffers from the lack of a well-characterized exposure system. The biological significance of small changes in melatonin concentrations is not clear.]

4.4.5.4 Exposure to magnetic fields for > 24 h

Groups of 6–28 adult (11–18-week old) male Wistar-King rats with standard day cycles (12 h light, 12 h dark) were exposed to 0.02, 0.1, 1, 5, 50, or 250 μT circularly polarized 50 Hz magnetic fields continuously for six weeks from a modified Helmholtz coil (Kato *et al.*, 1993). The uniformity of the system and stray fields were fully characterized (Shigemitsu *et al.*, 1993). Sham-exposed control rats were placed inside an unactivated coil system with stray fields that were 1/50th of those of the exposure fields. The room was constantly illuminated by four small, dim-red lights (< 0.07 lux in dark period). The animals were sacrificed at the end of exposure, and the concentrations of plasma and pineal gland melatonin were determined by radioimmunoassay. Significant decreases were found in plasma melatonin concentration during light (08:00, 12:00 h, $p < 0.05$) and dark (20:00, 24:00 h, $p < 0.05$) with an intensity of 5 μT and during light (08:00, 12:00 h, $p < 0.05$; 16:00, $p < 0.01$) and dark (24:00 h, $p < 0.01$) with an intensity of 250 μT ; in pineal melatonin concentration during dark (24:00 h, $p < 0.05$) at an intensity of 5 μT and during light (12:00, $p < 0.05$; 16:00, $p < 0.01$) and dark (24:00 h, $p < 0.01$) at 250 μT ; in daytime plasma melatonin concentrations at intensities of 0.1 ($p < 0.01$), 1 ($p < 0.05$), 5 ($p < 0.05$),

and 50 μT ($p < 0.01$) and in night-time concentrations ($p < 0.01$) at intensities of 1, 5, and 50 μT ; in night-time pineal melatonin concentrations at intensities of 1 ($p < 0.01$), 5 ($p < 0.05$), and 50 μT ($p < 0.01$); and in day-time pineal melatonin concentrations ($p < 0.01$) at intensities of 1, 5, and 50 μT . The authors concluded that plasma and pineal melatonin concentrations at night (24:00 h) are statistically significantly decreased after continuous exposure for six weeks to 50 Hz rotating magnetic fields stronger than 1 μT .

In a study with similar exposure, groups of 22–30 adult (11–18 weeks old) male, pigmented Long-Evans rats with standard day cycles were exposed to 0.02 or 1 μT circularly polarized 50 Hz magnetic fields continuously for six weeks (Kato *et al.*, 1994a). Significant decreases in plasma melatonin concentration ($> 20\%$, $p < 0.01$) were found at the mid-points of the dark and light phases at both 0.02 and 1 μT . Significant decreases in pineal melatonin concentration ($p < 0.01$) were found during the light phase at both intensities and during the dark phase at 1 μT .

In a further study, groups of eight adult (13–21 weeks old) male Wistar-King rats with standard day cycles were exposed to either 0.02 or 1 μT circularly polarized 50 Hz magnetic fields continuously for six weeks (Kato *et al.*, 1994b). Animals were sacrificed at the end of exposure, and the plasma melatonin concentrations were determined at that time and one and four weeks after cessation of exposure. The nocturnal melatonin concentration was reduced by 25% ($p < 0.05$), but the concentration one week after the end of exposure was normal, and no further change was observed four weeks later.

In yet another study, groups of 23–30 adult (11–20 weeks old) male Wistar-King rats were exposed to 0.02 or 1 μT linearly polarized 50 Hz magnetic fields continuously for six weeks (Kato *et al.*, 1994c). No significant change in plasma melatonin or pineal melatonin concentration was found.

Groups of 36 six-week-old female Sprague-Dawley rats with standard day cycles were either sham-exposed or exposed to a gradient of 0.3–1 μT linearly polarized 50 Hz magnetic field continuously through six cylindrical coils for 91 days beginning eight to nine weeks after intragastric administration of 20 mg (5 mg/week) DMBA (Löscher *et al.*, 1994). Sham-exposed rats were housed in the same room and experienced stray fields of 0.02–0.04 μT . The animals were sacrificed at the end of exposure, and the concentrations of plasma and pineal gland melatonin were determined by radioimmunoassay. The nocturnal melatonin levels were reduced by 20% ($p < 0.05$) at all intensities.

Groups of 99 six-week old female Sprague-Dawley rats with standard day cycles were either sham exposed or exposed to a 50 μT linearly polarized 50 Hz magnetic field continuously for 91 days after intragastric administration of 20 mg (5 mg/week) DMBA (Mevisen *et al.*, 1996b). The sham-exposed rats were housed in the same room and experienced stray fields of 0.05 μT . The animals were sacrificed at the end of exposure, and the concentrations of plasma and pineal gland melatonin were determined by radioimmunoassay. Determination of nocturnal plasma melatonin after 9 and 12 weeks of

exposure to 50 μT showed no significant difference between field-exposed and sham-exposed rats. In another study with the same experimental design but with exposures to 10 μT , a significant decrease was observed in serum but not in pineal melatonin concentration (Mevisse *et al.*, 1996a).

Groups of 12 male five-week-old Wistar rats with standard day cycles were exposed to either 1, 10, or 100 μT linearly polarized 50 Hz magnetic fields from rectangular coils for 18 h/d for 30 days (Selmaoui & Touitou, 1995). Sham-exposed animals were kept in a similar environment. The animals were sacrificed under dim-red light at the end of exposure during their dark phase. The nocturnal plasma melatonin concentration and pineal *N*-acetyltransferase activity were depressed at both 10 (27%, $p < 0.05$) and 100 μT (42%, $p < 0.05$). No effect was seen on hydroxyindole-*O*-methyltransferase activity.

Groups of 45 male Djungarian hamsters with long days (16 h light, 8 h dark) were exposed to a 300 μT linearly polarized 50 Hz magnetic field from Helmholtz coils continuously for 56 days (Niehaus *et al.*, 1997). Sham-exposed rats were simultaneously placed outside the coil system and experienced $< 3 \mu\text{T}$ stray fields. No effects on nighttime plasma or pineal melatonin concentrations were found as determined by radioimmunoassay.

Groups of eight adult male Sprague-Dawley rats with standard day cycles were exposed to a 1 mT linearly polarized 60 Hz magnetic field for 20 h/d for 10 d or six weeks or to 1 mT intermittently (1 min on, 1 min off) of a linearly polarized 60 Hz magnetic field for 20 h/d beginning 1 h before darkness for two days (John *et al.*, 1998). Sham-exposed rats were simultaneously placed in an adjacent coil system but without current ($< 0.17 \mu\text{T}$). Urine was collected at 2-h intervals. The circadian profile of urinary 6-sulfatoxymelatonin was examined before, during, and after exposure. No significant effect on excretion was observed during exposure.

Groups of 10 seven-week-old female Sprague-Dawley rats with standard day cycles were either sham-exposed or exposed to 100 or 500 μT linearly polarized 50 Hz magnetic fields or to a 100 μT linearly polarized 60 Hz magnetic field for 18.5 h/d for 4, 8, or 12 weeks, with intragastric administration of 8, 10, or 20 mg DMBA (NTP, 1998a). Control rats were housed in a separate room. The animals were sacrificed at the end of exposure, and the concentrations of plasma and pineal gland melatonin were determined by liquid chromatography and tandem mass spectrometry. No significant differences were found between field-exposed and sham-exposed rats. [The data varied considerably.]

[As in the studies of short-term exposure, confounding variables such as species (hamster vs. rat), strain (Wistar vs. Sprague-Dawley), sex, co-exposure (DMBA), field characteristics (polarization, intermittence), and measured outcome (plasma melatonin, pineal melatonin, pineal *N*-acetyltransferase activity, urinary 6-sulfatoxymelatonin) complicate interpretation of the database. Long-term exposure to circularly polarized 50 Hz magnetic fields may decrease dark-phase melatonin concentrations in rats, and long-

term exposure to 10 or 100 μT linearly polarized 50 Hz magnetic fields decreases plasma and pineal melatonin concentrations in male Wistar rats.]

4.4.5.5 Exposure to electric and magnetic fields

Groups of 10 female Suffolk lambs, eight weeks old and housed outdoors, were exposed to mean fields of either 4 μT and 6 kV/m or 3.77 μT and 6.3 kV/m from the electrical environment of a 500 kV transmission line and < 3 μT and < 0.01 kV/m or 0.02 μT and < 0.01 kV/m from a nearby pen (Lee *et al.*, 1995; Lee *et al.*, 1993). The sheep remained in these pens for eight months, and the fields were monitored continuously. Plasma samples were collected at 0.5–3 h intervals over eight 48-h periods from the same animals throughout the study. The melatonin concentrations in the plasma were determined by radioimmunoassay. The characteristic pattern of melatonin secretion during night-time (amplitude, phase, and duration) did not differ between control and treated groups.

Groups of three male baboons, aged seven to eight years, with long day cycles (15.5 h light, 8.5 h dark) were exposed to either 50 μT , 6 kV/m or 100 μT , 30 kV/m linearly polarized 60 Hz EMF without transients for three blocks of 4 h (08:30–12:30, 13:00–17:00, 17:30–21:30) each day for six weeks (Rogers *et al.*, 1995d). Homogeneous vertical electric fields were generated between a bus-suspended at 2.5 m and a large, nonferrous metal gate. Homogeneous magnetic fields were generated by a series of conductors beneath the grate. The field strengths were logged at 15-min intervals. Plasma melatonin concentrations were determined at 2-h intervals from the same animals throughout the day on days before, during, and after the six weeks of exposure period. No changes in plasma melatonin concentration were observed.

In a similar study, groups of two adult male baboons with long day cycles were exposed from the same sources to a complex schedule of 50 μT , 6 kV/m or 100 μT , 30 kV/m linearly polarized 60 Hz electric and magnetic fields for 0–24 h/d for 30 d (Rogers *et al.*, 1995e). Transients were purposely not avoided, and 300 Hz transients were observed. The night-time plasma melatonin concentrations during exposure were decreased by more than 80% from pre-exposure levels.

[The studies of mixed exposure, unlike the others summarized here, were all done on non-rodent species. Changes in plasma melatonin concentrations were found only by Rogers *et al.*; however, only two animals were used.]

4.4.5.6 Summary

The studies on melatonin in animals exposed to electric fields have both strengths and weaknesses; the latter are primarily in exposure characterization, statistical methods, and differences within studies. The evidence is lacking in both quantity and consistency, but the weight of the evidence leads to the conclusion that long-term exposure to electric

fields slightly decreases the concentrations of melatonin in rats. The biological significance of this apparent effect is not understood.

It was reported that long-term exposure to magnetic fields (100-1000 μ T) can reduce the nocturnal pineal or blood concentrations of melatonin in rodents, but other laboratories did not find similar results.

Field orientation and linear or circular polarization may be important. Reductions in melatonin levels were not found in sheep or baboons. Similarly, studies of the effects of acute exposure to magnetic fields in hamsters showed reductions in melatonin; nonsignificant results were obtained more frequently than significant ones, but all those that were significant showed suppression. The intensities used were relatively high, even when human-rodent scaling issues are considered. The biological significance of melatonin reduction is not clear.

There is weak evidence that exposure to electric and magnetic fields alters the levels of melatonin in rodents.

[This conclusion was supported by 14 members of the Working Group; there were 9 votes for 'moderate' support; 4 abstentions, and 2 absent.]

There is no evidence that exposure to electric and magnetic fields alters the levels of melatonin in sheep or baboons.

[This conclusion was supported by 14 members of the Working Group; there were 13 abstentions and 2 absent.]

Table 4.34 Studies of the effect of exposure to EMF on melatonin in experimental animals

Author	Waveform	n	Intensity	Animal	Measure	Effect
Long term exposure to electric fields						
(Wilson <i>et al.</i> , 1981)	60 Hz linear	5	1.7 - 1.9 kV/m 24 h for 30 days	Male Sprague-Dawley rat	Plasma MT, pineal MT, NAT, 5-MTOL	Pineal MT down at night
(Wilson <i>et al.</i> , 1986)	60 Hz linear	20	39 kV/m 24 h for 30 days	Male Sprague-Dawley rat	Pineal MT, NAT	Pineal MT, NAT down after 3, 4 weeks returned 3 days after exposure end
(Reiter <i>et al.</i> , 1988)	60 Hz linear	6-8	10, 65, 130 kV/m 19 h /d GD 0 to PND 23	Sprague-Dawley rat pups	Pineal MT	Pineal MT down at night
(Grota <i>et al.</i> , 1994)	60 Hz linear	7-16	65 kV/m 20 h for 30 days	Male Sprague-Dawley rat	Plasma MT, pineal MT, HIOMT, NAT	Plasma MT down at night
Single exposure to magnetic fields						
(Yellon, 1994)	60 Hz linear	4-6	100 μ T 15 min	Djungarian hamster	Plasma and pineal MT	Plasma and pineal MT down at night, not replicated
(Truong & Yellon, 1997)	60 Hz linear	6	10, 100 μ T 15 min	Djungarian hamster	Plasma and pineal MT	None
(Yellon & Truong, 1998)	60 Hz linear	5-7	100 μ T 15 min	Siberian hamster	Plasma and pineal MT	None
Short-term exposure to magnetic fields						
(Selmaoui & Touitou, 1995)	50 Hz linear	6	1, 100, 1000 mG for 12 h	Male Wistar rat	Plasma MT, pineal NAT, HIOMT	MT, NAT down at 1000 mG at night
(John <i>et al.</i> , 1998)	60 Hz linear	8	1 mT intermittent 1 h	Sprague-Dawley rat	6-OHMS in urine	None
(Bakos <i>et al.</i> , 1995)	50 Hz linear	5	5, 500 μ T 24 h	Wistar rat	6-OHMS in urine	None
(Bakos <i>et al.</i> , 1997)	50 Hz linear	5	1, 100 μ T 24 h	Male Wistar rat	6-OHMS in urine	Increased night after exposure

Table 4.34 (continued)

Author	Waveform	n	Intensity	Animal	Measure	Effect
Long-term exposure to magnetic fields						
(Kato <i>et al.</i> , 1993)	50 Hz circular	6-28	0.02, 0.1, 1, 5, 50, 250 μ T 22 h for 6 weeks	Male Wistar rat	Plasma and pineal MT	Plasma MT down at 0.1 μ T day and night pineal MT up at 0.1 μ T day
(Kato <i>et al.</i> , 1994a)	50 Hz circular	22-30	0.02, 1 μ T 22 h for 6 weeks	Male Long-Evans rat	Plasma and pineal MT	Plasma MT down day and night pineal MT down at 0.1 μ T day, 1 μ T night
(Kato <i>et al.</i> , 1994b)	50 Hz circular	8	0.02, 1 μ T 22 h for 6 weeks	Male Wistar rat	Plasma MT at night	Plasma MT down after exposure returns to normal 1 week later
(Kato <i>et al.</i> , 1994c)	50 Hz linear	23-30	0.02, 1 μ T 22 h for 6 weeks	Male Wistar rat	Plasma and pineal MT	None
(Löscher <i>et al.</i> , 1994)	50 Hz linear	36	0.3 - 1 μ T gradient 24 h for 91 days	Female Sprague-Dawley rat	Plasma MT at night	Plasma MT down
(Mevisen <i>et al.</i> , 1996b)	50 Hz linear	99	50 μ T 24 h for 9, 12 weeks	Female Sprague-Dawley rat + DMBA	Plasma MT at night	None
(Selmaoui & Touitou, 1995)	50 Hz linear	12	1, 10, 100 μ T 18 h for 30 days	Male Wistar rat	Plasma MT, pineal NAT, HIOMT	MT, NAT down at 100, 1000 mG
(Niehaus <i>et al.</i> , 1997)	50 Hz linear	45	300 μ T 24 h for 56 days	Male Djungarian hamsters	Plasma and pineal MT	None
(John <i>et al.</i> , 1998)	60 Hz linear	8	1000 μ T (continuous or intermittent) 20 h (10 or 42 days) 1 h (2 days)	Male Sprague-Dawley rat	6-OHMS in urine	None
(NTP, 1998a)	60 Hz linear	10	10, 500 μ T 24 h for 4, 8, 12 weeks	Female Sprague-Dawley rat + DMBA	Plasma and pineal MT at night	None

Table 4.34 (continued)

Author	Waveform	n	Intensity	Animal	Measure	Effect
(NTP, 1998a)	60 Hz linear	10	1000 mG 24 h for 9, 12 weeks	Female Sprague-Dawley rat + DMBA	Plasma and pineal MT at night	None
Mixed E/MF exposures						
(Lee <i>et al.</i> , 1993)	60 Hz powerline	10	4 μ T, 6 kV/m 24 h for 8 months	Female Suffolk lambs	Plasma MT	None
(Lee <i>et al.</i> , 1995)	60 Hz powerline	15	3.8 μ T, 6.3 kV/m 24 h for 8 months	Female Suffolk lambs	Plasma MT	None
(Rogers <i>et al.</i> , 1995d)	60 Hz linear	2-4	50 μ T, 6 kV/m or 100 μ T, 30 kV/m 12 h for 6 weeks	Baboons	Plasma MT	None
(Rogers <i>et al.</i> , 1995e)	60 Hz linear with transients	2	50 μ T, 6 kV/m or 100 μ T, 30 kV/m irregular for 30 days	Baboons (self controls)	Plasma MT	Plasma MT down

MT, Melatonin; NAT, N-acetyltransferase; 5-MTOL, 5-methoxytryptophol; H10MT, hydroxyindole-O-methyltransferase; GD, gestation day; PND, postnatal day; 6-OHMS, 6-OHMS, 6-hydroxymelatonin sulfate; DMBA, 7, 12-dimethylbenz [a] anthracene

4.4.6 Bone and tissue repair and adaptation

4.4.6.1 Clinical bone healing with pulsed electromagnetic fields

The clinical use of non-invasive exposure to EMF for the promotion of bone healing is characterized by three assumptions: its presumed physiological basis, the nature of the waveforms used, and the understanding that such exposure can be highly beneficial. While much of the concern about the hazards of exposure to EMF is related to the characteristics of the magnetic field, in the realm of bone healing it is the induced electric field that is considered to be the exclusive active agent of stimulation. The pioneering studies of Fukada and Yasuda (Fukada & Yasuda, 1957) and Becker (Becker, 1961) showed that substantial electric fields are endogenous to the skeleton, and these were presumed to form the basis of Wolff's law or the observation that bone architecture appears to adapt to mechanical loading imposed on the skeleton. Their application to the promotion of fracture healing was therefore obvious, and in early studies direct electrode coupling was used to permit exogenous electrical stimulation. The electrodes, however, necessitated surgical implantation and removal, produced electrochemical by-products, and limited the region that could be treated. For these reasons, alternative methods of inducing electrical currents in bone tissue have been developed, the most successful being based on magnetic induction (Bassett *et al.*, 1977).

The transition to reliance on magnetic induction required identification of a dynamic flux pattern to induce the appropriate electrical currents. Unlike the studies of hazard, which are based largely on sinusoidal fields, the development of clinical devices has focused almost exclusively on use of pulsed fields. This approach was primarily pragmatic, as high rates of change could easily be implemented for relatively low flux densities, permitting the induction of currents similar in magnitude to those observed during development or the mechanical deformation of bone structures (i.e. 0.1–1 V/m). The clinical PEMF signals typically consist of peak flux densities in the range of 0.1–5 mT with rise times on the order of hundreds of microseconds. This results in a typical dB/dt in the range of 1–50 T/s and corresponding peak induced electric fields of 0.1–1 V/m. The energy distribution in such complex fields is centered near the pulse repetition rate and the harmonics of this rate. The pulse repetition rates range from 15 Hz up to several kilohertz; however, many of the clinical signals involve a pulse burst pattern, in which a short burst of pulses is repeated at a low-duty cycle. Burst repetition rates are always in the ELF range, which can be as low as 1 Hz and rarely extend beyond several tens of hertz. Such pulse-burst signals have extremely complex energy distribution spectra which cover the frequency range starting at the burst repetition rate and extending to higher-order harmonics associated with the pulse width (McLeod & Rubin, 1990).

EMF-induced healing differs in two main ways from the most studies of the hazards of EMF. While the major emphasis in the development of these devices has been on induced electric fields, the preferred technique is to center the induction coils over the injury. The effect of this strategy is to minimize the magnitude of the induced electric field at the

focus of the injury while maximizing the induced field in the periphery. The maximum reported induced electric fields in the central region of healing are therefore far below the reported peak induced electric fields, perhaps by an order of magnitude or more. This exposures is, however, spatially far more consistent than those experienced in any study of whole-body exposure, in that the induction coils are generally strapped to the body, ensuring a fixed orientation of the flux to the body part and, correspondingly, a fixed electric field distribution. This spatial coherence may be a critical aspect of field-induced healing.

Pulsed electromagnetic field therapy for tibial fractures

PEMF have been used to promote bone healing under conditions of non-union, delayed union, osteotomy, and bone fusion. By far the majority of the published studies are retrospective analyses of patient populations. Representative of these reports is the multicenter review of cases of tibial non-union compiled shortly after the Food and Drug Administration approved PEMF devices as a safe and effective for the treatment of non-unions and failed fusions (Bassett *et al.*, 1981). In this report, the cases of 125 adult patients who had undergone PEMF therapy for delayed union (no evidence of union four to nine months after fracture) or non-union (no union nine months after fracture) were reviewed; true pseudoarthroses were specifically excluded from the study. The treatment consisted of cast immobilization and treatment of the fracture site for at least 10 h/d by exposure to a 15 Hz pulse-burst signal. A peak flux of 1.5 mT, decaying in 25 μ s, was used, with pulses repeated at a 4-kHz rate over the burst duration of 5 ms. This resulted in an induced electric field pulse in the bone tissue estimated to be on the order of 0.1–0.2 V/m. The reported overall success rate in this study was 87%, requiring an average duration of treatment of 5.2 months (range, 2–22 months). Failure to promote healing was attributed by the authors to absence of rigid immobilization, fracture gaps greater than 1 cm, use of the stimulus for less than 10 h/d, or off-center or skewed placement of the induction coils.

In 1984, the first of a series of double-blind, randomized, placebo-controlled trials of pulsed magnetic field therapy was published (Barker *et al.*, 1984), in which 16 patients with tibial fractures that had been un-united for at least 52 weeks were enrolled, immobilized in casts, and randomly assigned to treatment with either an active or placebo (no coil current) device. Patients were excluded if the fracture gap was greater than 0.5 cm, internal or external fixation was present at the fracture site, sepsis was present, or the patient was undergoing steroid treatment. Patients were instructed to use the device for 12–16 h/d with a minimum of 1 h/d. Satisfactory compliance was considered to be an average of 10 h/d, with less than 6 h/d use on no more than 7 d in each six-week period. The patients were monitored every six weeks. At 24 weeks, the fractures of five of the seven patients with placebo devices had healed as compared with five of nine patients with active devices. While the group with active devices was significantly older than the placebo group (38 years vs. 29 years), the authors concluded that conservative management of true tibial non-unions is as effective as magnetic field therapy.

At the same time, a randomized double-blind trial on delayed unions was undertaken (Sharrard, 1990), in which adult patients with tibial fractures that had not united at 16 weeks but had occurred less than 32 weeks previously and who had not undergone surgical treatment were enrolled. After the fractured limbs had been immobilized in long-leg plaster casts, those with apposition over less than 50% of the fracture surface or with a fracture gap greater than 0.5 cm were excluded. Over a period of six years, 51 patients were identified who met the study criteria. Patients were instructed to undergo therapy each day for a total of 12 h/d; treatment continued for 12 weeks, with the same exposure system as described by Barker *et al.* (Barker *et al.*, 1984). The study protocol was completed by 45 patients. Despite randomization, the age distribution was found to be significantly different in the two study populations, the mean age of patients in the active group being 35 years (median, 28), while that of the control group was 45 (median, 45). Radiographic assessment showed that five of the actively treated fractures had healed within 10 weeks, with progress in five and no progress in 10. Conversely, in the placebo group, one fracture had healed, progress was seen in one patient, and no progress was observed in 23 patients. The results were interpreted as demonstrating a significant effect of magnetic field therapy ($p < 0.002$). [The extended duration required to recruit this cohort and the significant age difference between the two groups raise serious concern about the actual efficacy of magnetic field therapy for this condition.]

Pulsed electromagnetic field therapy for osteotomies

Osteotomies are a distinctly different type of fracture from others. Normally, fractures progress through the process of secondary bone formation or endochondral ossification; that is, in a normally displaced fracture, healing is a sequential process starting when the hematoma is replaced by a fibrous fracture callus, which is replaced by cartilage, which subsequently calcifies. In a minimally displaced fracture (e.g. a hairline fracture), however, hematoma and callus do not form, and healing occurs by primary bone formation or the direct bridging of the fracture site by new bone. This primary healing process also occurs after osteotomies, the surgical procedure of transecting a bone in order to realign an articulating surface.

Promotion of osteotomy healing by magnetic field therapy has been investigated in two randomized, placebo-controlled clinical trials. In the first of these (Borsalino *et al.*, 1988), 32 patients treated by intertrochanteric osteotomy for degenerative arthritis of the hip were randomly assigned into treatment and placebo groups. Treatment consisted of exposure to a 75 Hz repetitive pulse signal consisting of a 1.8 mT flux with a rise time of 1.3 ms. The peak induced electric field intensities can be estimated to have been about 50 mV/m. Induction coils were not energized in the placebo devices. Exposure was for 8 h/d for 90 d. Healing was evaluated radiographically at days 40 and 90 in the 31 patients who completed the treatment protocol. Trabecular bridging was found to be significantly increased in the active treatment group at both 40 days ($p < 0.02$) and 90 days ($p < 0.001$).

Subsequently, a study of tibial osteotomy was undertaken (Mammi *et al.*, 1993), in which 40 consecutive patients treated with vagus tibial osteotomy for degenerative arthrosis of the knee were randomly assigned to placebo or treatment by order of admission. The distributions of sex and age were similar in the two groups. Exposure was given from a device similar to that used by Borsalino *et al.* (Borsalino *et al.*, 1988), consisting of a 75 Hz pulsed signal of 1.8 mT with a 1.3 ms pulse width, with instructions to use it for 8 h/d; the output current was shorted in the placebo devices. Healing was assessed radiographically by four independent orthopedic surgeons on a four-point scale. A total of 37 patients completed the protocol. At 60 days, the average score for the actively treated population was 3 vs. 2.1 for the placebo-treated group, reflecting a significant enhancement in healing rate ($p < 0.006$ by Fisher exact test).

Pulsed electromagnetic field therapy for lumbar spinal fusion

While lumbar spinal fusion is a common surgical procedure, the intervertebral space represents a wide vascular region, making it difficult to ensure revascularization of the bone graft. As lumbar fusions are therefore slow to achieve union, the potential for PEMF therapy to accelerate fusion has also been investigated. Mooney (Mooney, 1990) studied the efficacy of this therapy to stimulate fusion in a randomized double-blind trial involving 195 patients with autogenous, cadaverous, or combination grafts and patients with and without internal fixation hardware. Exposure was given from a 15 Hz pulse-burst signal, 1.5 mT in magnitude, with a 25 μ s rise time and 4 kHz pulse repetition rate for bursts of 5 ms. Patients in both the active and placebo groups were fitted with a brace that they were instructed to wear for 8 h/d. Radiographic analysis by the orthopaedic surgeon was used to determine time to fusion, with confirmation by an independent radiologist. The overall fusion rate was 92% in the 65 patients in the active group and 65% in the 98 patients on placebo. The spines of the 34 patients who used the treatment device sporadically (< 4 h/d) fused with the same success rate as those on placebo. The author interpreted the results to represent a significant increase in success rate with PEMF therapy ($p < 0.005$).

The most recent of the double-blind clinical trials addressing the clinical efficacy of PEMF on bone healing involved administration of pulse-field therapy during limb lengthening procedures (Eyres *et al.*, 1996). In this orthopedic procedure, an osteotomy is performed and external fixation hardware is inserted to obtain progressive distraction of the proximal and distal bone ends. Bone then regenerates in the distraction gap. After distraction is complete, the gap undergoes consolidation, similar to that seen in fracture healing. In this study, patients were randomly assigned to active treatment or placebo, with instructions to use the induction devices for 4 h/d. The characteristics of the field exposure were similar to those described above: 15 Hz pulse-burst field, 1.5 mT pulses with a 25 ms rise time, repeated 4 kHz pulse rate in a 5 ms burst. The effectiveness of the treatment was quantified by dual energy X-ray analysis, which provides bone density measurements at the mid-point of the distraction gap and proximal and distal to the osteotomy site. Densities were normalized to those of the contralateral, non-operated limb. The patients were followed for 12 months. No significant difference was observed in limb-lengthening

rate or in distraction gap bone density due to PEMF; however, large differences were observed in the proximal and distal segments of the bone. In the proximal segment, a significant ($p < 0.0001$) increase in bone mineral density was observed as compared with placebo controls, an effect which began after three months of stimulation and resulted in 20% greater bone mineral density than in controls at 12 months. On the distal side, the control bone mineral density dropped by 46% (such bone loss due to disuse is expected in this procedure), whereas the field-exposed population had a loss of less than 15% ($p < 0.0001$).

4.4.6.2 Experimental studies

The primary objective of most studies of the effects of induced fields on bone, nerve, and skin *in vivo* has been clinical applications. The studies reviewed here are the direct outcome of research in the 1950s and early 1960s to demonstrate the existence of endogenous electrical currents in the body, which arise not only from diffusive ‘injury currents’ but also as a result of the mechanical deformation of tissues which create currents through both piezoelectric and electrokinetic mechanisms. In the earliest studies of the efficacy of fields to affect tissue healing, the stated objective was commonly to imitate the endogenous fields in the absence of normal mechanical loading. Subsequently, the emphasis of studies in this area underwent a shift toward identifying those field characteristics that are most effective in stimulating a tissue response, the secondary goal being the tying of these observations to the underlying physiology.

Initial attempts to develop non-invasive electric field therapy involved capacitive coupling, although the effectiveness of this technique in the ELF regime was limited and electromagnetic coupling rapidly supplanted this simpler technique.

Exogenously induced field effects on bone tissue

After the demonstration of the piezoelectric properties of bone (Fukada & Yasuda, 1957), numerous investigators pursued measurements of electrical potentials in bone during deformation in order to determine whether the distribution of currents or charge might account for the adaptive responses of bone tissue. In 1968, McElhaney and Stalnaker hypothesized the converse, that application of electric fields results in a reverse piezoelectric effect, leading to deformation of the tissue sufficient to inhibit bone loss due to disuse. In their study, the right legs of 48 male Sprague-Dawley rats weighing about 100 g were immobilized in casts after 3/4 x 1/2 x 1/16-inch [19 x 12.7 x 1.6-mm] insulated and waterproofed copper electrodes had been fastened to the medial and lateral surfaces. The animals were assigned to four groups: sham exposure (no voltage applied to plates), DC control (100 V DC applied to plates), 3 Hz stimulus at 200 V, or 30 Hz stimulus at 200 V. [The induced electric field due to the time-varying electric field can be estimated to be 0.1–1 V/m. The DC field would induce no field in the tissue.] All animals were treated for 1 h every 12 h for 28 d. The bone cross-sectional area, hardness, and compressive strength were measured, and chemical and histomorphometric analyses were performed

on the left and right femurs of the 24 animals that survived the protocol. On the basis of this broad array of measures, the authors concluded that the most robust exposure, as compared with sham exposure, was the 30 Hz stimulus, the 3 Hz stimulus appearing less effective in maintaining the bone normally lost due to disuse; the DC exposure was the least effective. Eight apparent bone tumors or prolific new bone formation were seen in the 18 electrically treated animals. Five of these tumors occurred in the group exposed to 30 Hz, two in those at 3 Hz, and one in those exposed to DC. No tumors were found in the sham-exposed group.

In a study to specifically address the incidence of bone tumors reported by McElhaney *et al.* (McElhaney *et al.*, 1968) undertook a similar study of disuse osteoporosis in 50 male Sprague-Dawley rats weighing 150 g with limbs immobilized in casts. Four study groups were used: a control group with no implanted electrodes, a sham-exposed group with implanted electrodes (19 x 13 x 1.6 mm copper with epoxy insulation) but no excitation, a group exposed to a 30 Hz stimulus at 200 V peak–peak applied to the plates for 1 h every 12 h, and a group exposed to the same stimulus but for 8 h per weekday and 1 h/d on weekends. At 28 days, the animals were sacrificed, and the cortical area, mass, density, and percent ash of the femurs were determined. A much smaller effect on disuse was seen than in the previous study. [The greater size (and therefore age) of the animals may account for much of this difference.] A strong effect of exposure to 30 Hz was again observed, with a duration dependence, as the group exposed for 8 h/d had a greater increase in cross-sectional area than those exposed for 2 h. No evidence of tumors or hypertrophic growth was found in any of the animals examined. [Of concern in this trial is the asymmetric loss of animals in the various groups, prohibiting comparison of the groups exposed for 2 and 8 h with regard to three of the four properties assayed.]

Cruess *et al.* (Cruess *et al.*, 1983) revisited the question of osteoporosis, using PEMF to treat disuse osteoporosis in a rat model. Two groups of 250 g male rats underwent surgical removal of the gastrocnemius and soleus muscles bilaterally and were then placed in plaster casts. One of the groups was treated continuously by whole-body exposure to a repetitive 65–72 Hz pulse of 325 μ s in width, sufficient to induce an electric field of 150 mV/m at the tibia; the second group remained untreated. A third group of free-roaming normal rats was included in the study. After 14 days of exposure, the tibias were removed and morphological and biochemical assays performed. While the surgical procedure resulted in significant loss of body mass over the two-week period as compared with the free roaming controls, no significant difference in wet weight or in percent ash weight was observed between treated and untreated animals. Biochemical assays showed significantly ($p < 0.05$) higher collagen synthesis rates, lower collagenase activity, and higher mineral uptake in the treated group than in the operated group with no field exposure.

Enzler *et al.* (Enzler *et al.*, 1984) completed a study in a canine ulna non-union model system to test the efficacy of PEMF to accelerate fracture healing. Twelve female beagle dogs aged four to six years underwent bilateral surgical procedures for osteotomy of the ulna. The right limbs of six animals and the left limbs of the remaining six were exposed to

PEMF for 24 h/d, the contralateral limb being used as control. The pulse waveform was similar to that used in clinical studies: a 2-ms burst comprised of 10 pulses, with the burst repeated at a 10 Hz rate. [The magnitude of the peak flux density was not reported, although it can be expected to have been 1–2 mT, consistent with the other experimental devices produced by ElectroBiology, Inc. During the 1970s and 80s, this company was in the forefront of development of PEMF therapy and provided exposure systems to a large number of research groups. Two systems were commonly used: a 70–75 Hz repetitive pulse signal and a 1.5–15 Hz pulse-burst signal waveform, both with a peak flux range of 1–2 mT. In these studies, induced electric field intensity is estimated as the product of the peak time-rated change of the flux and a characteristic dimension of the exposed tissue. In this specific study, the approximate 30 μ s rise time would be consistent with a dB/dt on the order of 50 T/sec, corresponding to peak induced electric fields in the range of 1 V/m.] After sacrifice 22–30 days after the start of exposure, the fractures were tested for torsional stiffness and examined histologically. None of the osteotomies healed during the experimental period, no histological changes were evident, and no statistical differences in the torsional stiffness of the fracture calluses were observed between the treated and untreated limbs.

Bone tissue healing can be classified as comprising three distinct processes: fracture healing, appositional growth, and epiphyseal plate growth (lengthening) by endochondral ossification. While most early studies of the effects of EMF on bone healing emphasized the first two of these processes, Smith and Nagel (Smith & Nagel, 1983) investigated the effect of PEMF on bone elongation in the hind limbs of rabbits. In order to study the time of growth-plate closure, female rabbits aged 12 weeks at the beginning of the protocol were exposed for 18 weeks. To study bone elongation, the animals were exposed for eight weeks starting at the age of six weeks. Exposure was for 24 h/d to a 72 Hz repetitive pulse signal generated by hardware supplied by Electrobiology, Inc. [The peak flux densities were not reported but are presumed to be in the range of 1–2 mT.] Induction coils were attached to the left and right sides of the animals by a coil support, which permitted some movement. In addition to limb length and growth-plate closing time, blood flow was evaluated by technetium scanning, and glycosaminoglycan distribution was analyzed in extracted articular cartilage. No effect of exposure on the pattern of epiphyseal plate closure was observed, either with a 12-h on/off cycle of exposure or with continuous exposure ($n = 6$). Similarly, no effect on morphological measures of the tibia or on blood flow patterns was evident; however, the growth rate of the femurs of the animals experiencing continuous exposure was slightly inhibited ($n = 18$; $p < 0.06$), and the glycosaminoglycan content was significantly elevated (22%, $p < 0.003$). The authors interpreted their results as indicating that PEMF inhibits cartilage maturation.

It is not uncommon in orthopedic surgery for segmental, autogenous cortical bone grafting operations to fail due to graft–host non-union. Given the extensive anecdotal reports of healing of traumatic non-unions following PEMF therapy, Miller *et al.* (Miller *et al.*, 1984) studied the potential use of this therapy to promote healing in autogenous grafts. Twenty adult mongrel dogs underwent bilateral surgery to remove 4 cm long fibular segments, which were then inverted and replaced in the graft bed with no internal fixation.

One week post-operatively, one leg of the animal was exposed to a pulsed magnetic field from an orthosis incorporating a Helmholtz coil pair producing a 5 ms burst of 22 30 μ s wide pulses repeated at a 15 Hz rate. The estimated peak induced electric field was reported to be 1.5 V/m. All of the animals were exposed for 20 h/d, with 10 animals treated for two months and 10 for six months. All animals were sacrificed six months post-operatively and histological and biomechanical analyses performed. No statistically significant differences were seen in biochemical or biomechanical measures or in terms of time to union.

Aaron *et al.* (Aaron *et al.*, 1989) also studied the effect exposure to EMF on endochondral ossification, but in a model system based on subcutaneous implantation of decalcified bone matrix. In an early report, the effect of field exposure on collagen synthesis and matrix calcification was studied. Decalcified bone matrix (25 mg) obtained from the tibia and femur of mature male CD rats was implanted along the thoracic musculature in immature male CD rats. The animals were randomly assigned to one of three groups: free-roaming controls, sham-exposed, and treated groups. Sham- and field-exposed groups were confined in restraining boxes for 8 h/d during the animal's normal sleep cycle. The treated group was given a whole-body exposure to a pulse-burst magnetic stimulus consisting of a 4.5-ms burst containing 20 20 μ s pulses of 2.0 mT. The burst was repeated at a rate of 15 Hz. This waveform therefore produced a peak dB/dt of 100 T/s, corresponding to an estimated peak induced electric field on the order of 1 V/m. The animals were sacrificed at 2-d intervals over two weeks, and the ossicles were evaluated biochemically, histologically, and histomorphometrically. Exposure had no significant effect on the total volume of calcified tissue in the ossicles at any time. A transient increases in sulfate incorporation and in the volume of cartilage were observed in association with field exposure, peaking at day 8, and the calcium content of the developing ossicles was consistently higher than that in restrained control animals ($p < 0.05$). [A confounding aspect of this study is that the restrained controls had a significantly inhibited ossicle development pattern as compared with the free-roaming controls, such that the effect of field exposure was essentially to return the development process to normal.]

In a study of the ability of magnetic fields to promote appositional bone growth, McLeod and Rubin (McLeod & Rubin, 1992) coupled observations made with pulse fields to those based on exposure to sinusoidal ELF fields. Bone resorption and formation were studied in an avian model of disuse osteopenia. Bone loss due to disuse was initiated by proximal and distal osteotomies on the left ulna of adult male turkeys, and Delrin caps were installed over the bone ends to prevent re-union. Exposure to magnetic fields was accomplished from a Helmholtz-like coil pair strapped to the wing of the bird. Exposure was for 1 h/d, five days per week. Six experimental groups were used, representing disuse, sham exposure (unenergized coils), exposure to a 75 Hz pulsed field (0.2 mT peak with rise time of 380 μ s), and exposure to three sinusoidal fields at 75 and 150 Hz (representing the fundamental and second harmonics of the pulsed waveform) and 15 Hz. The flux densities of the sinusoidal fields were established to provide the same dB/dt as in the fundamental component of the 75 Hz pulsed stimulus. The electric fields induced in

the preparation were estimated to be on the order of 10–20 mV/m with the pulsed field and less than 1 mV/m with the sinusoidal fields. Morphological assessment after eight weeks showed a clear frequency dependence of the bone remodeling response, 150 Hz being less effective than 75 Hz, which was significantly ($p < 0.05$) less effective than 15 Hz. The 15 Hz stimulus was found to be more effective than the pulsed field exposure in initiating new bone formation, despite the similar peak flux density used (0.24 mT) and the much lower peak induced electric field. [As the peak dB/dt was kept constant for the sinusoidal fields, the current flow into the coils would have had to increase by 10-fold between the 150 Hz and 15 Hz stimuli. In the absence of an active sham-exposed control, this dose dependence may, to some degree, simply reflect a difference in heating of the induction coils.]

Takano-Yamamoto *et al.* (Takano-Yamamoto *et al.*, 1992) investigated the ability of magnetic fields to promote bone formation in a bone defect model. A 2 mm non-healing bone defect was surgically prepared in the premaxilla of 180 g male Wistar rats, and they were either treated with 7 mg demineralized bone matrix or not, with or without field exposure, yielding a total of five groups with the sham-operated group, with 4–10 animals per group. Animals were exposed in a 25 x 20 x 60 cm plastic container which was placed in a solenoid 30 cm in diameter and 60 cm in length. Exposure was for 12 h/d to a pulse-burst waveform composed of a 10 ms burst of 100 μ s pulses, with a burst repetition rate of 15 Hz. The peak flux densities were 0.15–0.18 mT. After sacrifice of the animals at days 0, 21, and 35, the defect sites were examined for histological alterations, alkaline phosphatase activity, and Ca^{45} incorporation. Defects treated with demineralized bone matrix graft and PEMF had significantly greater alkaline phosphatase activity and calcium incorporation ($p < 0.05$) than those with any of the four alternative treatment protocols. In addition, histological examination showed almost complete osseous bridging of the defect by day 35.

In another test of the efficacy of PEMF to promote bone growth, Buch *et al.* (Buch *et al.*, 1993) studied in-growth into a titanium bone harvest chamber. The titanium chamber (6 x 10 mm) was surgically implanted into the proximal tibia metaphyses of six male and female rabbits and became anchored within four weeks. Bone tissue was then harvested at three-week intervals with the implant *in situ*, providing a repeated measure of in-growth. Bone tissue was harvested once before field exposure, six times during the exposure period, and then twice after field exposure was terminated. The animals were restrained and underwent whole-body exposure 2 h/d from a Helmholtz-like coil pair. The waveform consisted of a 72 Hz repetitive pulse pattern with a peak flux density of 3 mT. [Because of the geometry and the presence of a metal chamber, the induced electric field cannot be easily calculated.] The mass of bone harvested from the bone chamber declined significantly after the first three-week harvest ($p < 0.003$ by repeated measures analysis). [While this result may well be due to the inability of the tissue to sustain a high level of bone in-growth, the decline coincides with the period of field exposure, resulting in an apparent inhibitory effect.] After termination of the field exposure at the time of the sixth harvest, bone in-growth into the chamber declined further ($p < 0.004$). The authors interpreted these results to indicate that field exposure sustains a level of in-growth that

would have continued to decline in the absence of stimulation. [Without concurrent sham-exposed controls, this conclusion is difficult to support.]

Pienkowski *et al.* (Pienkowski *et al.*, 1994) attempted to optimize PEMF therapy in a rabbit fibular osteotomy model. This study is unique in that it was fully blinded, with placebo devices for the controls. Fibular osteotomies were performed on the right limbs of 399 immature (2.8–3.2 kg) male rabbits, which underwent 20 experimental conditions. Field exposure was accomplished from a saddle-shaped induction coil placed around the right leg and centered over the osteotomy site. A pulse-burst waveform pattern was used in a 5-ms burst with a burst repetition rate of 15 Hz. The peak flux density and pulse width were varied in an attempt to identify optimal exposure conditions. The peak flux densities were 0.028–1.1 mT and the pulse widths were 0.5–10 μ s. All of the animals were sacrificed on day 16 after the operation, and the efficacy of treatment was evaluated by a three-point bending test of the mechanical stiffness of the fibula. While certain combinations of pulse width and amplitude appeared to result in a significantly stiffer ($p < 0.05$) callus, replication experiments did not confirm this observation. No clear pattern of dose- or duration-response was evident in this partially factorial experiment, suggesting that no consistent improvement in fracture healing resulted from field exposure.

In an extension of their studies on the acceleration of endochondral ossification by exposure to magnetic fields, Aaron and Ciombor (Aaron & Ciombor, 1996) investigated the effect of phased exposure. Immature (80 g) male rats received demineralized bone matrix pellets in the thoracic musculature and were exposed to a magnetic field stimulus for only a fraction of the 20-d experimental protocol. There were four exposure groups: on days 1–3, corresponding to the mesenchymal phase of ossicle development; on days 4–8, corresponding to the chondrogenic phase; on days 9–19, corresponding to the calcification phase; and for the full 20 days. Exposure was accomplished as described above, with a pulse-burst waveform of 5 ms bursts repeated at a 15 Hz rate, and a peak flux of 2 mT. Animals underwent whole-body exposure while confined in exposure containers. All of them were sacrificed on day 20, and glycosaminoglycan synthesis and Ca^{45} uptake were measured. While all of the exposed animals showed significantly increased calcium uptake and glycosaminoglycan synthesis rates as compared with unexposed controls, stimulation for just the first three days (mesenchymal phase) was found to be as effective in promoting ossicle development as exposure for the full 20 days.

McLeod and Rubin (McLeod & Rubin, 1998) also continued their studies on the response of the disuse avian ulna model to exposure to magnetic fields in an attempt to identify the frequency and dose-response characteristics of bone tissue. They continued to use proximal and distal osteotomies of the left ulnas of adult male turkeys to create a bone disuse situation; however, in this study the bone ends were capped with stainless-steel (non-magnetic) caps to prevent re-union, and external fixation hardware was used to prevent any inadvertent mechanical loading of the bone. In addition, a solenoid induction coil was used to impose the magnetic field along the long axis of the bone. The induced

electrical currents therefore had an essentially uniform two-dimensional distribution, permitting more accurate calculation of the induced current and field intensities. Groups of three to four treated ulnas were exposed for 1 h/d under one of 10 exposure conditions, which spanned the frequency range of 5–150 Hz (all at a constant dB/dt of 0.025 T/s) and a flux density ranging up to 2.5 mT at a frequency of 15 Hz. The bone cross-sectional area at the ulna mid-diaphysis was assayed after sacrifice of the birds eight weeks after operation. A distinct frequency response was observed, with sensitivity peaking at 15 Hz. The investigators noted that the very low sensitivity observed at 5 Hz removes concern about a possible heating effect, although no sham-exposed control was used. A dose-dependent response was observed for flux densities up to 250 μ T, with a significant effect ($p < 0.05$) as compared with no field treatment for flux densities as low as 2.5 μ T at 15 Hz. The authors considered that the lack of an increased response at 2.5 mT over that observed at 250 μ T confirms the non-thermal origin of the effect. The distributions of the induced electric fields, determined by two-dimensional impedance network techniques, indicate that the peak-induced 15 Hz electric field in the bone tissue at 250 μ T would be approximately 0.3 mV/m.

Effects of exogenous induced fields on nerve and skin healing

In principle, the same electrokinetic processes that give rise to electrical currents in bone tissue will also produce electrical currents in soft connective tissues. In fact, the normal (i.e. non-destructive) mechanical deformations of soft tissues during typical physiological activities far exceed that seen in bone tissue; however, with the exception of cartilage, the charge density in these tissues is far lower than that of bone. In addition, soft connective tissues lack the highly organized collagen structure that can permit a large piezoelectric coefficient. Thus, the predominant electrical currents in skin, tendon, and ligament probably arise through the extracellular currents generated during muscle contraction. The approval and extensive use of pulsed magnetic fields in the clinical setting for bone healing naturally led to investigations on the efficacy of pulsed fields to affect soft connective tissue healing, particularly over the last 10 years.

Following the report of several studies demonstrating effects of ELF fields on fibroblasts *in vitro* (Liboff *et al.*, 1984; McLeod *et al.*, 1987c; Ottani *et al.*, 1988) undertook a study to determine whether pulsed magnetic fields could affect skin wound healing *in vivo*. In this study, a 3 x 3-cm square of skin (with the cutaneous muscle) was surgically removed from the dorsal thoracolumbar region of four-month-old male Wistar rats (weighing 350–370 g). The animals were then exposed or sham-exposed, and eight animals from each group were sacrificed at days 6, 12, 21, and 42 for histological and ultrastructural analysis of the wounds. Field exposure was implemented in a 40 cm diameter solenoid driven by a 50 Hz triangular wave to a peak flux of 8 mT, providing a dB/dt of 0.8 T/s, sufficient to induce electric field intensities on the order of 10–20 mV/m. The animals were exposed for 30 min every 12 h. Rats undergoing sham exposure spent the same time in the exposure apparatus with no excitation. The rate of healing, as assayed by area of wound vs. time, was found to be significantly higher ($p < 0.001$ by linear regression) in exposed animals, reflecting an approximate halving of the healing time. The investigators noted the

appearance of a network of blood vessels in the wound as early as six days post-operatively. [The investigators also referred to unreported data collected at a variety of other exposure frequencies (e.g. 60 and 400 Hz) with which similar results were obtained and suggested that the waveform is probably not critical to ensure a physiological effect.]

Lin *et al.* (Lin *et al.*, 1993) reported similar studies using a ligament defect model in rabbits. In their investigation, 80 male rabbits underwent square resections (4 x 4 mm) of both the left and the right patellar ligaments. They were then assigned to one of four groups representing exposure to a 0.2, 1, or 5 mT peak or control. A pulse magnetic field was generated by a device of undescribed design, but which induced a 10 Hz electric field pulse of 25 μ s in width, consistent with a maximum dB/dt of 200 T/s, sufficient to induce electric field intensities in the range of 10–100 V/m. The animals were exposed for 6 h/d, and five animals from each group were sacrificed each week for four weeks. Blood flow, collagen synthesis, collagen typing, and histological assays were performed. Significant ($p < 0.05$) increases in the collagen content of the wounds were observed in all treated groups as compared with controls, and significant ($p < 0.05$) increases in blood flow and cross-sectional area were observed within two weeks in the group exposed to 5 mT, an effect sustained throughout the four-week experimental protocol. No differences in collagen type distribution were observed between the exposed and control groups. The authors noted that these results are consistent with those of their earlier studies.

Patino *et al.* (Patino *et al.*, 1996) reported the results of a study in which flux densities of 20 mT were used. A circular lesion was made on the backs of 22 male Wistar rats weighing 250–360 g, and the animals were then used as controls, treated with nitrofurazone, or treated with PEMF (35 min twice a day to a 20 mT, 50 Hz flux from a 23-cm diameter solenoid 50 cm in length). Planimetry of the wounds was obtained every 7 d over one month. Both the area and the perimeter of the wounds of the field-treated animals were significantly reduced as compared with sham-exposed controls ($p < 0.01$). Field treatment resulted in significantly smaller wounds on day 21 as compared with the nitrofurazone-treated group ($p < 0.01$).

Effects of induced fields on nerve tissue

As for bone and soft connective tissue healing, early investigations on the potential use of electric fields to promote nerve healing began with studies of DC fields in the 1970s. Investigations on the use of pulsed magnetic fields to promote nerve healing date from the 1980s, although these studies have been pursued by a relatively small group of investigators. O'Brien *et al.* (O'Brien *et al.*, 1984) made one of the earliest efforts to determine the efficacy of magnetic field therapy to enhance regeneration in the peripheral nervous system. The peroneal nerves of 12 cats were exposed, and compound action potentials were recorded to provide a baseline measure. The nerve was then transected and repaired by microsurgery. Five days post-operatively, the animals were assigned to one of four groups, representing untreated controls, sham-treated controls, magnetic field-treated with a pulse-burst waveform (15 Hz burst repetition rate), or treated with a 72 Hz repetitive pulse waveform. All treated animals were exposed for 10 h/d, 6 d per week,

for 12 weeks. The peak flux density is not reported, but the exposure hardware was provided by Electrobiolgy, Inc. [The peak flux was probably in the range of 1–2 mT.] Electrophysiological and histological assays were performed at 12 weeks. Both the area of the compound action potential and the retrograde transmission of horseradish peroxidase to the anterior horn of the spinal cord were significantly greater ($p < 0.01$ by ANOVA) in animals receiving the pulse-burst field than in the other three groups at 12 weeks. [This is a remarkable outcome, given that only three animals were available in each group.] The authors noted that no functional assays were incorporated to ensure successful regeneration.

A more thoroughly described study on nerve regeneration was later reported by Siskin *et al.* (Siskin *et al.*, 1989), in which a crush lesion was used rather than nerve transection. Male Sprague-Dawley rats weighing 300 g underwent a surgical procedure to produce a crush lesion in the right sciatic nerve. At days 3, 4, and 6, a pinch test (pinching the exposed nerve to produce muscle twitches) was performed under anesthesia to assay the extent of regeneration. Field exposure was accomplished with a 30 cm diameter Helmholtz coil pair, the rats being either restrained or free-roaming in plastic cages. A 2 Hz square wave drive was applied to the coils, creating a peak flux of 0.3 mT with a rise time of approximately 1 ms, thereby producing a peak induced electric field proportional to 0.3 T/s or on the order of 10 mV/m. The animals were exposed for 4 h/d; sham-exposed animals were placed in the exposure chamber without current excitation. No significant effect of restraint as compared with free roaming was observed in the control or the field-exposed group; however, field exposure was found to result in a significant (20%; $p < 0.001$) increase in regeneration rate. In collateral studies, no effect of magnetic field orientation (horizontal vs. vertical) or exposure duration (1 vs. 4 vs. 10 h/d) was observed, all variations resulting in significantly enhanced nerve regeneration rates. Similarly, exposure of the animals to fields for 4 d before creating the crush lesion also resulted in an increased regeneration rate post-operatively.

The frequency dependence of enhanced nerve regeneration capability was subsequently reported by Rusovan *et al.* (Rusovan *et al.*, 1992). A crush lesion of the sciatic nerve was induced in female Sprague-Dawley rats weighing 200 g. The animals were randomly assigned to one of eight groups corresponding to controls or exposure to one of seven 0.1 mT sinusoidal fields at a frequency of 50, 100, 250, 500, 1000, 1500, or 2000 Hz. The induced fields were estimated by the authors by assuming an average radius of 5 cm per rat, suggesting an induced electric field intensity of 15 mV/m at 1 kHz. The regeneration distance was evaluated by the pinch test at days 3, 4 and 6. While exposure to 50 or 100 Hz had no effect on regeneration, exposure to 250, 500, or 1000 Hz resulted in significantly enhanced regeneration rates ($p < 0.001$). The maximal effect was a 24% increase at 1 kHz, while the responses at 1.5 and 2 kHz were similar to that at 100 Hz. The authors noted that the increase in response as a function of frequency is consistent with an effect of the induced electric field, as the magnetic flux was held constant; however, they also note that similar decreases in sensitivity at higher field frequencies have been observed in numerous *in-vitro* systems.

This group of investigators continued their studies on the effects of magnetic fields on nerve regeneration, pursuing their observations of pretreatment effects (Kanje *et al.*, 1993). Female Sprague-Dawley rats weighing 200 g underwent a variety of pretreatment exposures, ranging from 15 min/d for 2 d to 4 h/d for 4 d. The sciatic nerves of the animals were then submitted to a crush injury, and the regeneration distance was assayed on days 1, 2, 3, 4, 7, and 14. Field exposure was accomplished with the apparatus described by Sisken *et al.* (Sisken *et al.*, 1989), consisting of a 30 cm diameter Helmholtz coil pair creating a vertical flux. Two peak flux densities, 60 and 300 μT , were used with a 2 Hz pulsed signal and a rise time of 0.8 ms, corresponding to peak induced electric fields on the order of 10 mV/m. The animals were allowed to roam freely throughout exposure. While the 60 μT pretreatment had no effect on subsequent regeneration rates, all 300 μT pretreatments, including treatments as short as 15 min/d for 2 d were found to significantly enhance the regeneration rates. Animals pretreated for 4 h/d for 2 d had an increased regeneration rate for at least 10 d.

4.4.6.3 Summary

Human clinical studies

If retrospective reports of the efficacy of PEMF in promoting the healing of fractures are ignored, there is little clinical evidence of a real effect of exposure to fields in accelerating or improving the probability of successful fracture healing. Two prospective, blinded trials of the treatment of non- and delayed unions were undertaken, but both have serious design flaws and furthermore show no or only a weak effect. The trial on limb lengthening appears to be both well designed and definitive in showing a lack of effect on bone fracture callus formation or on the process of secondary bone healing. In clinical use of PEMF devices, however, it has been the rule to center the induction coil over the fracture site. This technique may well have ensured a low success rate by minimizing the induced electric field intensity at the distraction or fracture gap.

Conversely, there appears to be substantial, accumulating evidence that complex clinical exposures to PEMF have a significant effect on primary bone healing processes. The studies of both osteotomy and spinal fusion show a robust effect. While quantification and analysis were weak in these two studies, they are prospective, randomized, double-blind trials, a rarity in the field of orthopedics. Perhaps the most convincing trial is that of the response of bone tissue during limb lengthening. While no effect on secondary bone healing was observed, there was significant inhibition of bone resorption and evidence of new bone formation. Unlike secondary bone healing, primary bone healing, new bone formation, and inhibition of bone resorption depend mainly on the state of vascularization of the tissue. The results of the two studies therefore indicate that the predominant effect of exposure to PEMF is on the vascular supply or on cells capable of stimulating revascularization, rather than a direct effect on the bone cell population. Of course, the issue of coil placement cannot be ignored in the study of limb lengthening, in which the proximal and distal segments of the bone would, in fact, experience the maximum induced

electric field intensities. The responses observed in these two regions may therefore simply reflect much higher field intensities.

In capacitive coupling, with application of a 3 Hz field, the distribution of the induced electrical currents is readily determined by the placement of the external plates, and the maximal field intensity can be expected to occur in the central region between the coupling plates. In electromagnetic coupling, however, the issue is more complicated, as the induced electric field will actually reach a maximum at the periphery of the magnetically exposed area. In clinical trials in which local exposure is desired, the investigators have typically centered the exposure coils over the site of interest, essentially ensuring that the induced electric fields in the region will not be maximal.

Studies in experimental animals

Although early trials suggested that non-union tissue responds to EMF, and despite extensive clinical use of magnetic field therapy for treatment of this condition, studies in animals *in vivo* indicate only limited efficacy. Magnetic field therapy appears incapable of enhancing the healing of osteotomies, in-growth of bone into a defect, bone elongation, or graft healing and, in at least one case (in-growth), may inhibit the normal process. The results obtained in a model of endochondral ossification after exposure of whole animals suggest, however, that magnetic field therapy can be effective. This raises two possibilities. One is that neither magnetic fields nor induced electric fields have any direct effect on the endochondral ossification process but have an effect at the systemic level manifested by accelerated growth processes. Alternatively, the ossification model differs critically from bone healing *in situ* in that the induced electric fields are distributed in both the healing tissue and the surrounding tissue. Exposure to local fluxes can result in minimal induced electric field intensities at the healing site. As the distribution of induced fields is quite complex, however, the effect of this variable may be beyond interpretation.

Conversely, magnetic fields appear to have a strong, reproducible effect on the process of appositional (surface) bone growth and on inhibition of bone resorption. Moreover, the fact that exposure to pure electric fields and time-varying magnetic fields can inhibit bone loss suggests that this effect is mediated by the induced electric field. In the studies reviewed here, the frequency range within which maximal bone tissue responses are observed is consistent, induced fields in the range of 15–75 Hz appearing to be optimal in all of the studies. The effect of field intensity is much less clear; however, in a study that specifically addressed this factor (McLeod & Rubin, 1998), a threshold intensity of < 0.1 mV/m was established for exposure at 15 Hz.

Consistent effects on the healing of soft connective tissue have been reported by numerous groups. Perhaps the most notable feature is that remarkably high flux densities (5–20 mT) are required to ensure an enhanced healing rate. Because no active sham-exposure device was used in any of these studies, there is clearly potential concern about

warming of the animals. In addition, the fact that whole-animal exposure was used in these studies suggests the possibility of neuroendocrine stimulation.

Consistent responses were also seen in the studies of nerve regeneration, although they usually represented only about a 20% enhancement in growth rate. These studies confirm the results of the studies of soft and hard connective tissue healing, particularly with regard to the sensitivity of the nerve healing process to frequency. In addition, attention was drawn to the angiogenic properties of stimulation of nerve regeneration by magnetic fields, as has been observed repeatedly in studies of both skin and bone healing. This observation may be critical with regard to the role of magnetic fields in the promotion of tumor growth, which is known to depend on angiogenesis.

As in the clinical studies, the nature of the exposure of the target tissue is not precisely defined. Whole-body exposure has commonly been used in studies of small animals, which can result, for sites of interest near the periphery of the body, in maximal induced electric field intensity. This type of exposure may also affect many other sites in the body, producing systemic responses that could influence tissue healing. For example, calcitonin, a growth hormone which has strong effects on bone growth in young animals, is produced by the C cells of the thyroid. The location of the thyroid at the periphery of the body ensures maximal exposure to electric fields under the conditions of either vertical or horizontal exposure to magnetic fields. Stimulation of the thyroid could therefore result in enhanced bone growth or healing, independent of any local effect on the bone or surrounding tissue. This Working Group did not address the possible adverse side-effects of exposure to electromagnetic fields on bone and tissue repair and adaptation.

There is strong evidence that exposure to electric and magnetic fields affects bone repair and adaptation.

[This conclusion was supported by 14 Working Group members; there were 5 votes for 'moderate' evidence, 8 abstentions, and 2 absent.]

The Working Group could not reach a conclusion about whether exposure to electric and magnetic fields affect nervous and non-bone connective tissue repair and adaptation in vertebrates.

[This conclusion was supported by 12 Working Group members; there were 10 votes for 'moderate' evidence, 6 votes for 'weak' evidence, and 1 absent.]

4.5 Epidemiological studies of non-cancer health effects in humans

4.5.1 Occupational exposure

This review includes only the studies that are the strongest methodologically, on the basis of exposure assessment, on occupational exposure to EMF and neurodegenerative and psychological diseases, reproductive disorders, and cardiovascular disease (see Table 4.35).

Table 4.35. Minimal exposure assessment required for a study to be included in this review

Disease	Exposure assessment
Spontaneous abortions after maternal exposure to VDTs	Measurements on VDTs
Other reproductive abnormalities due to maternal exposure	Questions about VDT use ^a
Reproductive abnormalities due to paternal exposure	Job titles
Alzheimer disease (or dementia)	Job titles of electrical workers ^{a,b}
Amyotrophic lateral sclerosis	Job titles of electrical workers ^{a,b}
Suicide	Job titles of electrical workers ^a
Depression	Full-shift monitoring
Cardiovascular disease	Job titles of electrical workers

VDT, visual display terminal

^a Includes one or more studies with full-shift measurements

^b Includes studies with expert judgments of magnetic field exposures

4.5.1.1 Reproductive effects

(a) Adverse birth outcomes and maternal exposure to electromagnetic fields

Possible reproductive effects of women's exposure to EMF from video display terminals (VDTs) were examined in four studies (Table 4.36). VDTs emit EMF with saw tooth waveforms in both ELF (3–3000 Hz) and VLF (3000–30 000 Hz). VDT fields have markedly different characteristics from the sinusoidal ELF fields that are the primary component of environmental EMF. The magnitudes of the magnetic fields around a VDT vary widely with the model (Juutilainen & Saali, 1986b; Moss & Booher, 1995; Schiffman *et al.*, 1998), and that information has been used to categorize such exposures for studies of reproductive effects.

Schnorr *et al.* (Schnorr *et al.*, 1991) conducted a retrospective study of spontaneous abortions in women employed as telephone operators by two large telephone companies in 1983–86. The study base consisted of 4246 married women aged 18–33 who were identified from company records and agreed to an interview about their reproductive, medical, and occupational histories (76.6% of the 5544 woman identified). The 136 cases were pregnancies resulting in spontaneous abortions while the respondent worked as a telephone operator. The 737 controls were pregnancies among operators who had live

births. Exposure to EMF was assessed by job title and validated by field measurements. Women considered to be exposed were directory assistance operators who had always used conventional VDTs with cathode ray tubes during the study period. Those considered to be unexposed were general telephone operators who had worked at monitors with light-emitting diode or neon glow tube displays up to 1986; these monitors emitted no VLF fields and lower ELF magnetic fields than the VDTs (Bracken, 1991; NIOSH, 1990). The EMF fields from the VDTs had rough saw tooth waveforms with principal frequencies of 45 Hz for one model and 60 Hz for another; the non-VDT monitors had 60 Hz sinusoidal waveforms. The exposure of the operators to EMF at the level of their abdomen varied considerably with the worker's location and the type of monitor. In measurements taken at a sample of work sites with Holiday Industries model HI 3600-01 and 3600-02 meters, the geometric mean operator exposure to ELF magnetic fields was 0.078 μT for one model and 0.073 μT for the other. The exposure from VDTs was the same as from the light-emitting diode monitors (geometric mean = 0.078 μT) and higher on average than that from the neon glow tube monitors (0.041 μT). In comparison with those in other office environments, this ELF exposure of the telephone operators is not elevated, although VLF fields were rare before the introduction of computers.

The spontaneous abortion rate was similar for the VDT-exposed and the general telephone operators (14.8 and 15.9%, respectively). No associations were found with VDT use at any period of pregnancy, either when the analyses were unadjusted or when they were adjusted for such risk factors as smoking, thyroid disorders, alcohol consumption, and spontaneous abortions before the study period. [As the comparison of VDTs with non-VDT monitors produced a clear differential in exposure to VLF (but not ELF) EMF, this study does not allow any conclusions about the risks for spontaneous abortion from exposure to ELF magnetic fields. Derivation of information on spontaneous abortions from questionnaires has limitations.]

Grajewski *et al.* (Grajewski *et al.*, 1997) examined the risk for preterm births and reduced birthweights among VDT operators from the study population of Schnorr *et al.* (Schnorr *et al.*, 1991). They evaluated 304 singleton pregnancies in 284 women who had worked as VDT telephone operators during the first 28 weeks of pregnancy and 403 among 363 unexposed operators. Birthweight, gestational age, birth defects, and the reproductive risk factors studied by Schnorr *et al.* were determined during interviews. The self-reported data were validated from birth certificates and medical records and found to be within ± 100 g for birth weight and \pm two weeks for gestational age for more than 80% of the subjects. The number of hours that the subject had been exposed to VDTs was estimated from the time she had spent working as a directory assistance operator in the telephone company's payroll records, which also reported the number of hours of work per day, leave, and vacations. The following potential confounders were included in the analysis: diabetes, maternal weight gain during pregnancy, thyroid conditions, hypertension medications, pre-eclampsia, toxemia, interpregnancy interval, and adverse pregnancy outcomes (including previous reduced-weight or preterm births) before the study period.

No association was found between length of work with VDTs at any period of the pregnancy and either reduced birth weight (< 2800 g) or preterm birth (21–37 weeks gestation). Seven cases of major birth defects (2.3%) were reported by the VDT-exposed operators and four (1.0%) by the unexposed; however, only three of the 11 self-reported birth defects could be confirmed from medical records. [See summary of Schnorr *et al.* for comments on limitations of the study. Some validation of outcome was possible from medical records.]

Lindbohm *et al.* (Lindbohm *et al.*, 1992) performed a retrospective study of spontaneous abortions among women using VDTs. The study base consisted of women employed as bank clerks and clerical workers by three large companies during the years 1975–85. The 368 cases of spontaneous abortion among study base members aged 20–35 identified from the Finnish pregnancy registry had to be confirmed by questionnaire for the subject to be included in the analysis (8.5% of miscarriages unconfirmed). The 1069 controls were woman who had given birth to liveborn infants in the registry. Job histories, VDT use, reproductive risk factors, and ergonomic factors were requested on the questionnaires, which were returned by 191 cases (52%) and 394 controls (36%). Exposure to VDT fields was assessed from the questionnaires, company records on the VDT models used by different work groups, and laboratory measurements of VLF and ELF magnetic fields at a fixed location (approximating the fetus' position) near the various VDT models. Exposure to magnetic fields was expressed as the time derivative (dB/dt) for VLF fields and the peak-to-peak magnitude for ELF fields. [In order to compare peak-to-peak values in this study with the root-square-squared (rms) magnitudes used in other studies, a range of conversion factors (0.266–0.010) was derived empirically from the Finnish VDT measurements reported by Jokela *et al.* Because these are saw tooth waveforms, the empirical conversion factor is less than the better-known value: $1/2\sqrt{2} = 0.354$ derived for sinusoidal waves.] (Jokela *et al.*, 1989)

An increased risk was reported in association with exposure to ELF magnetic fields from VDTs, expressed both as rms magnitude $\geq 0.24 \mu\text{T}$ and cumulative exposure per week; the increase was significant for the highest exposure category (see Table 4.36). [There appeared to be exposure–response relationships, although they were not tested statistically]. The relative risk for high exposure was markedly greater for late spontaneous abortions, ≥ 12 weeks into the pregnancy (8 cases; OR = 9.5; 95% CI = 1.8–52). No association was seen with VLF VDT fields, but a significant association was seen with the time-weighted average exposure per week (which incorporated time spent at VDTs, calculated from company records) in the group with high exposure (2.7; 1.2–6.1). The relative risks were adjusted for self-reported work load, exposure to solvents, number of previous births, use of intrauterine devices, and frequency of breakdowns in automatic data processing machines. [The response rate was very poor, particularly among controls, and subjects for whom all VDT models could not be identified were excluded. The magnetic fields were measured in the laboratory, with high background ELF fields, rather than in workplaces.]

Bracken *et al.* (Bracken *et al.*, 1995a) performed a prospective cohort study of fetal growth and exposure to EMF (see section 4.5.2.1 for a full description of the study). Although the focus was residential sources of EMF, such as electrically heated beds and wire codes, occupational exposures were also assessed by seven-day monitoring of magnetic fields and questions about VDT use. The study population consisted of women with a uterine pregnancy and no diabetes who had received prenatal care in the New Haven, Connecticut, area over a four-year period. The participating subjects (83% of eligible women) were interviewed before 16 weeks of estimated gestational age and took part in a program of EMF measurements that included the AMEX-2 wrist monitor. The monitoring encompassed much occupational exposure, because 81.3% of the subjects worked outside the home. The outcomes were low birthweight (< 2500 g) and intrauterine growth retardation (< 10th percentile of weight for gestational age). Neither outcome was associated with VDT use or TWA exposure to magnetic fields. [The AMEX-2 has a magnetic field sensor in only one direction and therefore provides very inaccurate measures in comparison with three-axis monitors. See Section 4.5.2.1 for comments on the limitations of this study.]

(b) Adverse reproductive effects from paternal exposure to EMF

Concern about the effects on children of paternal EMF exposure first arose from cross-sectional studies of workers in high-voltage substations in the former USSR (Asanova & Rakov, 1966). At that time, ELF electric fields were the exposure considered most likely to be responsible for adverse health effects. The average exposure in the substations was 98 V/m, compared with 5–10 V/m in offices and homes (Bracken *et al.*, 1995a). It is only in two recent studies that broader assessments of exposure to EMF have been considered. Two studies were focused on the male:female ratio of offspring (Mubarak & Mubarak, 1996); (Irgens *et al.*, 1997) [but the exposure assessments were inadequate].

Tornqvist (Tornqvist, 1998) studied reproductive effects among electric workers in the utility industry, in a large retrospective study and a small prospective study of perinatal survival, multiple births, low birthweight, sex ratio, congenital malformations, and childhood cancers (also discussed in section 4.2.1). In the retrospective study, Swedish census data were used to establish a cohort of 2077 male electrical workers and to obtain information on their work histories and spouses or cohabitants for a 25-year period. Information on 3350 children born to these couples was obtained from the Medical Birth Registry, and any cancers that the children incurred were ascertained from the National Cancer Registry. For each child, the father's exposure to EMF was determined from job titles reported in the five-year censuses before and after the year of the birth. The father was considered to have been exposed if he had held electrical occupations at both censuses spanning the prenatal year; otherwise, he was considered to be unexposed. Since the unexposed fathers held electrical occupations either before or after the child was conceived, they are assumed to belong to a socioeconomic class similar to that of the exposed fathers. Relative risks were calculated for the various reproductive outcomes relative to those in the total population of births, adjusted for maternal age, parity, and

year of birth. Relative risks were also calculated for the exposed vs. the unexposed fathers.

In the prospective study, the health of a cohort of 460 young electrical workers whose first job was in the power industry was followed. Questionnaires covering job histories and reproductive issues were part of the health examinations administered every three years. Over a 10-year period, these men fathered 364 children. Exposure to EMF during the prenatal year were derived from the job histories and a JEM based on measurements taken in the Swedish power industries (Lindh *et al.*, 1997). Workers considered to be highly exposed were those with exposure to both TWA magnetic fields $> 0.5 \mu\text{T}$ and electric fields $> 30 \text{ V/m}$ for at least 10 min per shift; low exposure was defined as exposure to both electric and magnetic fields below these thresholds.

Neither study showed any significant association with multiple births, low birth weight, sex ratio, or congenital malformations. The proportion of malformations was slightly increased among the offspring of highly exposed fathers in both the retrospective study (OR = 1.1; 95% CI, 0.82–1.5) and the prospective study (1.6; 0.43–14.8). [The paper gives 1.48 as the upper confidence limit, which must be a typographical error.] The author noted that the retrospective study involved large numbers and crude information on exposure, while the prospective study involved small numbers but good information on exposure.

4.5.1.2 Neurodegenerative diseases

Alzheimer disease is a progressive, irreversible degenerative disease of the brain that presents as dementia, usually in people over the age of 65. The diagnosis includes symptoms of dementia (e.g. loss of memory and mental and cognitive functions) and excludes other causes such as Parkinson disease, head trauma, alcoholism, and stroke (vascular dementia). Alzheimer disease is biologically distinct from other dementias, but its characteristic form of brain degeneration is seen only at autopsy. Alzheimer disease is the commonest form of dementia: e.g. of the 77 cases of dementia studied by Feychting *et al.* (Feychting *et al.*, 1998), 71.4% were diagnosed as Alzheimer disease, 15.6% as vascular dementia, 10.4% as other forms, and 2.6% as unspecified dementia. Two hypotheses have been advanced with regard to the effect of EMF on dementia. Sobel and Davanipour (Sobel & Davanipour, 1996) proposed that EMF contributes to the neurodegenerative processes behind Alzheimer disease, while Feychting *et al.* (Feychting *et al.*, 1998) hypothesized that the brain damage caused by EMF could increase the risks for all forms of dementia. EMF as a risk factor for Alzheimer disease or all dementias has been the subject of six studies (Table 4.37).

Sobel *et al.* (Sobel *et al.*, 1995) used three case-control sets to study ‘sporadic’ Alzheimer disease, i.e., patients who had no first-degree relatives with the disease. The cases were diagnosed at hospitals and university clinics in Finland (53 in 1982-85 and 198 in 1977-78) and southern California (136 in 1982-83). For the older Finnish series, the diagnostic

criteria were different than those used in California and for the other Finnish series (those of the National Institute of Neurologic and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; NINCDS-ADRDA), and the agreement between the clinical diagnosis and autopsy results in a sample of cases was only 82%, in comparison with 90-98% in the other series. In the first Finnish series and the California series cases with familial disease were eliminated by questioning next-of-kin about Alzheimer disease among relatives. The controls were patients with sporadic vascular dementia in the first Finnish series, hospital patients with not neurological disease in the second series, and neighborhood volunteers who were neurologically normal in the California series. Information on the primary lifetime occupation was obtained by interviewing a proxy respondent for demented subjects and by direct interview for healthy controls. High, medium, or low exposure to ELF magnetic fields was attributed to each job by an industrial hygienist. Since the commonest occupation with medium-to-high exposure in this population were seamstresses and tailors, magnetic fields were measured around a sample of industrial and home sewing machines; the average spot measurement was 1.93 μ T. [To judge the quality of these exposure assessment, the occupation judged to involve medium-to-high exposure was compared in Table 2.4 with measured TWAs; 87% are above the 540th percentile for men, excluding occupations for which these were no measurements.]

A significant association was found in women with exposure to medium-to-high magnetic fields (OR = 3.9; 95% CI, 1.7-8.9) and for the men and women combined (2.9; 1.6-5.4). Despite the different composition of the three case-control series, elevated risks were found consistently, except among men in the series in which people with vascular dementia were used as controls (0.7; 0.1-8.9) with one exposed case). [The limitations of the study are use of different control groups in the three series, particularly patients with vascular dementia who may in fact have had Alzheimer disease; obtaining job histories by questionnaires; lack of validation of exposure of the study population; dependence on proxy respondents for job histories for cases but not for some of the control; and failure to take into account potential confounding by heredity. These limitations make interpretation of the results problematic.]

Sobel *et al.* (Sobel *et al.*, 1996) used a similar study design for a new case-control series drawn from an Alzheimer disease clinic in California. The cases were dementia or probably Alzheimer disease diagnoses in 86 men and 240 women at the clinic [period unspecified] by the criteria of the NINCDS-ADRDA. The controls were 76 male and 76 female patients at the clinic in whom other dementias (excluding vascular dementia and mixed diagnoses) were diagnosed. In a departure from the method of Sobel *et al.* (Sobel *et al.*, 1995), subjects under the age of 65 were excluded from the analysis, but those reporting a family history of Alzheimer disease were included because the reports could not be verified. Information on primary occupation and education was available from clinical records. Work with sewing machines was again prevalent among cases. High, medium, or low exposure to ELF magnetic fields were attributed to each of these jobs following the classification used in the previous study. The high and medium exposure categories were combined into a single category for the analyses. Odds ratios were

adjusted for education (an apparent risk factor), gender, and age of onset (possible confounders) by logistic regression. An association with magnetic fields was noted, which was significant in men, but not in women: the odds ratios were, respectively, 4.9 (1.3-7.9) and 3.4 (0.76-16) for men and women. [The odds ratios in this study were higher for men than for women, contrary to what had been observed in the previous study. The limitations of this study were that the cases included 24 patients with unclear diagnoses; the controls were not matched by age or gender to the cases and were from the same clinic, which specialized in Alzheimer disease; job histories were obtained by questionnaire; and the exposure of the study population was not validated. The different designs used in this study and in the three other studies of Sobel *et al.* lead to a diverse collection of relative risks and potential biases that make interpretation of these results very difficult.]

Feychting *et al.* (Feychting *et al.*, 1998) examined exposure to magnetic fields in the population of a study of dementia in Swedish twins (Gatz *et al.*, 1997) in which twins in the Swedish registry were screened for dementia by a complete clinical work-up including neurological and neuropsychological assessments and neuro-imaging (81% response rate); the diagnoses followed the criteria of the NINCDS-ADRDA but were not confirmed by autopsy. All 77 cases in this study were dementia, and 71% (55) were Alzheimer disease. When both twins were demented, one of them was selected randomly to be a case in the study. Controls were twins found to be free of dementia at clinical examination. To obtain enough older controls, 14% of the control population was recruited from a twin registry population different than that from which the cases were derived. Two independent control groups of 228 and 238 subjects, respectively, were formed so that sibling twins could be assigned to different groups, eliminating double representation of the same genes among the controls. Complete histories of jobs and exposure in the workplace were obtained by structured interviews with controls and people who knew the case patients. For the job held the longest and the job held last, TWA magnetic field magnitudes were assigned from a JEM based on full-shift TWA magnetic field magnitudes were assigned from a JEM based on full-shift measurements (Floderus *et al.*, 1994). Risk estimates were adjusted for age at onset, education, and birth date.

A significant association was found between all dementias and exposure to TWA magnetic fields $> 0.2 \mu\text{T}$ in the job held last (OR, 1.6; 95% CI, 0.6–4.0 for TWA 0.12–0.19 μT and 3.3; 1.3–8.6 for $> 0.20 \mu\text{T}$, compared with $< 0.12 \mu\text{T}$). The association was smaller and not significant when the primary occupation was considered. The association between Alzheimer disease and exposure to TWA magnetic fields $> 0.2 \mu\text{T}$ in the job held last was also increased but not significantly so (2.4; 0.8–6.9). When the disease was diagnosed in the patient before the age of 75, significant relative risks were found between exposure to TWA magnetic fields $> 0.2 \mu\text{T}$ and all forms of dementia combined (5.8; 1.4–24) and with Alzheimer disease alone (5.0; 1.1–21). The risks reportedly increased further when fewer than 10 years had elapsed between the last job and disease onset. The relative risks for a small number of non-Alzheimer dementia cases are also elevated. [The limitations are the small number of cases, particularly of Alzheimer disease; possible selection bias due to twins who refused to be examined; potential information biases in

the job histories, which were obtained for cases from proxy respondents; lack of autopsy confirmation of the diagnosis of Alzheimer disease; and failure to evaluate potential confounding by heredity.]

Johansen and Olsen conducted a cohort mortality study of neurological disorders among electrical utility workers, using a JEM based on expert judgments from magnetic field measurements (Johansen, 1998). The study design is similar to that of their cancer cohort study, reviewed in section 4.2.1.1 (Johansen & Olsen, 1998). Only four deaths due to senile dementia were found, and the SMRs were not elevated at any level of exposure to magnetic fields. [The major limitations of this study are the use of death certificates to assess dementia, which is often not the immediate cause of death; failure to take into account potential confounding by heredity; and the very small number of cases.]

Savitz *et al.* also studied mortality from neurodegenerative disease and exposure to magnetic fields in the cohort of men working at five US electric utilities (described in section 4.2.1.1) (Savitz *et al.*, 1998a). The cohort was followed from mortality in 1950-88. These were 24 cases of Alzheimer disease, 45 of Parkinson disease, and 28 of amyotrophic lateral sclerosis (ALS) listed on death certificates as either the underlying or secondary cause of death. The magnitudes of cumulative exposures to TWA magnetic fields were calculated for five durations (total career, ≥ 2 , 2-10, 10-20, and ≥ 20 years) from job histories and a JEM based on full-shift measurements taken for the previous study. Mortality rate ratios relative to the cohort were computed of the five exposure categories by Poisson regression with adjustment for age, decade of death, race, social class, retirement status, and exposure to solvents.

For Alzheimer disease, a non-significant association with career exposure was noted, with relative risks of 1.4 (0.4-5.3) for 0.54-1.13 μT -years, 1.8 (0.5-6.7) for 1.13-2.06 μT -years, and 2.0 (0.6-7.0) for 2.06-4.75 μT -years. The risk was highest for the highest exposure category (2.7; 0.8-8.9) for exposures received ≥ 20 years previously. No increase in risk or exposure-response relationship was apparent for Parkinson disease. [The major limitations of this study are the use of death certificate to assess outcome, particularly since Alzheimer disease is difficult to diagnose and is often underreported on death certificates; the failure to take into account potential confounding by heredity; and the very small number of cases.]

Savitz *et al.* considered mortality rates from neurodegenerative disease among working-age men in 25 states in the USA, using death certificates from National Center for Health Statistics (Savitz *et al.*, 1998b). Over the period 1985-91, 1,768,411 death certificates met the inclusion criteria. The underlying cause of death was Alzheimer disease for 256 subjects, Parkinson disease for 168, and ALS for 114. For each case, three controls who had died of other causes were selected by frequency matching on cases' age and year of death. A subject was considered to have been exposed if the job on his death certificate was one of 14 electrical occupations. [As shown in Table 2.4, 71% of these electrical occupations involve exposure to TWA magnetic fields above the 50th percentile for male workers.] Internally standardized mortality odds ratios for the electrical occupations were

calculated by logistic regression with adjustment for age, year of death, social class, and race.

The relative risk for Alzheimer disease for men in all electrical occupations was weak but significantly elevated (1.2; 1.0-1.4), mainly due to an excess of deaths in men over 65 (1.2; .1-1.4). No association between electrical occupations and Parkinson disease was observed (1.1; 0.9-1.2). [As in the two previous studies, the use of death certificates for diagnosis of Alzheimer disease is a limitation as is failure to take into account confounding by heredity and the absence of validation of exposure in the study population; see also section 4.2.1.1 for comments on limitations of this study.]

(b) Amyotrophic lateral sclerosis and other motor neuron diseases.

Motor neuron diseases are progressive degenerative diseases that are invariably fatal. The most common form is ALS; others are progressive bulbar palsy and progressive muscular atrophy, which differ in the location of the symptoms. ALS and motor neuron diseases as a whole in relation to occupational exposure to EMF have been studied epidemiologically (Table 4.38).

Deapen and Henderson (Deapen & Henderson, 1986) conducted a case-control study of ALS with an *a priori* hypothesis that the cause is electrical shocks. Their 678 cases had voluntarily registered with the Amyotrophic Lateral Sclerosis Society in 1977-79 and had filled out a mailed questionnaire. The names of the 518 controls of the same gender and age were solicited from the patients [no criteria given]. All 518 case-control pairs completed questionnaires about job histories, genetic factors, electric shocks resulting in unconsciousness, and other exposure. Nineteen cases and five controls reported electrical occupations. Odds ratios were determined by a matched analysis for all risk factors, including a group of 19 electrically related occupation-industry combinations. [As indicated in Table 2.4, 71% of the electrical occupations in this paper involve exposure to TWA magnetic fields above the 50th percentile for male workers.] The relative risks were significant for both electrical occupations (3.8; 1.4-13) and shocks (2.8; 1.0-9.9), but the number of exposed cases was small. [Limitations of this study are that exposure to EMF was assessed from job titles based on responses to the questionnaire, failure to report the criteria for control selection, and the potential recall bias inherent in using occupational histories and reports of electric shock.]

Davanipour *et al.* (Davanipour *et al.*, 1997) conducted a case-control study involving 28 patients at an ALS clinic. The cases were diagnosed ALS with no history of polio or ALS apparent in the family. The controls were one blood relative and one non-blood relative (except spouses), if they existed and were willing to participate, matched on age and gender when possible. In total, 28 controls were recruited, but eight cases had no control. Occupational histories were obtained by interviewing the subjects. For each job, exposure to magnetic fields was judged to be high, medium, or low by an industrial hygienist with experience in measuring EMF but blinded to the disease status of the person. [As shown

in table 2.4, 75% of the occupations judged to involved medium-to-high exposure were those in which the TWA magnetic fields were above the 50th percentile for male workers.] Scores for cumulative exposure to magnetic fields were calculated for each subject's working life. In the highest exposure category, the odds ratios adjusted for gender were 2.5 (0.80-6.6) for all subjects and 7.5 (1.4-38) for subjects with ≥ 20 years' work experience. Logistic regression analysis revealed a statistically significant exposure-response relationship for workers with ≥ 20 years' experience ($p < 0.02$) but not for all subjects. [The study is limited by the small sample size and potential control selection bias.]

Johansen and Olsen (Johansen & Olsen, 1998) conducted a cohort study of mortality among electrical utility workers, using a JEM based on expert judgment from magnetic field measurements. Details of the study design are described in section 4.2.1.2. There were 14 deaths from ALS. The risks for this condition appeared to increase across exposure categories (SMR = 2.8 for TWA magnetic fields $> 1.0 \mu\text{T}$) but are too imprecise to be significant. The authors attributed the association between ALS and exposure to magnetic fields to confounding by non-lethal electric shocks. Although they had no data on exposure to shocks to test their hypothesis of confounding, they noted that deaths from electrical accidents correlate with exposure to magnetic fields (SMR = 0 for background vs. SMR = 31 for fields $> 1.0 \mu\text{T}$; $p < 0.05$). [The very small number of ALS cases and the absence of confidence intervals make these results difficult to interpret; diagnosis of ALS from death certificates has a 5–10% error rate; and family histories of ALS were not assessed.]

Savitz *et al.* included ALS in their cohort study of mortality from neurodegenerative disease and exposure to magnetic fields (see above) (Savitz *et al.*, 1998a). No association was seen between total career exposure and mention of ALS as a cause of death (28 cases), but a non-significant increase was seen for exposure in the highest category for ≥ 20 years (RR = 2.4; 95% CI, 0.7–8.0). [Limitations of this study are the modest number of ALS cases, diagnosis from death certificates, and the absence of data on electric shocks or the family's disease history.]

Savitz *et al.* examined ALS in their study of mortality from neurodegenerative diseases in US working-age men (see above) (Savitz *et al.*, 1998b). There were 114 deaths from ALS. The mortality odds ratio for this disease category was slightly elevated for electrical occupations (1.3; 1.1–1.6). [The diagnosis of ALS from death certificates in this study was based on ICD9, which groups ALS with other motor neuron diseases. Other limitations of this study include the fact that only one occupation was taken from death certificates and the absence of data on important confounders, such as familial neurodegenerative disease or exposure to electric shocks.]

4.5.1.3 Suicide and depression

As depression is a proven risk factor for suicide, the sparse literature on these two outcomes and occupational exposure to EMF are reviewed together (Table 4.39). In the best papers, exposure was assessed on the basis of job titles for depression and JEMs for suicide. A study of suicide based on job titles (Baris & Armstrong, 1990) was not reviewed. Wilson (Wilson *et al.*, 1998) hypothesized that EMF could contribute to depression by an effect on melatonin, but this mechanism has no corollary for epidemiological studies.

Savitz *et al.* studied depression and exposure to EMF in a cohort of US Army veterans who had been examined in the Vietnam Experience Study (Savitz *et al.*, 1994). In this study, a sample of male veterans whose service had started in 1965–71 and lasted for a single term underwent medical and psychological examinations (52% participation rate). The population of the study of EMF was 4044 men who were employed at the time of the examination. They were asked in an interview about the job held currently, the job held the longest and its duration, demographic information, and data on potential confounders. At the time of the examination, the 183 exposed subjects had a job belonging to a group of 15 electrical occupations (Table 2.4). Depression was assessed on the basis of the Diagnostic Interview Schedule and the Minnesota Multiphasic Personality Inventory. For this study, the results of the former were used to test for three diagnoses of depression and eight symptoms; and the latter gave eight indicators of depression and five symptoms. The risk ratios for these outcomes were adjusted for race, marital status, education, alcohol use, and duration of employment.

Subjects who had held their most recent job for less than 10 years were generally more likely to be depressed. Some non-significant associations were found between electric work and markers of depression (see Table 4.39). Neither electricians nor electrical workers had an increased frequency in thoughts of death (OR = 0.8; 95% CI, 0.3–1.8). [Some of the elevated risks could be due to chance, given the many outcomes analyzed. Other problems are the very small number of exposed cases, exposure assessment based on job title, and the difficulty in generalizing results for Army veterans, especially with the low participation rate.]

Baris *et al.* (Baris *et al.*, 1996a) examined suicide in a case–cohort study of the Hydro Québec workers who had been studied by Thériault *et al.* Deaths in the cohort were tracked over 18 years through company records for current employees, pension records for retirees, and Québec death certificates for former employees. Forty-nine suicides were found on the death certificates. The reference group was a 1% sample of the entire cohort ($n = 217$). Exposures were assessed from JEMs for electric fields, magnetic fields, and PEMF as described above (Armstrong *et al.*, 1994; Thériault *et al.*, 1994). The TWA and the GM over the shift were used as exposure metrics for EMF, while the TWA was the only metric for PEMF. For each employee, both cumulative and current exposures were calculated from the company's job records and JEMs for these five metrics. The company's records from periods before employment of the subject and annual medical

examinations was examined for information on alcohol consumption and changes in marital status. The cohort's sick-leave records were scanned for any diagnoses of mental illness, which was a strong risk factor for suicide in this population (RR = 15; 95% CI, 6.8–34).

The results showed no significant association with cumulative or current TWA exposure to magnetic fields (OR = 1.6; 0.69–3.8 for TWA \geq 0.37 μ T). Of the 10 types of exposure analyzed, only cumulative GM electric fields in the intermediate category were associated with a significant suicide rate (3.1; 1.9–8.2), but the risks declined with greater exposure, making a causal relationship less likely. In addition, the association with intermediate electric fields decreased somewhat after adjustment for previous mental disorders (2.8; 0.93–8.1). According to the authors, mental illness could be either an intermediate variable, if depression were caused by EMF, or a confounder, if psychological disorders predispose workers toward jobs with high or low exposure to EMF. The hypothesis that mental illness is an intermediate variable receives some support from the finding of a decrease in suicide risk after adjustment for mental disorders. Support for the hypothesis that it is a confounder is provided by the finding that 70.2% of the 20 cohort members with absences for mental illness had had geometric mean exposure to electric fields above the 50th percentile. The authors noted that their study did not have the complex design needed to distinguish a confounding from an intermediate variable. [For former employees of Hydro Québec, minor errors may have been introduced owing to lack of information on suicides occurring outside the Province. Data on confounders of suicide, such as alcohol use, are difficult to obtain accurately from company records. Moreover, the analysis of 10 exposure measures may have generated associations by chance.].

Johansen and Olsen (Johansen & Olsen, 1998) also examined suicides and exposure to magnetic fields in the cohort study described in section 4.2.1.2. A slight nonsignificant increase in the relative risk for suicide (OR = 1.4) was reported for exposure to TWA magnetic fields estimated to be $>$ 1.0 μ T.

4.5.1.4 Cardiovascular disease

For a cohort of Hydro Québec workers included by Thériault *et al.* (see section 4.2.1.1) (Thériault *et al.*, 1994), Baris *et al.* (Baris *et al.*, 1996b) reported a significant decrease in the SMR for death reported on death certificates as due to 'circulatory diseases' among workers exposed to $>$ 1.6 μ T when compared with workers with lower exposure (based on 217 deaths). [The grouping 'circulatory disease' might be too broad, and the 1.6 μ T cut-point might not include groups with sufficiently high exposure.]

Savitz *et al.* (Savitz *et al.*, 1998c) reported the results of an analysis of mortality from specific types of cardiovascular disease in their study of five utilities (Savitz & Loomis, 1995) (described in section 4.2.1.1) in relation to exposure to magnetic fields. The investigation was motivated by clinical findings that suggested a decrease in heart rate variability in people exposed to 20 μ T 60 Hz magnetic fields. Various categories of causes

of death from heart disease, based on the *International Classification of Diseases*, were combined into four groupings: arrhythmia-related (212 deaths), acute myocardial infarct (4238 deaths), atherosclerosis (142 deaths), and chronic coronary heart disease (2210 deaths). These causes accounted for 88% of all cardiovascular deaths identified in the cohort. The groupings were chosen *a priori* because the underlying pathological lesions of the first two potentially involve disruption of autonomic nervous system control of cardiac function, whereas loss of autonomic nervous system control is not believed to be critical for the second pair. The exposure of a random sample of workers in 28 occupational categories was measured over 2842 full shifts with an AMEX 3D meter. In all of the analyses, adjustment was made for age, calendar year, race, social class, and work status (active versus inactive).

As predicted, no association was found between total exposure to magnetic fields and the risk for atherosclerosis or chronic coronary heart disease (see Table 4.40). The relative risks for myocardial infarct were consistently and statistically significantly increased in each category of total exposure: 1.1 (1.0–1.3) for cumulative exposure of $0.4 \leq 1.2 \mu\text{T-years}$, 1.2 (1.1–1.3) for $1.2 \leq 2.0 \mu\text{T-years}$, 1.4 (1.2–1.5) for $2.0 \leq 4.3 \mu\text{T-years}$, and 1.6 (1.5–1.8) for $3 \text{--} 4.3 \mu\text{T-years}$. Significant increases were also seen for each category of exposure more than 5, 10, and 20 years previously, while significant decreases were seen for people in the highest exposure categories during the previous five years. In addition, the increased relative risks showed a statistically significant dose–response trend. Arrhythmia-related diseases were related similarly but less consistently to cumulative exposure. Although no direct information on known risk factors was available, the authors argued that it is unlikely that smoking and other lifestyle factors were important confounders, since no association was seen between exposure to magnetic fields and death from atherosclerosis or coronary heart disease. [The analysis of death from cardiovascular disease was an addition to the existing cohort study of cancer, and death certificates were used for the diagnosis of cardiovascular disease. See section 4.1.1.1 for comments on the limitations of the study. It is unclear why significant decreases in risk were observed for myocardial infarct and arrhythmia-related diseases after exposure during the five-year period prior to death, while significant increases were consistently found for exposure at the other times considered.]

4.5.1.5 Summary

Adverse reproductive effects from mother's exposure to EMF

The relationship between spontaneous abortion and exposure to ELF EMF was considered in two studies. In the first (Schnorr *et al.*, 1991), no association with VDT use was observed; however, ‘exposed’ and ‘unexposed’ subjects had similar levels of exposure to ELF fields but different levels of exposure to VLF fields. In the second study, a significant association was seen with exposure to high magnetic and VLF fields; however, the response rate was very poor, particularly among controls.

The association with low birthweight was assessed in two studies (Bracken *et al.*, 1995a; Grajewski *et al.*, 1997), which found no association with either use of VDTs or exposure to magnetic fields.

Intrauterine growth retardation was considered by Bracken *et al.*, who found no association with either use of VDTs or exposure to magnetic fields.

One study addressed the association between preterm birth and use of VDTs (Grajewski *et al.*, 1997). No association was found.

Adverse reproductive effects from the father's exposure to EMF

The effect of paternal exposures to EMF on the frequency of congenital anomalies was considered in one study (Tornqvist, 1998). No increase was seen among the offspring of exposed male workers.

Alzheimer disease

The association between exposure to EMF and Alzheimer disease was considered in five studies. Two of these (Savitz *et al.*, 1998a; Savitz *et al.*, 1998b) are given little weight in the evaluation as they are based on diagnoses from death certificates. In one (Savitz *et al.*, 1998b), no increase in risk was seen for all electrical workers. In the other four studies, risk was considered by intensity of exposure to magnetic fields. Significant associations with intermediate and high intensity magnetic fields were seen in both studies of Sobel *et al.* (Sobel & Davanipour, 1996; Sobel *et al.*, 1995) in specific groups of subjects. The limitations of these studies include the fact that different groups of cases and controls were used, some of the control groups including persons with other types of dementia; and proxy information was used to define the exposure of cases. Feychting *et al.* (Feychting *et al.*, 1998) found a nonsignificantly increased risk for occupational exposure to TWA magnetic fields $> 0.2 \mu\text{T}$. This study, which was based on data for twins, also suffered from a number of limitations. A nonsignificant increase was seen with exposure throughout a working career in the study of Savitz *et al.* (Savitz *et al.*, 1998a), which was based on diagnoses reported on death certificates.

Feychting *et al.* (Feychting *et al.*, 1998) also considered a possible association with all dementia, including Alzheimer disease, and found a significant association with exposure to TWA magnetic fields $> 0.2 \mu\text{T}$. As mentioned above, this study has limitations and the results are therefore difficult to interpret.

Amyotrophic lateral sclerosis

The association between exposure to magnetic fields and amyotrophic lateral sclerosis (ALS) was assessed in three studies. Adequate adjustment could not be made for

confounding by exposure to electric shocks or a family history of ALS. The study of Davanipour *et al.* (Davanipour *et al.*, 1997) showed an increased risk for workers with the highest exposure, which was significant for those with 20 years' or more experience. The study had a limited sample size and potential control selection bias. A nonsignificant increase in the mortality rate from ALS was also seen by Johansen and Olsen (Johansen, 1998), based on a very small number of exposed cases. In the mortality study of Savitz *et al.* (Savitz *et al.*, 1998a), no increase in risk was seen with career exposure, while a nonsignificant increase in risk was seen with exposure 20 years previously. The study was based on diagnoses from death certificates and did not account for potential confounders.

Suicide and depression

One study addressed the risk for depression among electrical workers in a cohort of Viet Nam veterans. A nonsignificantly increased risk was observed for only one of the 24 measures of depression used. Given the small number of cases and the many outcomes analyzed in the study, the finding may be due to chance.

The risk for suicide was considered in two studies. No significant association with exposure to EMF was seen by Johansen and Olsen (Johansen, 1998), while an increased risk was seen with only one of 10 measures of exposure by Baris *et al.* (Baris *et al.*, 1996a).

Cardiovascular disease

Two studies have assessed possible adverse cardiovascular outcomes that may result from exposure to magnetic fields. In the first study (Baris *et al.*, 1996a), a significant decrease in risk in a broadly defined cardiovascular grouping was observed; however, the study had severe limitations.

Savitz *et al.* (Savitz *et al.*, 1998c) examined data from their study of five utilities, motivated *a priori* by a biological hypothesis based on clinical data and the results of human studies *in vivo*, which predicted increased numbers of deaths due to arrhythmia and acute myocardial infarct but no increase in risk for arteriosclerosis and chronic coronary heart disease. Significant, exposure-dependent associations were reported. Although no direct information on potential confounder was available, the authors provided indirect justification that smoking and life-style factors are unlikely to strongly confound the observed association.

Evaluation

There is inadequate evidence that maternal occupational exposure to ELF EMF causes adverse birth outcomes.

[This conclusion was supported by 22 Working Group members; there were 2 votes for ‘lack’ of evidence, 1 abstention, and 4 absent.]

There is inadequate evidence that paternal occupational exposure to ELF EMF causes reproductive effects.

[This conclusion was supported by 20 Working Group members; there were 3 votes for ‘lack’ of evidence, 2 abstentions, and 4 absent.]

There is inadequate evidence that occupational exposure to ELF EMF causes Alzheimer disease.

[This conclusion was supported by 23 Working Group members; there was 1 vote for ‘lack’ of evidence, 1 abstention, and 4 absent.]

There is inadequate evidence that occupational exposure to ELF EMF causes amyotrophic lateral sclerosis.

[This conclusion was supported by 24 Working Group members; there was 1 abstention and 4 absent.]

There is inadequate evidence that occupational exposure to ELF EMF causes suicide or depression.

[This conclusion was supported by 17 Working Group members; there were 6 votes for ‘lack’ of evidence, 2 abstentions, and 4 absent.]

There is inadequate evidence that occupational exposure to ELF EMF causes cardiovascular disease.

[This conclusion was supported by 24 Working Group members; there was 1 abstention and 4 absent.]

4.5.2 Environmental exposure

4.5.2.1 Pregnancy outcome

Wertheimer and Leeper (Wertheimer & Leeper, 1986) investigated the relationship between use of electrically heated water-beds and electric blankets and pregnancy outcome—specifically, length of gestation, birth weight, congenital abnormalities, and fetal loss—in Colorado, USA. The study population consisted of the 1806 (out of 4271)

families in which a birth had occurred in two Denver-area hospitals in 1982, for which a birth announcement had been published. Of these, 1318 (73%) could be reached by telephone for an interview on their use of electrically heated water-beds and electric blankets in the previous eight years. Information was successfully obtained on 1256 births (95% response rate). The Colorado birth records were consulted to obtain more detailed information on these births and on 528 of the 692 other births that had occurred to the same parents from 1976 onwards. The data available from these records included parents' age and education, birth weight, mothers' last menstrual period, parity, reported abnormalities of pregnancy, labor, or fetal development, and date of most recent fetal loss, if any (this included both spontaneous and induced abortions).

Seasonal patterns of occurrence of slow fetal development were observed among users of electric waterbeds and blankets, suggesting that use of these appliances at the time of conception might have had an adverse effect. The proportion of above-median gestational periods was significantly greater for conceptions in September–June than for those in July–August (56% vs. 38%, $p < 0.0005$) and was shown to follow a marked seasonal pattern among users, being high for babies conceived in winter and low in summer; the proportion was approximately constant at about 58% in the period October–April and decreased regularly down to around 40% during May–September [data presented only in graphical form]. No seasonal pattern was observed among non-users of electric blankets and water-beds. The prevalence of birth weight < 2500 g was similar in users and non-users (4.5 and 4.1%, respectively). Owing to a tendency not to announce the births of babies with congenital malformations, these were analyzed only among the 528 sibling births. One of 335 births among non-users (0.3%) and five of 193 among users (2.6%) had congenital defects. The frequency of abortions during the year preceding conception of a live infant was significantly higher ($p < 0.05$) among electric blanket users (7.8%; 24 cases)—but not among water-bed users (6.3%; 28 cases)—than among those who had used neither electric blankets nor water-beds (4.2%; 50 cases). A significant excess of abortions in September–January was noted among users of electric blankets and water-beds. [The ascertainment of pregnancy outcome may have been biased by the fact that the study population was defined on the basis of publication of birth announcements (only 42% of all births at the hospital) and that the sample was further restricted to those who could be located by telephone, who were presumably of higher socioeconomic status than the general population. Further, although efforts were made to exclude induced abortions by studying fetal loss in the year before conception of a live infant, some induced abortions were probably still included; the frequency of these is likely to have varied with socioeconomic status, as does the frequency of use of electric blankets and water-beds. It is also unclear whether the ascertainment of spontaneous fetal loss is complete from birth records. Finally, only recognized fetal losses followed by a live birth are included.]

A population-based case–control study of congenital malformations among children born in the 57 counties in upstate New York and registered in the New York State Congenital Malformation Registry was carried out by Dlugosz *et al.* (Dlugosz *et al.*, 1992). The cases were 224 neural tube defects and oral cleft defects (121 cleft palates and 197 cleft lips) diagnosed among children in 1983–84 and 224 neural tube defects diagnosed in

1983–86. Three controls were randomly selected from birth registration records for each case and individually matched by maternal race, age, home county, month of mother's last menstrual period, and child's gender. Maternal exposure to heated water-beds or electrical blankets one month before to three months after conception was assessed from responses to a questionnaire mailed or administered by telephone. Information on maternal education, prenatal vitamin intake, parity, smoking, high fever during pregnancy, and occupation was also requested. The response rates were 83% for the cases and 77% among controls. No association was found, with or without adjustment for other risk factors, for various measures of exposure to EMF. For use of electric blankets at any time during pregnancy, the adjusted odds ratios were 0.69 (95% CI, 0.25–1.9) for cleft palate, 0.70 (0.36–1.4) for cleft lip, and 0.77 (0.40–1.5) for neural tube defects. For use of waterbeds at any time during pregnancy, the corresponding odds ratios were 0.66 (0.23–1.9), 0.63 (0.33–1.2), and 1.1 (0.59–1.9). No association was seen when different levels of exposures were considered, such as duration of use and heat-control setting. No seasonal pattern of time of conception was observed. [No information was available on patterns of use, such as continual use throughout the night, and other sources of exposure were not collected.]

The association between loss in early pregnancy and domestic exposure to ELF EMF was investigated in a case–control study in Finland (Juutilainen *et al.*, 1993). The study was nested within a cohort study of work and fertility in 443 healthy volunteer women who were trying to become pregnant over the period 1984–86. Each woman in the cohort was followed-up for six months or until she became pregnant. Pregnancy and loss in early pregnancy (defined as pregnancies that ended before they became clinically apparent) were detected by measuring serum human chorionic gonadotropin on the first day of menstruation. All 107 women in this cohort whose first pregnancy resulted in an early loss were sought for inclusion in the study, with a random sample of 122 women with normal pregnancies from the cohort. After exclusion of cases and controls for whom information on exposure to EMF could not be obtained (refusals, address not found or incomplete), 89 cases and 102 controls remained for analysis. Magnetic field intensity was measured in the residences of the women at the time they participated in the study of work and fertility. Measurements were made at the front door of each residence and, for 48% of case and 57% of control residences, in the living-room, the kitchen, and the parents' bedroom, with a self-constructed magnetic field meter with a small ferrite-core measuring coil similar to that used by Juutilainen and Saali (Juutilainen & Saali, 1986b). Occupational exposure to EMF was assessed on the basis of job classification and some measurements. Odds ratios were calculated by the Mantel-Haenszel procedure, with adjustment for mother's smoking, age, and type of dwelling; separate analyses were carried out for front-door measurements, average magnetic field in the home, and maximum field. When the analyses were based on exposure in three categories, elevated odds ratios were observed for the highest group versus the lowest: front door, $> 0.126 \mu\text{T}$ vs. $< 0.63 \mu\text{T}$ (OR = 5.1; 95% CI, 1.0–26); average field strength, $\geq 0.252 \mu\text{T}$ vs. $< 0.63 \mu\text{T}$ (4.6; 0.9–25); maximum field, $\geq 0.63 \mu\text{T}$ vs. $< 0.126 \mu\text{T}$ (2.7; 0.6–12), but intermediate groups did not have a higher risk than baseline. For dichotomous exposure classification, only average magnetic field strengths was associated with loss in early pregnancy (5.4; 1.1–28 for ≥ 0.252 vs. $< 0.252 \mu\text{T}$) The authors concluded that their

results suggest a causal association, possibly with a non-linear dose–response relationship. [Measurements inside houses were available for only a small proportion of subjects.]

Bracken *et al.* (Bracken *et al.*, 1995a) carried out a prospective study of pregnancy outcome in 3591 pregnant women living in the New Haven, Connecticut, area and receiving prenatal care from 11 private obstetrical practices and two health maintenance organizations in the period 1988–91. The outcomes considered were intrauterine growth retardation (being in the lowest tenth percentile of birth weight for each week of gestational age), low birth-weight prevalence, birth weight, and gestational age. Information on pregnancy outcome was obtained from the records of the health facilities. Women were asked in a questionnaire interview to provide information on their frequency and duration of use of electric blankets and water-beds and also on the type and temperature setting. Electric-blanket field strength was estimated in temperature-controlled chambers on the basis of data about several blankets at selected chamber temperatures and blanket settings. Other information collected during the interview included age, race, marital status, education, religion, medical history, contraceptive use, smoking, job title, drug use, alcohol and caffeine consumption, and exercise. The participation rate was 82.6%: thus, information was available on 2967 women.

A nested study design was used to monitor exposure at various stages of pregnancy by both direct and indirect methods. Women who reported use of electrically heated beds and a random sample of non-users were placed in an intensively monitored group for subsequent monitoring at approximately 20 (446 women), 28 (431 women), or 36 (427 women) weeks of gestation. The entire monitoring protocol was completed by 307, 281, and 261 women, respectively (compliance was higher among electric bed users than among non-users: 70.8 vs. 62.7%). The monitoring program included seven-day personal exposure assessment with AMEX-2 personal monitors; 24-h measurements of EMF in the center of a room [not otherwise specified] with EMDEX meters; duty cycle measurements of water-beds (i.e. proportion of time the bed's heating elements were switched on); and wire coding of residences (up to four for women with more than one residence). The wire coding was evaluated by the approach of Wertheimer and Leeper; however, as the thickness of the wires could not be assessed because of insulation, electric utility company circuit maps were consulted to determine actual wire gauges.

None of the measures of exposure was significantly associated with any of the adverse outcomes considered. There was no suggestion of an effect of use or heat setting of electrically heated beds at the time of conception or during the first four or the last three months of pregnancy on birth weight, low birth-weight rate (< 2500 g), or intrauterine growth retardation. The results were similar with use of wire codes and of directly measured exposures in the monitored sub-sample.

Belanger *et al.* (Belanger *et al.*, 1998) reported on the 135 spontaneous abortions that occurred in the same cohort between 7 and 25 weeks. No significant association was found between the incidence of spontaneous abortion and any measure of exposure to

EMF. For blanket use at the time of conception, the odds ratio, adjusted for ethnicity, gestational age at interview, maternal age, and caffeine consumption, was 1.7 (95% CI, 0.96–3.2); no association, however, was seen for daily rather than less frequent use. Logistic regression analyses for duration of exposure (hours of use per day) and intensity of exposure showed a slight increase in the risk for spontaneous abortion with increasing duration and intensity of use. The small numbers of exposed cases, however, precluded a conclusive interpretation of these results. The odds ratio for water-bed use was 0.59 (95% CI, 0.33–1.1); no association was found with frequency, duration, or intensity of use. Although strong associations were observed with several other risk factors such as intrauterine growth retardation and marital status, ethnicity, education, reproductive history, and smoking, these did not have a confounding effect. [Ascertainment of loss in early pregnancy was not complete, as only 14% of the cohort was interviewed before 10 weeks of gestation. Spontaneous abortion was assessed by interview.]

Li *et al.* (Li *et al.*, 1995) studied electric blanket use during pregnancy in relation to the risk for congenital urinary tract anomalies in a case–control study in Washington State, USA. The cases were identified from the Washington State Birth Defects Registry over the period 1990–91, and 118 cases with no chromosomal abnormalities and 369 controls, consisting of births randomly selected from all single live infants delivered in five hospitals of King County in the study period, were included. Questionnaire interviews were completed with 62.6% of the case mothers and 67.6% of control mothers. Information was collected on history of reproduction, contraceptive use, smoking, alcohol consumption, and other substances [not specified]. The hypothesis was that any effect on fetal development of exposure to EMF during pregnancy might be more pronounced in susceptible subpopulations, such as women with a history of subfertility.

No association was observed between the incidence of congenital urinary tract anomalies and use of water-beds or blankets during the entire pregnancy or the first trimester. Elevated risks associated with electric blanket use were found among subfertile women, although this finding was based on few exposed cases (OR = 4.4; 95% CI, 0.9–22; 5 cases during the entire pregnancy; OR = 10; 95% CI, 1.2–85; 3 cases during the first trimester). The risk also appeared to increase with increasing duration of use of electric blankets. No association was found with use of water-beds or VDTs during the entire pregnancy or the first trimester. Recall bias might have influenced the results owing to media attention, but the association was observed only in subfertile women. No information on other sources of exposure to EMF was available. The authors hypothesized that hormonal disturbances caused by EMF (estrogen and progesterone production is affected by melatonin) could explain the findings. [The definition of subfertility as no pregnancy after unprotected intercourse for a year is inadequate, and applied to 23% of the study population. The finding in ‘subfertile’ women is hypothesis generating.]

4.5.2.2 Neurodegenerative diseases and neurobiological disorders

No studies have addressed residential exposure to EMF and the risk for neurodegenerative diseases. In two studies ‘electric shock’ was mentioned as a risk factor for ALS (Gallagher & Sanders, 1987; Savettieri *et al.*, 1991).

4.5.2.3 Summary

Pregnancy outcome

The risk for congenital anomalies in relation to use of heated water-beds and electric blankets by the mother around the time of conception was evaluated in one study in the USA, in which no association was observed.

Pregnancy loss was investigated in two cohort studies. Early pregnancy loss was studied in one study in Finland, in which an increased risk was observed in the highest but not the intermediate category of exposure to magnetic fields. Pregnancy loss toward the end of the first trimester or later was studied in the USA; an elevated risk was found among users of electric blankets but not among users of water-beds.

In the same study in the USA, intrauterine growth retardation was assessed in a cohort of pregnant women. No association with residential exposure to EMF was found on the basis of a variety of measures, including use of electric blankets or water-beds and wire coding.

Depression

Two studies have addressed depression in relation to exposure to EMF from transmission lines. In the study in the USA, depressive symptoms were not related to measures of magnetic fields taken at the door of the subject’s residence. In the Finnish study, an increased risk for severe depression was observed among subjects with higher calculated exposures. This observation was based, however, on only four cases with unconfirmed diagnoses and relatively low exposures ($\geq 0.17 \mu\text{T}$).

There is inadequate evidence that environmental exposure to ELF EMF has adverse effects on pregnancy outcome or is associated with depression.

[This conclusion was supported by 23 Working Group members; there was 1 vote for ‘no evidence’, 1 abstention, and 4 absent.]

Table 4.36 Adverse pregnancy outcomes and maternal exposure to EMF

Reference; country	Study population	Exposure classification	No. OR (95% CI) of cases	Comments
(Schnorr <i>et al.</i> , 1991); USA	From a cohort of telephone operators, 2705 directory assistance operators using VDTs were compared with 2839 general operators using light-emitting diode or neon glow tube units.	VDT use > 25 h/week in first trimester in first 28 weeks	Spontaneous abortion 169 1.0 (0.6-1.6) 179 0.9 (0.6-1.5)	OR adjusted for smoking, thyroid disorders, alcohol consumption, and previous spontaneous abortions. EMF measured on a sample of VDTs and other monitors.
(Lindbohm <i>et al.</i> , 1992); Finland	Cohort of women 20-35 weeks of age in various Finnish companies, mainly banking and clerical work. Pregnancy information from nationwide database. 191 spontaneous abortions treated in hospitals. 394 controls were mothers of normal children matched for year of conception.	ELF magnetic field from VDT 0.11-0.24 $\mu\text{T rms}^a$ > 0.24 $\mu\text{T rms}$ Cumulative ELF fields per week medium high VLF magnetic field from VDT 5-30 $\mu\text{T/s}$ > 30 $\mu\text{T/s}$ Cumulative VLF fields per week medium high	Spontaneous abortion 19 1.9 (0.9-3.9) 20 3.4 (1.4-8.6) 17 1.7 (0.8-3.6) 22 3.8 (1.6-8.8) 7 0.8 (0.3-2.4) 25 1.6 (0.8-3.4) 29 1.2 (0.6-2.4) 21 2.7 (1.2-6.1)	OR adjusted for h/week of VDT use, work load, solvent exposure, number of previous births, previous spontaneous abortions, IUD use, and frequency of ADP equipment breakdowns. Magnetic field exposure measured in lab on VDT models reportedly used by subjects. To convert the peak-to-peak magnitudes for ELF fields to root-mean-square (rms) magnitudes, a conversion factor = 0.266 was derived from VDT measurements reported by Jokela <i>et al.</i> (Jokela <i>et al.</i> , 1989).
(Bracken <i>et al.</i> , 1995a); Connecticut (USA)	Women receiving care at 13 New Haven area obstetrics practices and HMOs. About 2550 women in the study (not all women completed all questions) and 1304 were monitored for EMF exposure.	VDT use < 20 h \geq 20 h TWA magnetic field per week 0.1-0.19 μT \geq 0.2 μT VDT use < 20 h \geq 20 h TWA magnetic field per week 0.1-0.19 μT \geq 0.2 μT	Low birth weight 835 0.5 (0.3-0.8) 424 0.6 (0.3-1.1) 122 0.7 (0.2-2.9) 58 1.4 (0.3-6.1) Intrauterine growth retardation 835 0.9 (0.6-1.3) 424 1.2 (0.8-1.8) 122 0.4 (0.1-1.2) 58 1.2 (0.4-3.1)	OR adjusted for maternal religion, race, height, gravidity, age work in pregnancy, third trimester smoking, and caffeine consumption. Primary interest was in exposure to electric bed heaters, but VDT use determined by questionnaire. Women who reported using electric bed heaters monitored with personal AMEX meters.

Table 4.36 (continued)

Reference; country	Study population	Exposure classification	No. OR (95% CI) of cases	Comments
(Grajewski <i>et al.</i> , 1997); Southeastern US	Cohort of 284 married pregnant telephone operators using VDTs and 363 unexposed operators serving as controls (same as Schnorr <i>et al.</i> , 1991)	Any VDT exposure	Preterm births 24 0.7 (0.4-1.1)	OR adjusted for race, parity, gravidity, alcohol, smoking, gestational age, previous problem pregnancies, diabetes, thyroid conditions, diuretics, pre-eclampsia, toxemia, and intra-pregnancy interval.
		VDT exposure	Reduced birthweight 303 0.9 (0.5-1.7)	
		1-25 h/week	116 0.4 (0.1-1.0)	
		≥ 25 h/week	120 1.4 (0.7-3.1)	

^a OR, odds ratio; CI, confidence interval; VDT, visual display terminal; ELF, extremely low frequency; IUD, intrauterine device; ADP, automatic data processing; VLF, very low frequency; HMO, health maintenance organization

Table 4.37 Alzheimer disease and dementia in association with exposure to EMF

Reference; type of study; country	Study population	Exposure classification	No. of cases	RR (95% CI)	Comments		
(Sobel <i>et al.</i> , 1995); case-control; Finland and California (USA)	Two case series with sporadic Alzheimer disease, i.e. no cases in family (n=53 and 136), and one series with both sporadic and familial forms of the disease (n=198). Controls had vascular dementia for one sporadic disease series (n=70) or were normal neighborhood subjects for the other (n=299); the series with both forms of Alzheimer disease had hospital controls with no neurological symptoms (n=106).	Medium / high magnetic fields	Sporadic Alzheimer disease		OR adjusted for age at onset, education, and social class. Exposures estimated by industrial hygienist for the reported primary occupation.		
		Males	Controls with vascular dementia	1	0.7 (0.1-8.9)	First series had 90% agreement between clinical and autopsy diagnosis, and the second series had 98% agreement. The third series involved an older diagnosis scheme and had 82% agreement.	
		Females		5	10.2 (1.1-95.3)		
		Males	normal neighborhood controls	5	1.7 (0.3-10.3)		
		Females		6	3.7 (0.4-33.6)		
		Males	All Alzheimer disease Hospital controls without dementia	7	2.7 (0.7-9.8)		
		Females		12	3.5 (1.3-9.6)		
Both sexes	All risks combined	36	2.9 (1.6-5.4)				
(Sobel <i>et al.</i> , 1996); Case-control; California (USA)	326 clinic-based Alzheimer disease patients. 152 controls were cognitively impaired patients at the same clinic (excluding vascular dementia).	Medium / high magnetic fields	All Alzheimer disease controls with non-vascular dementia		OR adjusted for age of onset, education, and gender. Exposure estimated by expert judgment from occupational history.		
		Males		15		4.9 (1.3-7.9)	
		Females		24		3.4 (0.8-16.0)	
		Both sexes		39		3.9 (1.5-10.6)	
(Feychting <i>et al.</i> , 1998); Case-control; Sweden	77 dementia cases (including 55 with Alzheimer disease) identified in Swedish twin study. Controls use twins without dementia. 2 control groups (228 and 238 subjects) formed to keep only one member of a twin pair in each group	TWA magnetic fields	Dementia control group 1		OR adjusted for age of onset, education, and birth date. Exposure based on JEM constructed from occupational magnetic field measurements made 1988-92.		
		Primary occupation		16		1.1 (0.4-2.6)	
		0.12-0.19 μ T		14	1.5 (0.6-4.0)	Results for control group 2 are similar, e.g. dementia OR = 3.8 (1.4-10.2) for last job's TWA > 0.2 μ T.	
		> 0.2 μ T	Last occupation		16		1.6 (0.6-4.0)
		0.12-0.19 μ T		19	3.3 (1.3-8.6)		
		> 0.2 μ T	Last occupation		9		1.0 (0.4-2.9)
0.12-0.19 μ T		12	2.4 (0.8-6.9)				
> 0.2 μ T							

Table 4.37 (continued)

Reference; type of study; country	Study population	Exposure classification	No. of cases	RR (95% CI)	Comments
(Johansen & Olsen, 1998); Cohort study; Denmark	Cohort of male employees of 99 Danish utility companies, 21236 total, 3540 deaths	TWA magnetic fields low exposure 0.1-0.25 μ T medium 0.3-9.99 μ T high > 1.0 μ T	Senile dementia 1 2 1	0.4 (NS) 0.8 (NS) 0.6 (NS)	SMR adjusted for age, education, and birth date. Magnetic fields in subject's first job from a JEM based on expert judgment and 24-h measurements.
(Savitz <i>et al.</i> , 1998a); Cohort; USA	138905 men employed in 5 electric utilities followed for mortality 1950-86. 20068 deaths; 24 deaths for which Alzheimer disease was mentioned as an underlying cause of death and 56 for which it was mentioned as cause of death.	Cumulative magnetic fields Total career exposure Highest category (2-4.7 μ T-year) Exposure-response (RR / μ T-year) Exposure \geq 20+ year in past highest category (2.3-14.5 μ T-year) Exposure-response (RR / μ T-year)	Alzheimer disease Underlying cause of death 9 24 8 24	2.0 (0.6-7.0) 1.1 (0.9-1.2) 2.7 (0.8-8.9) 1.1 (0.9-1.3)	SMR adjusted for age, decade of death, race, class, retirement status, and solvent exposure. Magnetic field exposure based on company job records and JEM from full-shift measurements (Savitz <i>et al.</i> 1995).
(Savitz <i>et al.</i> , 1998b); Cohort; USA	National Center for Health Statistics database of 25 states; 1931379 male deaths; 256 Alzheimer disease deaths. Schulte <i>et al.</i> (1996) analyzed Alzheimer's disease risks by occupation with the same database.	Electrical workers All < 65 years \geq 65 years	Alzheimer disease 256 10 246	1.2 (1.0-1.4) 0.9 (0.5-1.7) 1.2 (1.1-1.4)	MOR adjusted for age, year of death, social class, and race. Exposure is work in an electrical occupation as reported on death certificate.

NS, non-significant; RR, relative risk; CI, confidence interval; OR, odds ratio; TWA, time-weighted average; JEM, job-exposure matrix; SMR, standardized mortality ratio; MOR, mortality odds ratio

Table 4.38 Amyotrophic lateral sclerosis in association with exposure to EMF

Reference; type of study; country	Study population	Exposure classification	No. of cases	RR (95% CI)	Comments	
(Deapen & Henderson, 1986); case-control; USA	678 cases of ALS, self-selected by responding to questionnaire. Cases asked to nominate candidate controls of same gender and age. 518 controls selected.	Electrical occupations Electric shock resulting in unconsciousness	Univariate analyses		OR	
			19	3.8 (1.4-13.0)	Exposure category based on self-reported work experience	
		Electrical occupations Electric shock	14	2.8 (1.0-9.9)		
			Bivariate re-analysis		Bivariate re-analysis based on report that 3 cases and 0 controls were exposed to both factors	
			3.5	(1.3-9.5)		
			2.4	(0.9-6.8)		
(Davanipour <i>et al.</i> , 1997); case-control; California (USA)	28 clinic-based ALS patients. 32 controls were genetic relatives (17) and non-blood relatives (15) of cases, of same gender and similar age as case.	Cumulative magnetic fields > 75th percentile OR per unit exposure	All subjects		OR calculated by logistic regression, Exposure scores calculated from occupational history and magnetic fields estimated by industrial hygienist.	
			NR	2.5 (0.9-8.1)		
		> 75th percentile OR per unit exposure	28	1.0 (1.0-1.0)		
			Subjects with ≥ 20 years work			
			NR	7.5 (1.4-38.1)		
			20	1.0 (1.0-1.0)		
(Johansen & Olsen, 1998); Cohort; Denmark	Male employees of 99 Danish utility companies, 21236 total, 3540 deaths	TWA magnetic fields Low exposure, 0.1-0.25 μT Medium, 0.3-9.99 μT High, > 1.0 μT High + medium > 0.3 μT			SMR adjusted for age, education, and birth date. Magnetic field exposures from a JEM based on expert judgment and 24-h measurements. SMR for electrical accidents = 31 (<i>p</i> < 0.05) for fields > 1.0 μT.	
			4	1.9 (NS)		
			5	2.3 (NS)		
			4	2.8 (NS)		
			9	2.5 (1.1-4.8)		
(Savitz <i>et al.</i> , 1998a); cohort; USA	138 905 men employed for > 6 mo. in 5 electric utilities followed for mortality from 1950-86. 20068 deaths, 33 deaths in which ALS was mentioned as cause of death.	Cumulative magnetic fields Total career exposure Highest category (1.1-15.4 μT-year) Exposure-response (RR / μT-year)	Mentioned cause of death		SMR adjusted for age, decade of death, race, social class, retirement status, and solvent exposure. Cumulative magnetic field exposure based on job history in company records and JEM from 2842 full-shift measurements (Savitz <i>et al.</i> 1995).	
			16	1.2 (0.5-3.0)		
			33	1.0 (0.9-1.2)		
			Exposures ≥ 20 year previously			
			5	2.4 (0.7-8.0)		
			33	1.1 (0.9-1.3)		
			Exposure-response (RR / μT-year)			

Table 4.38 (continued)

Reference; type of study; country	Study population	Exposure classification	No. of cases	RR (95% CI)	Comments
(Savitz <i>et al.</i> , 1998b); cohort; USA	National Center for Health Statistics database of 25 states; 1931379 male deaths; 114 ALS deaths	Electrical workers All ages < 65 year old ≥ 65 year	114 56 58	1.3 (1.1-1.6) 1.4 (1.0-1.9) 1.2 (0.9-1.6)	MOR adjusted for age, year of death, social class, and race. Work in electrical occupation as reported on death certificate.

RR, relative risk; CI, confidence interval; ALS, amyotrophic lateral sclerosis; OR, odds ratio; NR, not reported; TWA, time-weighted average; NC, not significant; SMR, standardized mortality ratio; JEM, job-exposure matrix; MOR, mortality odds ratio

Table 4.39 Suicide and depression in association with exposure to EMF

Reference; type of study; country	Study Population	Exposure Classification	No. of cases	RR (95% CI)	Comments			
(Savitz <i>et al.</i> , 1994); cohort; USA	In the Vietnam Experience Study, a cohort of 4044 male US Army veterans was given a personal health exam, including the diagnostic interview survey and the Minnesota multiphasic personality inventory from which depression was diagnosed and its symptoms were determined.	Electrical occupations Electricians	Diagnosis of depression (last month)		OR adjusted for race, marital status, education, duration of employment, and alcohol use. Exposure determined from current job at time of psychological testing. Most indicators of depression were not elevated.			
			5	1.7 (0.7-4.3)				
		Electrical occupations Electricians	Thoughts of death	3		2.5 (0.8-7.5)		
			6	0.8 (0.3-1.8)				
		Electrical occupations Electricians	Obvious depression	3		1.1 (0.4-3.4)		
			20	1.2 (0.8-2.0)				
(Baris <i>et al.</i> , 1996a); Case-cohort; Quebec (Canada)	Cohort of 21744 male electrical utility workers at Hydro Quebec from Thériault <i>et al.</i> (1994). Deaths were traced through records of the company, its pension fund, and death certificates.	Cumulative exposures ELF electric fields (GM) 23.1-40.3 V/m ·per year > 40.3 V/m ·per year	Suicide		RR adjusted for socioeconomic status, alcohol use, and marital status. Cumulative exposure based on job history plus JEMs from 2066 work-week EMF measurements. TWA (arithmetic mean) electric and magnetic fields were the <i>a priori</i> metrics, but only the GM electric fields were significant.			
			20	3.1 (1.2-8.2)				
		ELF magnetic fields (GM) 1.25-2.08 μT·years >2.08 μT·years	13	2.2 (0.6-7.8)				
			14	1.3 (0.5-3.1)				
		High-frequency pulsed EMF 1.1-6.4 man-weeks and > 100 ppb	11	1.9 (0.3-2.5)				
			10	1.1 (0.2-5.8)				
		High-frequency pulsed EMF > 6.4 man-weeks and > 100 ppb	19	1.2 (0.3-5.7)				
		(Johansen & Olsen, 1998); cohort; Denmark	Male employees of 99 Danish utility companies, 21236 total.	TWA magnetic fields Low exposure, 0.1-0.25 μT Medium, 0.3-9.99 μT High, > 1.0 μT		Suicide		SMR adjusted for age, education, and birth date. Magnetic field exposures for subject's first job taken from a JEM based on expert judgment and 24-hr measurements.
						37	0.8 (NS)	
41	0.9 (NS)							
36	1.4 (NS)							

RR, relative risk; CI, confidence interval; OR, odds ratio; ELF, extremely low frequency; GM, geometric mean; JEM, job-exposure matrix; TWQ, time-weighted average; NS, not significant; SMR, standardized mortality ratio

Table 4.40 Mortality from cardiovascular disease in relation to exposure to magnetic fields (Savitz *et al.*, 1998c)

Exposure level (percentiles)	Arrhythmia-related			Acute myocardial infarct			Atherosclerosis			Chronic coronary heart disease		
	No. of cases	RR	95% CI	No. of cases	RR	95% CI	No. of cases	RR	95% CI	No. of cases	RR	95% CI
0 ≤ 0.6	47	1.0		1031	1.0		43	1.0		664	1.0	
0.6 ≤ 1.2	49	1.6	1.0-2.4	852	1.1	1.0-1.3	34	1.1	0.7-1.8	422	0.9	0.8-1.0
1.2 ≤ 2.0	42	1.3	0.8-2.0	899	1.2	1.1-1.3	27	0.8	0.5-1.3	452	0.9	0.8-1.0
2.0 < 4.3	40	1.2	0.8-2.0	946	1.4	1.2-1.5	26	0.7	0.4-1.2	441	0.9	0.8-1.0
4.3+	34	2.4	1.5-3.9	510	1.6	1.5-1.8	12	0.7	0.4-1.3	241	1.0	0.9-1.8
RR per μT-year	212	1.1	1.0-1.1	4238	1.0	1.0-1.1	142	1.0	0.9-1.0	2210	1.0	1.0-1.0

4.6 Laboratory studies of non-cancer health effects in humans

Health risks, particularly those associated with environmental factors, are often the result of biological effects that accumulate over time and depend on dose. Thus, detailed knowledge of effects is important in understanding risks. Biological effects and, to a limited extent, health effects—those physiological changes that exceed normal ranges for brief periods—can be studied safely and effectively in the laboratory with human volunteers, although there are obvious limitations to the duration of exposure and the types of tests that can be performed. The focus in human studies is usually on effects that occur within a time-frame of minutes, hours, days, or perhaps weeks; longer-term studies in which exposure is adequately controlled are difficult, if not impossible, to carry out with human volunteers in a laboratory setting. The selection of physiological mechanisms to be studied is also limited to those that can be measured by non-invasive or minimally invasive procedures.

Laboratory studies on humans have certain advantages. They focus directly on the species of main public interest, thus avoiding the problems of extrapolation from data obtained in other species; furthermore, even negative results can be of immediate use in addressing public concern. Such studies can also be used to directly evaluate the effects of exposure on higher-order cognitive functions important in daily life, such as memory, attention, and information processing, as well as their underlying electrophysiological and neurochemical substrates. Controlled laboratory testing with human volunteers can help to define dose metrics and response categories for epidemiological studies, and can guide animal research to areas in which more invasive mechanistic investigations might be valuable. Like animal studies, human laboratory studies allow separate testing of the effects of electric, magnetic, and combined fields to determine whether any effects found are related to specific characteristics of the exposure situation or to their interactions.

The effects of experimental human exposure to EMF are derived from three major research initiatives and from efforts in individual laboratories. These include a long series of studies of utility workers begun in the 1960s in the former USSR (Asanova & Rakov, 1966), the human laboratory research conducted in the 1970s in Germany (Hauf & Wiesinger, 1973; Silny, 1986), and the human laboratory research program started in 1982 at the Midwest Research Institute in the USA (Graham *et al.*, 1990). Dedicated facilities for human exposure testing have been designed and constructed in Australia (Wood *et al.*, 1997), Canada (Blondin *et al.*, 1996), England (Stollery, 1986), France (Selmaoui *et al.*, 1996b), Germany (Hauf & Wiesinger, 1973), New Zealand (Podd *et al.*, 1995), the Russian Federation (Lyskov *et al.*, 1993b), and the USA (Cohen *et al.*, 1992; Doynov *et al.*, 1998). Research with human volunteers is currently under way in many of these facilities.

4.6.1 Sensation and perception

The ability of humans to perceive EMF is of interest for several reasons. If such exposure is considered to be a low-level environmental stressor (Bell *et al.*, 1991), the reported effects may be by-products of stress. Individual differences in field perception may also be related to individual differences in sensitivity to other possible health-related effects of exposure. Investigation of the biological mechanisms that subserves human perception can lead to a better understanding of how these fields affect the human organism.

4.6.1.1 Field perception

Humans can perceive power frequency, time-varying (AC), and static (DC) electric fields, depending on field characteristics and other factors noted below. In contrast, there is little evidence for human perception of power-frequency magnetic fields, until field intensities well above ambient are encountered. Perception of AC electric fields can result from the alternating electric charge induced on the surface of body hairs; the charge causes the hairs to vibrate, and the subjective sensation is usually one of itching or tingling. For other possible mechanisms, see section 4.4.3. Delaplace and Reilly (Delaplace & Reilly, 1978) placed 122 men subjects directly under overhead transmission lines in various environmental conditions; 90% of them could perceive a 20 kV/m 60 Hz electric field, and perception reached a self reported 'annoyance' threshold for 10%. A small percentage reported perception at field strengths below 5 kV/m.

Graham and Cohen (Graham & Cohen, 1985) performed a laboratory-based study of the perception of 60 Hz electric fields (0–15 kV/m) and of magnetic fields (0–40 μ T) by 10 men and 10 women aged 21–35. The men and women had similar sensitivity. The threshold of 90% of the group was ≥ 9 kV/m. Perception improved when the field onset was abrupt and when the volunteer changed body position in the field. Perception of initial field onset ceased after about 20 min of continuous exposure but was immediately re-established by body movements within the field. No evidence was found for perception of magnetic field ≤ 40 μ T, and the presence or absence of the magnetic field did not influence perception of the electric field. These results replicate two earlier, well-controlled laboratory studies of perception of magnetic fields by human volunteers: Schmitt and Tucker (Schmitt & Tucker, 1978) and Tucker and Schmitt (Tucker & Schmitt, 1978) tested the ability of 200 volunteers to perceive 60 Hz magnetic fields over the range 0.7–1.5 mT and reported little evidence for perception.

4.6.1.2 Visual effects

Phosphenes are flickering visual sensations caused by non-photic stimulation such as pressure on the eyes and mechanical shocks. They are generated in the retina, not in the optic nerve or the visual cortex (Lovsund *et al.*, 1979). Volunteers can reliably experience these sensations, now referred to as magnetophosphenes, during exposure to AC ELF

magnetic fields (Silny, 1986). Phosphenes can also be induced by direct application of weak electric currents to the head. This is one of the few known and accepted physiological effects of exposure to magnetic field in humans. The alternating magnetic field induces electric fields which stimulate the visual receptors in the retina. The threshold current density in the retina for induction of magnetophosphenes is estimated to be about 10 mA/m² at 20 Hz, a level well above typical endogenous current densities in electrically excitable tissues.

The magnetophosphene phenomenon is also of interest in connection with the ‘melatonin hypothesis’. Exposure to light at night is known to reduce circulating concentrations of the pineal hormone melatonin. Wood *et al.* (Wood *et al.*, 1997) suggested that magnetic field-induced phosphenes may play a role similar to light at night and thus represent a possible biological mechanism to account for the reported reduction in melatonin during nocturnal exposure to magnetic fields. [The authors did not evaluate this possibility, and it does not seem to be a particularly promising avenue of research.] Induction of magnetophosphenes in humans is sharply frequency dependent and requires magnetic flux densities more than 10 000 times higher than those usually encountered in residential settings. Maximum sensitivity occurs between 20 and 30 Hz; higher thresholds have been observed for both lower and higher frequencies (Lovsund *et al.*, 1979). The minimum flux density required to induce detectable magnetophosphenes is > 3–5 mT at 20 Hz (Silny, 1986). At 60 Hz, the threshold at the retina for perception of magnetophosphenes is at least an order of magnitude greater than at 20 Hz.

4.6.2 Central nervous system

The central nervous system is a potential site of interaction between biological systems and electric and magnetic fields because of the electrical sensitivity of the tissues. In the early studies of occupational exposure to EMF reported by Asanova and Rakov (Asanova & Rakov, 1966) and Sazonova (Sazonova, 1967), switchyard workers were reported to suffer from an abnormally high incidence of neurophysiological complaints. Clinical EEG measurements were reported to show desynchronization of the alpha rhythm (the dominant frequency range in the human brain, 8–12 Hz) and other abnormalities in EEG activity. Although later studies of EEG results from periodic health examinations failed to confirm these initial observations, the topic has continued to be of interest. Table 4.41 summarizes the results of 10 recent studies designed to evaluate the effects of occupational and laboratory-generated EMF on the basic bioelectrical characteristics of EEG activity in human volunteers.

4.6.2.1 Electroencephalographic spectral analysis

In the four studies summarized in the first half of Table 4.41, EEG activity from multiple standardized scalp locations was tested in paradigms that allowed comparison of field-exposed and unexposed conditions. The raw data were submitted to fast Fourier

transform spectral analysis to obtain information about possible field-induced alterations in the absolute and relative power of the dominant brain frequency, the total amount of energy being generated, and the distribution of energy in different frequency bands and over various regions of the head. Gamberale *et al.* (Gamberale *et al.*, 1989), for example, performed standard clinical EEG examinations on experienced utility company linemen before and after performance of their usual duties under typical exposure conditions on one day and under simulated conditions on a second day. They found that acute exposure over one day to fields associated with a 400 kV transmission line had no negative effects on the nervous system in this group of healthy men.

Lyskov *et al.* (Lyskov *et al.*, 1993a; Lyskov *et al.*, 1993b) performed two double-blind laboratory-based studies of the effects of continuous and intermittent (1 s on, 1 s off) exposure to magnetic fields on EEG activity in 17 male and 17 female volunteers. A Helmholtz-type coil device was used to produce a horizontal magnetic field (45 Hz, 1.26 mT, 25% uniformity) around the head of each volunteer, for 60 min in study 1 and for 15 min in study 2. EEG activity measured immediately before and after exposure and sham-exposure periods indicated that effects were predominantly associated with intermittent exposure. The 60-min exposure was associated with decreases in absolute and relative power in the lower EEG frequency bands (delta, 1–4 Hz; theta, 4–7 Hz) and increases in power in the higher frequency bands (alpha, 8–12 Hz; beta, 13–20 Hz). Field exposure had significantly ($p < 0.05$) different effects from sham exposure in 14 of 36 measures. This result was much greater than the two significant differences to be expected purely by chance alone. Intermittent exposure for 15 min under the same test conditions also resulted in significant ($p < 0.05$) effects on EEG activity. The most prominent change was an increase in both absolute and relative power in the alpha band; absolute power in the beta band also showed a non-significant increase. Short-duration exposure, however, had no effect on the lower frequency bands. The authors suggested that this pattern of EEG changes is indicative of the combined effects of relaxation and activation caused by the magnetic field on different structural and functional systems of the brain.

Since 1991, Bell and Marino and their coworkers have examined the effects of magnetic fields on human EEG activity. The study of Bell *et al.* (Bell *et al.*, 1992) summarized in Table 4.41 is representative of the approach taken by these investigators. A Helmholtz-type coil device is used to repeatedly expose the head and chest of neurological patients or volunteers from the general population to DC fields or to AC magnetic fields of varying frequency (≤ 60 Hz) and intensity (≤ 100 μ T), either alone or in combination, in a test series of second-duration exposure epochs interspersed with no-exposure epochs. EEG activity during exposure epochs is compared with that in the preceding no-exposure epochs by non-traditional analytical techniques, in which the EEG spectrum is divided into 0.05 Hz bands and a field effect is defined as a change, either positive or negative, in the power coefficients in one or more bands. [The findings across these studies are ambiguous and not informative with regard to dose–response relationships. A number of potential sources of error and artifact are associated with this type of test and analysis, including fatigue, lapses of attention, body movements, visual-induced artifacts, and

transients. The mixed use of neurological patients and normal volunteers in the same experiment creates additional ambiguity.]

4.6.2.2 Event-related potential

Presentation of a stimulus evokes a transient electrophysiological response in the human EEG, commonly referred to as an event-related potential (ERP). Computer averaging of such responses results in a complex waveform with distinct electrically positive and negative components. ERP components are usually identified by their electrical sign (negative, N; positive, P) and by the sequence in which they appear in the waveform (e.g. N100 represents a negative peak that appears in the waveform about 100 ms after the stimulus; P300, a positive peak that appears about 300 ms after the stimulus). Short-latency ERPs (< 50 ms) are used clinically to evaluate hearing and vision in the newborn, brain function during coma, and as one criterion of brain death. Longer-latency ERP components (100–500 ms after stimulus) are also well documented and have been linked to specific human information processing activities, such as attentional gating, stimulus evaluation and discrimination, decision making, memory updating, and motor response. The amplitude of ERP components is significantly affected by the value or attention-getting properties associated with a stimulus (meaning, signal value, rarity). In neurotoxicological studies, ERPs have been used to assess changes in neural function in response to such toxicants as ethanol, carbon monoxide, xylene, methylene chloride, and trichloroethylene (Arezzo *et al.*, 1985; Dick & Johnson, 1986).

The lower half of Table 4.41 summarizes the results of six recent laboratory studies designed to evaluate the effects of magnetic fields on ERP components. Graham *et al.* (Graham *et al.*, 1995) measured short-latency (< 50 ms) ERP components to visual, auditory, and somatosensory stimuli in a double-blind study of exposure to a 60 Hz 10 μ T, 20 μ T field of 36 healthy young men and women. ERP measures of neural conduction time during exposure and under sham-exposure conditions were not statistically significantly different in any of the three sensory modalities. In a study with similar measures, described in section 4.4.3, Dowman *et al.* (Dowman *et al.*, 1989) obtained similar results in monkeys. [These results suggest that exposure to combined EMF or to magnetic fields alone at levels higher than those found in most residences has no effect on neural conduction time in peripheral or central sensory afferent pathways.]

Four double-blind cross-over studies (Table 4.41) (Cook *et al.*, 1992; Graham *et al.*, 1987; Graham *et al.*, 1990; Graham *et al.*, 1994) showed that exposure of human volunteers for up to 6 h to combined EMF at intensities as high as 12 kV/m and 20 μ T per axis had no effect on longer-latency components of the visual ERP. These results replicate those of an earlier report by (Silny, 1986) who used 50 Hz magnetic fields up to 5 mT. In contrast, replicable effects of whole-body exposure to combined electric and circularly polarized 60 Hz magnetic fields on the auditory ERP have been reported in three laboratory studies (Cook *et al.*, 1992; Graham *et al.*, 1987; Graham *et al.*, 1994). The field levels in these studies ranged from 6 kV/m and 10 μ T to 9 kV/m and 20 μ T. [All of the studies conducted in this laboratory involved circularly polarized magnetic fields, and flux is

reported as per axis (e.g. a 20 μT per axis circularly polarized field gives a resultant field of 28.3 μT .) Auditory ERP measures were obtained while volunteers performed a widely used neurophysiological target detection task, the ‘oddball task’ (Donchin, 1984; Harbin, 1985; Otto *et al.*, 1985). In comparison with sham exposure, field exposure was associated with a significant ($p < 0.05$) increase in the amplitude of P300, the primary cognitive component of the auditory ERP waveform. In the context of the oddball task, increases in amplitude indicate possible interference in the normal physiological processes involved in distinguishing relevant from irrelevant stimuli (i.e. increased susceptibility to distraction). [These studies of auditory ERP activity represent within-laboratory replications.] Lyskov *et al.* (Lyskov *et al.*, 1993a) reported somewhat contradictory results: the P300 component of the auditory ERP when measured in response to the presentation of simple tone stimuli was not affected by 15 min of cephalic exposure to a 50 Hz 1.26-mT horizontal magnetic field.

[The studies of the effects of exposure to EMF on human EEG activity differ in a number of important respects, e.g. exposure duration, strength, orientation, polarity, whole-body vs. cephalic exposure, physiological recording parameters, and analytical techniques. Taken as a whole, however, they suggest that EEG measures are affected by exposure to electric and/or magnetic fields; however, the reported effects do not appear to result from alterations in neural conduction time in major sensory modalities and may well be related to shifts in physiological arousal and attention during testing. The biological magnitude (< 10 %) of the changes observed is well within normal ranges for the EEG parameters assessed. The data are insufficient to suggest a health effect.]

4.6.2.3 Sleep electrophysiology

Sleep is a complex biological process controlled by the central nervous system and which is necessary for proper cognitive, metabolic, and immune function. Asanova and Rakov (Asanova & Rakov, 1966) were the first to suggest that occupational exposure to power-frequency EMF might have a detrimental effect on night sleep. The switchyard workers they evaluated made numerous complaints of exposure-related decrements in both the quantity and quality of sleep. Individuals who consider themselves hypersensitive to EMF most commonly report disturbances of night sleep and feelings of tiredness and fatigue on awakening (Arnetz, 1997; Berg *et al.*, 1992). Few studies have obtained objective EEG measures of night sleep from human volunteers exposed to known field conditions in a controlled laboratory environment.

Two recent reports (see Table 4.42) suggest that exposure to magnetic fields in the ELF range also disrupt objective EEG measures of night sleep in human volunteers. Akerstedt *et al.* (Akerstedt *et al.*, 1997a; Akerstedt *et al.*, 1997b) performed a double-blind laboratory study to evaluate the effects of all-night exposure to a 50 Hz, 1 μT horizontal magnetic field on EEG sleep parameters and endocrine or hormonal measures in 18 men and women, 24–49 years old. Each subject slept in the exposure facility for two nights. The first night was considered an adaptation session in which the subjects became used to sleeping in the laboratory while wearing physiological recording sensors. On the second

night, half of the subjects at random were sham exposed, and half were continuously exposed to the magnetic field. Sleep EEGs were recorded throughout the test nights, and blood samples were obtained six times per night from an indwelling catheter. In comparison with sham-exposure conditions, field exposure was associated with a significant ($p < 0.01$) reduction in the duration of slow-wave sleep (sleep stages III and IV), which is often considered to be the restorative portion of night sleep. The nights of field exposure nights were also associated with reduced total sleep time, reduced sleep efficiency, and reduced rapid-eye-movement (REM) sleep; these effects did not reach statistical significance.

Graham and Cook (Graham & Cook, 1998) performed a double-blind, laboratory-based study to evaluate the effects of exposure to magnetic fields on EEG measures of nocturnal sleep patterns in 24 healthy men aged 18–35. Each man slept in the exposure facility from 23:00 to 07:00 h for three nights. The first two nights were adaptation sessions during which the subjects became used to sleeping in the laboratory. On the third night, eight men were sham exposed; seven men were continuously exposed to a 60 Hz, 20 μT per axis (resultant, 28.3 μT) circularly polarized magnetic field; and nine men were exposed intermittently (1 h on, 1 h off) to the same field. The sleep EEG was recorded throughout the night. Physiological data collection, sleep scoring, and statistical analyses were all performed in a blinded fashion. The results seen with continuous exposure did not differ from those in sham-exposed controls for any measure, while intermittent exposure resulted in a significant distortion of nocturnal sleep in six of the 10 measures evaluated. Intermittent exposure was associated with less total sleep time ($p = 0.003$), reduced sleep efficiency ($p = 0.003$), increased time in stage 2 sleep ($p = 0.009$), decreased REM sleep ($p = 0.001$), and increased REM latency ($p = 0.04$). Subjects exposed intermittently to the field also reported sleeping less well ($p = 0.001$) and feeling less rested in the morning ($p = 0.03$) than subjects in the other two groups.

[The exposure and test procedures were quite different in these two studies, and the different results obtained may be due to those differences. The findings of Akerstedt *et al.* (1997a) are relevant to levels of residential exposure. However, the possible confounding effect of serial blood sampling on EEG measures of nocturnal sleep should be examined further. The exposure in the study of Graham and Cook are more relevant to occupational exposure in the utility industry than to residential exposures, but they observed little slow-wave sleep, suggesting that the volunteers were not completely adapted to the laboratory environment. It will be important to determine whether the findings of these preliminary studies are replicable, to extend them to women and to older individuals, and to ascertain whether daytime exposure also alters sleep architecture. The available data on the effects of ELF fields on sleep are insufficient to suggest a health risk; however, poor sleep quality can have a detrimental effect on worker safety and performance, and modification of REM sleep has been associated with decrements in memory function and learning processes.]

4.6.2.4 Cognition and performance

The ability to perceive the world around us, to process information quickly and accurately, and to maintain appropriate levels of attention and arousal are all significant human functions. Even subtle changes in such functions can have important consequences. Performance depends on intact, functioning physiological systems, and changes in performance in toxicological or exposure studies can provide important information about underlying neuronal dysfunction. The most frequently used performance measures in research on EMF with human volunteers are reaction time, vigilance or sustained attention, memory function, and tasks involving time perception and information processing. Many earlier studies were reviewed by Carstensen (Carstensen, 1987).

Table 4.43 summarizes the results of 10 recent studies. Even a cursory review of the Table indicates that the results for performance have been very mixed. For example, two studies found improvements in a reaction-time task, two found decrements in reaction time, and five found no effect. A similar lack of consistency is evident in the results of studies of more complex performance, partly because different investigators seldom use the same task and the range of exposure conditions is limited. The mixed results may also be due to differences in protocol between laboratories and to variations in volunteer motivation. More standardization in this area of research is needed.

[Human performance of many types of task appears to be unaffected by exposure to relatively high electric and/or magnetic fields. When effects are observed, however, the magnitude of the alteration is generally in the order of 10% or less, and little reliable evidence exists for a consistent dose–response relationship. Thus, there is insufficient evidence at this time to indicate that daytime exposure to ELF EMF at occupational levels presents a health risk. The extent to which performance is disrupted by fields of low intensity similar to those found in offices and residences, however, has not been well evaluated. Similarly, it is not known if nocturnal field exposure has detrimental effects on daytime performance.]

4.6.3 Cardiovascular system

4.6.3.1 Heart rate

Sazonova (Sazonova, 1967) examined groups of switchyard workers in the former USSR, who differed in the duration and intensity of their exposure to 50 Hz fields. The pulse rates of people in the group with an average exposure for > 5 h/d to 12–16 kV/m were lower by 2–5 beats/min at the end of the day, although they had been equivalent at the start of the day, and this difference was found even after exercise ($p < 0.05$). Early studies of effects on the heart rate in human volunteers were reviewed by Carstensen

(Carstensen, 1987) and Cook (Cook *et al.*, 1992). A number of the earlier studies were published as meeting abstracts or in non-English-language journals.

Table 4.44 presents the results of six recent studies of this phenomenon. Replicable field-related slowing of the heart rate was reported in four laboratory-based studies with double-blind cross-over experimental designs (Cook *et al.*, 1992; Graham *et al.*, 1987; Graham *et al.*, 1990; Graham *et al.*, 1994). Negative results have also been found, however. The biological mechanism underlying the phenomenon is unknown, and the magnitude of the observed effects across studies is small (< 10 % change from the mean).

Korpinen *et al.* (Korpinen *et al.*, 1993) see table 4.44 used ambulatory recording techniques to perform an extensive series of studies of the effects of occupational exposure to EMF on heart rate. No field-related changes in mean heart rate were found as a result of exposure to the 50 Hz fields directly under power transmission lines ranging in intensity from 110 to 400 kV. [There are insufficient data to suggest a health risk.]

4.6.3.2 Heart-rate variability

Heart-rate variability (HRV) results from the action of neuronal and cardiovascular reflexes, including those involved in the control of temperature, blood pressure, and respiration. Quantitative spectral analyses of alterations in HRV with digital Fourier transform provide useful indicators of beat-to-beat variations in sympathetic and parasympathetic nerve activity *in vivo*. This type of variability is not consciously perceived, and it should not be confused with heart-rate reactivity, which is the slowing or speeding of the heart rate in direct response to perceived situational or personal stimuli (e.g. exercise, anxiety, and relaxation). Certain alterations in HRV have recognized prognostic value for coronary artery disease (Hayano *et al.*, 1990; Liao *et al.*, 1997), post-infarction risk (Bigger *et al.*, 1993; Kleiger *et al.*, 1987), diabetic autonomic neuropathy (Bernardi *et al.*, 1992), and systemic hypertension (Huikuri *et al.*, 1996; Liao *et al.*, 1996). Data from large longitudinal human studies in the USA and other countries have indicated that quantitative spectral assessment of HRV in healthy and diseased populations offers prognostic information for the risk of sudden cardiovascular death and death from all causes, beyond that provided by the evaluation of traditional risk factors. In the Framingham Study (Tsuji *et al.*, 1996; Tsuji *et al.*, 1994), HRV was examined in a middle-aged and elderly cohort after exclusion of subjects with cardiovascular disease or medications that could affect HRV. Reduced HRV was significantly associated with subsequent sudden cardiovascular death, even after all previous risk factors (e.g. blood pressure and cholesterol concentrations) had been taken into account. Similar results were obtained in a 25-year prospective study of a middle-aged and elderly cohort (Dekker *et al.*, 1997); these results complement more recent concordant findings (Liao *et al.*, 1997).

Sastre *et al.* (Sastre *et al.*, 1998); see Table 4.44, described three recent double-blind studies in which sufficient data were collected to examine HRV in detail in 77 volunteers as they slept through the night (23:00–07:00 h) in the laboratory while being exposed to

intermittent (1 h on, 1 h off) or continuous 60 Hz magnetic fields at intensities of 1 or 20 μT . In study 1, intermittent exposure to 20 μT reduced HRV in the spectral band associated with the neural control of thermoregulation and blood pressure (known as the 'low band') in comparisons with sham-exposure conditions and field exposure to 1 μT ($p = 0.03$). In study 2, each of the 23 volunteers served as his own control. They were sham exposed in one session and exposed to the 20 μT field in a second session. In comparison with sham-exposure conditions, intermittent field exposure was again associated with a reduction in low-band power ($p = 0.02$) and also with a significant ($p = 0.008$) increase in the power in the spectral band associated with natural respiration-induced alterations in heart rate (known as the 'high band'). In a third study performed to determine the effects of continuous rather than intermittent exposure, no significant effects on HRV were found. [Taken together, these findings are consistent with the hypothesis that intermittency of exposure to magnetic fields is an important parameter in the human cardiac responses that result from those exposures.]

In the studies of Sastre *et al.*, low-band power was reduced by approximately 17% by nocturnal exposure to an intermittent magnetic field of 20 μT , whereas the biological magnitude of the reduction in low-band power typically seen in clinical studies is 20–40%. In the studies of Sastre *et al.*, none of the volunteers reported any cardiovascular difficulties associated with the night-time exposures; secondly, the changes seen to date as a function of intermittent exposure are similar but not identical to those reported as predictive of cardiovascular morbidity and mortality. In the clinical studies, a higher cardiovascular risk was associated with a reduction in low-band power coupled with modest reductions or no change in high-band power (Barron & Lesh, 1996; Bernardi *et al.*, 1992; Bigger *et al.*, 1993; Hayano *et al.*, 1990; Huikuri *et al.*, 1996; Kleiger *et al.*, 1987). The pattern seen with field exposure is a reduction in low-band power with an increase in high-band power. This pattern has, to our knowledge, been reported only for changes in HRV associated with stage 2 sleep (Vaughn *et al.*, 1995).

Extrapolation of the laboratory data described by Sastre *et al.* (Sastre *et al.*, 1998) in combination with the results of clinical studies of HRV lead to the biological hypothesis that chronic occupational exposure to intermittent power-frequency magnetic fields may affect specific types of cardiovascular disease by altering cardiac autonomic control. Under this hypothesis, such exposures would be linked to increased risks for arrhythmia-related deaths and deaths due to acute myocardial infarct. No increase in risk would be predicted for deaths due to cardiovascular events that are the end-product of processes that develop independently from autonomic nervous input over extended periods of time (i.e. atherosclerosis and chronic coronary heart disease). Savitz *et al.* (Savitz *et al.*, 1998c) recently reported results that support both the positive and the negative predictions derived from this hypothesis, in a cohort analysis of 139 903 male electric utility workers. The study is described in detail in section 4.5.1.

[Primarily because of the small number of studies reported at this time, there is insufficient evidence of a health risk.]

4.6.4 Other effects

4.6.4.1 Melatonin

Stevens *et al.* (Stevens *et al.*, 1997) proposed that exposure-related suppression of nocturnal melatonin might provide a plausible biological mechanism to account for some of the epidemiological reports linking occupational or residential exposure to EMF with increased cancer risks. Much of the evidence for the melatonin hypothesis, however, is based on data for rodents (see section 4.4.5). A crucial link for this hypothesis is to determine whether melatonin is suppressed when humans are exposed to magnetic fields at night.

Humans and rodents differ in regard to melatonin. Rodents are nocturnally active, and their nocturnal melatonin concentrations are more easily suppressed by light. Differences in the geometry of the skull and the anatomical location of the pineal gland may cause stronger eddy currents in field-exposed rodents. People show large individual variation in their melatonin patterns, while inbred laboratory strains of rodents do not. Among healthy young men, for example, the peak melatonin concentrations at night can range from 10 pg/ml to over 100 pg/ml (Graham *et al.*, 1998). Human melatonin concentrations also vary as a function of age: in general, they are highest at the age of 1–3, decrease sharply until adolescence, remain fairly stable through adulthood, and finally begin a further decline after about the age of 50 (Waldhauser *et al.*, 1993). Little is known about the basic biology of melatonin in humans and how differences in the concentrations and patterns of this hormone affect individual health and well-being.

The effects of exposure to electric and/or magnetic fields on blood concentrations of melatonin and its major urinary metabolite 6-hydroxymelatonin sulfate (6-OHMS) in humans have been examined in 12 studies (Table 4.45), six with exposure in the laboratory and six observational studies of occupational and residential exposure. The results of five of the six laboratory studies were negative. All-night exposure of human volunteers to magnetic fields under controlled exposure and lighting conditions in the laboratory had no apparent effect on nocturnal blood concentrations of melatonin when compared with equivalent sham-exposure conditions. The exposure parameters evaluated included field frequency (50 or 60 Hz), field polarity (linear or circular), field type (continuous or intermittent), and field intensity (1–20 μ T). The studies were performed under double-blind control, and four had a cross-over experimental design in which each volunteer served as his own control to further reduce error variance. When suppression of melatonin has been observed in experimental animals, it was typically a 25–30% reduction (Portier *et al.*, 1998). Two of the three studies reported by Graham *et al.* (Graham *et al.*, 1997; Graham *et al.*, 1996) had statistical power greater than 0.80 to detect a similar degree of suppression of melatonin in humans at the $p < 0.05$ level of significance.

The laboratory study of Wood *et al.* (Wood *et al.*, 1997) is the single one with not completely negative results. They first determined the nocturnal melatonin curve for each individual in their study and then timed presentation of the magnetic field to occur before, during, or after the time of the peak concentration of melatonin in the circulation. Exposure during the rising portion of the nocturnal melatonin curve significantly ($p < 0.01$) delayed peak onset in one individual, with possible trends for similar effects in several other individuals. The authors note that, while the results are suggestive, the study should be considered only preliminary and the results interpreted with caution. [Owing to the exploratory nature of this study, a number of concerns could be raised in regard to the experimental design, statistical analysis, and interpretation of the findings.]

All six of the studies of occupational and residential exposure listed in Table 4.45 provide at least some evidence of field-related suppression of 6-OHMS, the major urinary metabolite of melatonin. [As would be expected, there is wide variation in exposure conditions, the duration, precision, and type of measures obtained, the presence of possible confounders (e.g. light at night, shift work), and the general characteristics and health status of the individuals studied. Nevertheless, these studies are directly relevant to the effects of magnetic fields under present-day environmental conditions. The study of Burch *et al.* (1998) is perhaps the most relevant for occupational exposure in the utility environment, and that of Kaune *et al.* (1997) for assessing the effects of residential exposure.] Burch *et al.* reported that TWA magnetic field intensity, intermittency, or cumulative exposure had little influence on morning concentrations of 6-OHMS in the workplace. At home, morning concentrations of 6-OHMS were significantly ($p < 0.05$) associated with 24-h measures of magnetic fields if the exposure remained temporally stable over at least 3–5 min. Additional analyses suggested that morning 6-OHMS concentrations were most likely to be reduced in individuals who were exposed to temporally stable magnetic fields both at home and in the workplace.

Using 72-h measurements of magnetic fields in bedrooms made with EMDEX-2 monitors, Kaune *et al.* (Kaune *et al.*, 1997) reported a significant ($p < 0.05$) decrease in the log 6-OHMS concentration in morning urine samples as the log mean magnetic field intensity increased (range, 0–1.5 μT). For example, a twofold increase in average magnetic field resulted in a 6–8% decrease in urinary metabolite concentration. This effect was strongest in summer and was limited to women who used medications known to reduce melatonin (e.g. beta blockers). A similar relationship was observed as a function of the proportion of night-time bedroom measurements $> 0.2 \mu\text{T}$. Additional analyses indicated that 6-OHMS concentrations were not altered as a function of wire code, short-term variation in bedroom or personal dosimetry measurements, or the proportion of light-at-night measurements $> 10 \text{ lux}$. No relationship was observed between 6-OHMS concentrations in urine and menopausal status, current smoking, or use of an electric blanket within the previous month.

[The data are inadequate to suggest an effect of EMF on melatonin concentrations; however, additional research is needed to better understand the differences found in the laboratory and in observational studies. Obvious factors to consider include single versus

long-term exposure, the type and complexity of the exposure parameters assessed, and the characteristics of the individuals studied. More needs to be known about the effects of exposure at different times of day. Inclusion of morning urine samples to assess the contribution of melatonin in studies of occupational or residential exposure might be useful.]

4.6.4.2 Neuroendocrinology

Five double-blind, laboratory-based studies have been conducted to evaluate the effects of exposure to power-frequency electric and/or magnetic fields on a variety of biochemical measures in humans. The volunteers in these studies were unable to detect a difference between field and sham exposure. Selmaoui *et al.* (Selmaoui *et al.*, 1997) described the results of additional analyses performed on the data collected by Selmaoui *et al.* (Selmaoui *et al.*, 1996b) to evaluate pituitary, thyroid, and adrenocortical hormones. No significant differences were observed between sham- and field-exposure (50 Hz, 10 μ T, 8 h) in the concentrations of thyroid-stimulating hormone, follicle-stimulating hormone, luteinizing hormone, triiodothyronine, thyroxine, free triiodothyronine, thyroxine-binding globulin, cortisol, or 17-hydroxycorticosteroids. Gamberale *et al.* (Gamberale *et al.*, 1989) also failed to find any field-related change in the concentrations of testosterone, thyroid-stimulating hormone, luteinizing hormone, follicle-stimulating hormone, cortisol, or prolactin in his study of the exposure of 26 linesmen working on a 400 kV transmission line. Maresh *et al.* (Maresh *et al.*, 1988) reported no effect of exposure to a 9 kV/m, 20 μ T field on the concentrations of cortisol, growth hormone, testosterone, and plasma lactic acid or on the hematocrit or hemoglobin content in comparison with sham-exposure conditions. Graham *et al.* (Graham *et al.*, 1990) also reported no effects of multiple 6-h sessions of exposure to combined EMF (9 kV/m, 20 μ T) on the concentrations of dopamine, cortisol, epinephrine, norepinephrine, 5-hydroxyindoleacetic acid, homovanillic acid, or vanillylmandelic acid, which include the traditional measures of stress (cortisol, epinephrine, norepinephrine, and dopamine).

[These studies provide no evidence for detrimental effects of exposure to ELF EMF for at least 8 h on human hypothalamic, pituitary, thyroid, or adrenal hormonal systems or on traditional biochemical measures of the human stress response; however, very little is known about the response of women to EMF or about possible effects on female reproductive hormones.]

4.6.4.3 Immune system

Few laboratory studies have examined the effects of exposure to EMF on immune function in human volunteers. In perhaps the most comprehensive report to date, Selmaoui *et al.* (Selmaoui *et al.*, 1996a) described the results of additional analyses of the data they collected in 1996 to evaluate hematological and immune system measures. No significant differences were observed between sham- and magnetic field-exposed (50 Hz, 10 μ T, 8 h) men in hemoglobin concentration, hematocrit, or erythrocyte, platelet, total

leukocyte, monocyte, lymphocyte, eosinophil, or neutrophil counts. The results of flow cytometric analysis of immunological variables (CD3, CD4, CD8, natural killer cells, and B cells) before and after exposure and control sessions were also unchanged. Earlier, (Hauf, 1982) and Graham *et al.* (Graham *et al.*, 1990) also reported no reliable field-related changes in blood chemistry, leukocyte or lymphocyte counts, blood gases, lactate concentration, or circulating stress hormones.

[All of the results of laboratory studies obtained to date are based on short-term exposure of healthy young men; no published reports have addressed possible differential effects as a function of age or gender, although the observational studies of suppression of the melatonin metabolite suggest that such studies might be appropriate. The data are inadequate to suggest a health risk.]

4.6.5 Mood disturbances

Various authors have suggested that environmental exposure to electric and/or magnetic fields acts as a low-level stressor or is associated with an increased frequency of a variety of negative mood states, including clinical depression, suicidal tendencies, feelings of irritability, and loss of libido (Bell *et al.*, 1991; Poole *et al.*, 1993; Reichmanis *et al.*, 1979; Wilson, 1988). In this context, it would be important to determine whether field exposure under controlled laboratory conditions has a negative effect on traditional self-reported measures of mood and personality or on objective biochemical indicators of the human stress response. [The use of double-blind control procedures is essential in this type of evaluation, since the primary purpose of such procedures is to allow a distinction between any effects due to field exposure *per se* and any effects associated with the subjective expectation about being exposed.]

Eight double-blind studies have addressed this issue (Akerstedt *et al.*, 1997a; Akerstedt *et al.*, 1997b; Cook *et al.*, 1992; Graham *et al.*, 1987; Graham *et al.*, 1990; Graham *et al.*, 1994; Maresh *et al.*, 1988; Selmaoui *et al.*, 1997; Stollery, 1986; Stollery, 1987), with overwhelmingly negative results. The range of exposure parameters assessed in these studies included field frequency (50 and 60 Hz), magnetic field flux density (1–30 μ T), electric field strength (0–12 kV/m; and injection of electric current equivalent to 36 kV/m), and exposure duration (2–8 h). [Short-term exposure of healthy young volunteers to EMF has no apparent health consequences for stress levels or mood.]

4.6.6 Electromagnetic hypersensitivity

Reports of individuals who claim to be sensitive to electricity first began to appear in the late 1970s with the introduction of VDTs into the modern office environment (Pearce, 1984). Thousands of employees, primarily in Sweden, have reported they are sensitive to EMF (for recent reviews, see (Bergqvist & Vogel, 1997; Liden, 1996)). Although there is

substantial variation among individuals, the reported subjective symptoms and physiological reactions include sleep disturbances, general fatigue, headache, difficulty in concentrating, dizziness, eye strain, facial skin problems (e.g. dry skin, rosacea, seborrhetic eczema, and sensations of itching, burning, or stinging). Typically, the symptoms appear only intermittently at first, subsiding when the individual is away from the VDT. Over time, however, the symptoms may become more pronounced and persistent and begin to interfere with the ability to work or to stay in the general work environment (Bergqvist & Wahlberg, 1994; Sandström *et al.*, 1997). Other electromagnetic devices and appliances (e.g. office equipment, fluorescent lights, household appliances, televisions, and mobile telephones) have also been reported to trigger these adverse reactions in afflicted individuals.

A number of ‘provocation’ studies have been carried out to evaluate individual sensitivity to DC fields, electrostatic fields, AC 50 Hz and 60 Hz EMF, low-MHz radio-frequency fields, and EMF of the type described by Kavet and Tell (Kavet & Tell, 1991) as associated with both plasma and cathode ray tube VDTs (Andersson *et al.*, 1996; Arnetz, 1997; Arnetz *et al.*, 1997; Sandström *et al.*, 1997; Swanbeck & Bleeker, 1989). These studies have been performed in a controlled laboratory environment with double-blind control procedures. Healthy controls and volunteers suffering from electrical sensitivity were asked to detect when they were being exposed in a series of standardized test trials. The measures included detection accuracy, self-reported measures of stress and arousal, blood samples for analysis of stress biochemistry, and histological samples from facial skin.

In general, patients and volunteers in these studies were not able to reliably distinguish exposed from unexposed conditions, and neither subjective symptoms nor biochemical measures were significantly related to the actual exposure conditions. Patients did, however, report accentuated symptoms when they believed they were being exposed, regardless of the actual conditions (Andersson *et al.*, 1996). Berg *et al.* (Berg *et al.*, 1990) performed a histopathological study of 134 individuals with skin complaints. Analysis of objective biopsy data revealed no significant difference between 83 persons highly exposed to VDTs and 51 persons with low exposure to VDTs. No dose–response effect was observed between the amount of VDT exposure and objective skin signs.

Some positive results have, however, been reported. Rea (Rea *et al.*, 1991) found that 16 patients out of 100 had symptoms and signs in response to blind exposure. This finding could not be replicated in a subsequent study (Wang *et al.*,). Similarly, Johansson *et al.* (Johansson *et al.*, 1994) performed an uncontrolled provocation study in which two patients sat in front of a television set. Analysis of skin biopsy samples revealed total disappearance of somatostatin-positive cells after 3 h of exposure. [Few procedural or exposure details were given, and the study has not been replicated.]

Sandström *et al.* (Sandström *et al.*, 1995) performed a case–control study of 163 VDT-exposed workers with skin rashes and found an increased odds ratio (3.0; 95% CI, 1.2–7.2) for symptoms in people who worked in rooms with a 50 Hz background electric field

> 31 V/m in comparison with workers in rooms with background electric fields < 10 V/m. After adjustment for possible confounding factors (e.g. work duration, psychosocial climate, and job stress), the odds ratio increased to 4.0 (1.2–13). Further work (Sandström *et al.*, 1997) indicated that the odds ratio was even higher when only females were considered in the analysis (6.6; 1.7–26). [To date, this is the only well-controlled study showing an association between exposure to ambient fields and skin rashes. It is not known, however, whether this association implies a causal relationship between exposure and the symptoms.]

Various alternative hypotheses have been advanced to account for this phenomenon. These include an imbalance in the autonomic nervous system (Portier *et al.*, 1998), enhanced neurophysiological sensitivity to flicker from fluorescent lights (Sandström *et al.*, 1997), general hypersensitivity to environmental stimuli (Lyskov *et al.*, 1998) occupational stress resulting from increased work load and lack of personal autonomy and social support (Berg *et al.*, 1992; Eriksson *et al.*, 1997), and variations in the physical and chemical quality of the indoor environment (Arnetz *et al.*, 1997; Nielsen & Schneider, 1998; Stenberg *et al.*, 1995). Others have noted a similarity in the symptoms of individuals with electrical hypersensitivity and individuals suffering from ‘multiple chemical hypersensitivity’, ‘environmental somatization syndrome’, ‘environmental illness’, and ‘twentieth century disease’ (Black *et al.*, 1990; Liden, 1996).

[Some individuals have subjective symptoms apparently related to VDT use in the office environment. The evidence is inadequate to relate such symptoms to the EMF associated with that use. Some individuals appear to show positive responses to EMF challenges, but no high-quality double-blinded challenge studies have been conducted which conclusively establish the existence of sensitivity to EMF. There is also no established mechanism for electrical hypersensitivity.]

4.6.7 Summary

There is weak evidence that short term human exposure to ELF EMF causes changes in heart-rate variability, sleep disturbance, or suppression of melatonin.

[The conclusion for effects on heart-rate variability was supported by 13 Working Group members; there was 1 vote for ‘moderate’ evidence, 2 votes for ‘no’ evidence, 8 abstentions, and 5 absent.]

[The conclusion for effects on sleep disturbances was supported by 15 Working Group members; there were 9 abstentions and 5 absent.]

[The conclusion for effects on melatonin was supported by 16 Working Group members; there was 1 vote for ‘moderate’ evidence, 2 votes for ‘no’ evidence, 5 abstentions, and 5 absent.]

There is no evidence that such exposure has other effects on the biological end-points studied in the laboratory.

[This conclusion was supported by 12 Working Group members; there were 2 votes for 'weak' evidence, 11 abstentions, and 5 absent. The tie vote was broken by the Chair.]

Table 4.41 Effects on exposure to EMF on measures of electrical activity in human brain

Reference	Subjects	Exposure parameters	End-points	Major results
Spectral analysis				
(Gamberale <i>et al.</i> , 1989)	26 experienced utility linemen aged 25-52 years	Men inspected insulators on 50 Hz, 400 kV transmission line, line active on one of the two test days (0700-1700 h; personal dosimeter: average exposure 2.8 kV/m, 23.3 μ T	Standard 21-lead clinical EEG exam given at start and end of each test day	No evidence of EEG abnormalities, no evidence of changes in the stability or amplitude of the EEG alpha (8-12 Hz) rhythm
(Lyskov <i>et al.</i> , 1993b)	9 male and 11 female volunteers	1-h no-exposure sham control condition. 1-h exposure of the head to a 45 Hz, 1.26 mT horizontal (ear-to-ear) magnetic field, either continuously or intermittently (1s on, 1 s off).	Spectral analysis (FFT) of the EEG recorded from 7 scalp sites before and after exposure and control conditions	Effects seen primarily with intermittent exposure. Absolute and relative power decreased in low frequency EEG bands (1-7 Hz)*, and increased in higher frequency EEG bands (8-20 Hz)*
(Lyskov <i>et al.</i> , 1993a)	8 male and 6 female volunteers	15-min no-exposure sham control condition. 15-min intermittent (1 s on, 1 s off) exposure of the head to above magnetic field condition.	Same as above.	Absolute and relative power increased in higher frequency EEG bands (8-20 Hz)*, but 15-min exposure had no effect on lower frequency bands.
(Bell <i>et al.</i> , 1992)	10 volunteers and 10 neurological patients	The head of each subject was exposed in a series of 2 s on, 5 s off trials under four test conditions: no-exposure control; 78 μ T, AC magnetic field; 78 μ T, DC magnetic field; and combined 78 μ T AC and DC magnetic field conditions	EEG recorded from multiple sites. Effect defined as change (\pm) in any 0.5 Hz EEG spectral band compared with previous control period.	No EEG effects found in control. Overall, AC magnetic field associated with EEG changes in 19 of 20 subjects* (30% responded to DC field, 70-80% responded to AC field). Combined AC/DC exposure not different from AC exposure alone
Event-related-potential				
(Graham & Cohen, 1985)	18 men 18 women 18-35 years	12 in sham-exposed control group 12 in 60 Hz, 10 μ T exposure group 12 in 60 Hz, 20 μ T exposure group	Short-latency (< 50 msec) neural conduction components of auditory, visual and somatosensory ERPs recorded during magnetic field and control conditions	Main ERP neural conduction time measures not influenced by magnetic field in any sensory modality. One exception: amplitude decreased for somatosensory ERP mid-latency components**, an effect similar to that seen in monkeys by Dowman <i>et al.</i> , 1989
(Graham <i>et al.</i> , 1987)	12 men 18-35 years	All subjects participated in four, 6-h test sessions; half sham, half involving exposure to a 60 Hz 9 kV/m, 20 μ T combined field.	Long-latency (> 100 msec) ERPs recorded in standard "oddball" target-detection paradigm before and after test sessions.	No effects on visual ERP. Exposure associated with increased amplitude of P300 component of the auditory ERP*

Table 4.41 (continued)

Reference	Subjects	Exposure parameters	End-points	Major results
(Cook <i>et al.</i> , 1992)	30 men 21-35 years	18 men exposed and sham-exposed equally over four, 6-h sessions to a continuous 9 kV/m, 20 μ T combined field. 12 men exposed to combined field in all sessions.	Long-latency ERPs recorded in "oddball" task before, during, and after test sessions	No effects on visual ERP. Exposure associated with increased amplitude of the P300 component of the auditory ERP*. Effects on ERP components greatest soon after field activated, and again at end of day when field switched off.
(Graham <i>et al.</i> , 1994)	54 men 18-35 years	All subjects sham exposed in one 6-h session. In a similar session: 18 exposed to a 60 Hz, 6 kV/m, 10 μ T field 18 exposed to a 60 Hz, 9 kV/m, 20 μ T field 18 exposed to a 60 Hz, 12 kV/m, 30 μ T field	Same as above	Exposure to low and intermediate-strength groups associated with a timing delay (latency) in the appearance of P300 component in ERP waveform**. Effect did not occur in the high EMF group. Amplitude of the N200/P300 component complex increased in all field-exposed groups compared with sham control*.
(Graham <i>et al.</i> , 1990)	28 men 18-35 years	14 subjects in sham control 6-h test session. In a similar session, 14 subjects exposed to a continuous 60 Hz, 12 kV/m, 30 μ T field	Same as above	No effects found for visual ERP. Equipment problems resulted in ambiguous effects on latency and amplitude measures of the P300 component of the auditory ERP.

EEG, electroencephalogram; AC, alternating current; DC, direct current; ERP, event-related potential

* $p < 0.05$

** $p < 0.01$

Table 4.42 Laboratory studies of the effects of magnetic fields on electroencephalographic measures of human sleep

Reference	Subject	Magnetic field parameters	Endpoints	Major results
(Graham <i>et al.</i> , 1998)	24 men 18-35 years	60 Hz, circular polarization 8 No-exposure sham controls 7 Continuous exposure (20 μ T/per axis, 2300-0700 h) 9 Intermittent exposure, 1 hr on, 1 h off (20 μ T/per axis, 2300-0700 h)	10 objective EEG sleep measures, sleep quality report measures	Continuous exposure not different from sham on any EEG measure. Intermittent exposure different from sham on 6 of 10 EEG measures** (e.g., less total sleep time, reduced sleep efficiency, increased time in stage 2 sleep, and decreased REM sleep). Sleep quality data reflected EEG disturbances*.
(Akerstedt <i>et al.</i> , 1997a)	18 men & women 24-49 years	50 Hz, Linear polarization 9 No-exposure sham control 9 Continuous exposure 1 μ T, (2300-0700 h) In dwelling catheter for serial blood draws	Objective EEG measures, self-report measures, melatonin, Cortisol, GH, ACTH, Prolactin	Exposure associated with a significant* reduction in slow wave sleep (stages 3 and 4). Exposed subjects also had less total sleep time and reduced sleep efficiency. No effect on hormones.

EEG, electroencephalogram; REM, rapid eye movement; GH, growth hormone; ACTH, adrenocorticotrophic hormone

* = $p < 0.05$

** = $p < 0.01$

Table 4.43 EMF effects of exposure to EMF on human cognition and performance

Reference	Subjects	Exposure parameters	Endpoints	Major results
(Cook <i>et al.</i> , 1992)	30 men 21-35 years	18 men exposed and sham exposed equally over four, 6-hr sessions to a continuous 9 KV/m, 20 μ T combined field. 12 men exposed to combined field in all sessions.	Pre- and post- session multi-task test battery (e.g., RT, math, vigilance, time estimation, memory).	EMF exposure effects on performance different from sham-exposed on only one task in the test battery (exposed subjects made fewer errors when performing the choice RT task *).
(Gamberale <i>et al.</i> , 1989)	26 linesmen 25-52 years	Men inspected insulators on 50 Hz, 400 KV transmission line. Line active on one of the two test days (0700-1700 h; personal dosimeter: average exposure 2.8 kV/m, 23 μ T)	RT, vigilance, memory, and perceptual speed tests before and after exposure and control days.	Performance on exposure days did not differ from performance on control days.
(Graham <i>et al.</i> , 1987)	12 men	Four 6-hr test sessions; half sham, half involving cont. exposure to a 60 Hz 9 kV/m, 20 μ T field.	Pre- and post- session multi-task test battery. (RT, math, vigilance, time estimation, memory).	EMF exposure effects on performance were different from sham -exposed on only one of the battery tasks (exposed subjects made less errors when performing the choice reaction time task *).
(Graham <i>et al.</i> , 1990)	28 men 18-35 years	14 men in sham control 6-h test session. In a similar session, 14 men exposed to continuous 60 Hz, 12 kV/m, 30 μ T field.	4 administrations of multi-task battery (RT, math, vigilance, memory, time estimation).	Performance on exposure days did not differ from performance on control days.
(Graham <i>et al.</i> , 1994)	54 men 18-35 years	All men sham exposed in one 6-h session. In a similar session: 18 men: 60 Hz, 6 kV/m, 10 μ T field 18 men: 60 Hz, 9 kV/m, 20 μ T field 18 men: 60 Hz, 12 kV/m, 30 μ T field	RT, attention, and time perception tests given before, after, and 2 times during exposure and control sessions.	Only exposure at the lowest level was associated performance changes, compared with sham-exposed conditions. RT was slower (12%) and accuracy decreased (13%) on the time perception task*.
(Lyskov <i>et al.</i> , 1993b)	9 men 11 women	1 h no exposure control condition	RT to auditory stimuli	Performance on exposure days did not differ from performance on control days
(Lyskov <i>et al.</i> , 1993a)	8 men 6 women	Same as above, except exposure duration in all conditions was 15 min	RT to auditory stimuli	Performance on exposure days did not differ from performance on control days.
(Stollery, 1986)	76 men 18-65 years	All men sham exposed in one session. In 2nd session, 50 Hz, 50 μ Amp current injected from 10:30-16:00 h into each of 10 electrodes on body. (Equivalent to 36 kV/m)	Memory, attention, vigilance, and reasoning tasks given 4 times a day	No EMF effects on vigilance, sustained concentration, or verbal reasoning were observed.

Table 4.43 (continued)

Reference	Subjects	Exposure parameters	Endpoints	Major results
(Podd <i>et al.</i> , 1995)	6 men 18 women 19-55 years	5-min exposure of head to a 0.1 mT, 0.2 Hz or 43 Hz magnetic field, or to a sham-exposed condition	RT to visual stimuli	Performance on exposure days did not differ from performance on control days.
(Teresiak & Szuba, 1989)	64 men 22-63 years	Study 1: 50 Hz ambient electric field (0, 4.4, 10.9, and 13 kV/m). Study 2: 50 Hz current injected into men (0, 50, 135, and 160 μ amps). Equivalent to Study 1.	RT to the presentation of visual and auditory signals	Significant slowing of RT found in the presence of the 13 kV/m field*, and with current injection of 160 μ A*.

RT, reaction time

* = $p < 0.05$

** = $p < 0.01$

Table 4.44. Effects of exposure to EMF on heart rate and heart rate variability in human volunteers

Reference	Subjects	Exposure Parameters	Endpoints	Major Results
(Graham <i>et al.</i> , 1987)	12 men 21-35 years	All men participated in four, 6-h test sessions; half sham, half involving continuous exposure to a 60 Hz 9 kV/m, 20 μ T field.	Electrocardiogram (R-R interval)	HR slowing was greater after EMF exposure than in sham exposure*.
(Maresh <i>et al.</i> , 1988)	11 men 21-29 years	Sham exposure (2 h) EMF exposure (2 h, 60 Hz, 9 kV/m, 20 μ T) Each preceded by 45 min of rest or exercise	Electrocardiogram (R-R interval)	HR slowing was greater during EMF exposure than in sham exposure*.
(Cook <i>et al.</i> , 1992)	30 men 21-35 years	18 men exposed and sham exposed equally over four, 6-hr sessions to a continuous 9 kV/m, 20 μ T combined field. 12 men exposed to combined field in all sessions.	Electrocardiogram (R-R interval)	HR slowing was greater during EMF exposure than in sham exposure** Also lower in subjects who were field exposed in all sessions, but the effect was not significant.
(Graham <i>et al.</i> , 1994)	54 men 18-35 years	All men sham-exposed in one 6-hr session. In a similar session: 18 men: 60 Hz, 6 kV/m, 10 μ T field 18 men: 60 Hz, 9 kV/m, 20 μ T field 18 men: 60 Hz, 12 kV/m, 30 μ T field	Electrocardiogram (R-R interval)	HR slowing greater after EMF exposure at 9 kV/m, 20 μ T*, but not at lower or higher exposure conditions.
(Graham <i>et al.</i> , 1990)	28 men 18-35 years	14 men in sham-exposed 6-hr test session. In a similar session, 14 men exposed to a continuous 60 Hz, 12 kV/m, 30 μ T field.	Electrocardiogram (R-R interval)	HR was not slower at higher EMF exposure than in sham exposure.
(Korpinen <i>et al.</i> , 1993)	41 men 21-48 yrs	26 men sat for 1-h under a 400 KV line (3-4 kV/m, 1.4 μ T), and at 200 m from the line. 15 men also tested in sham conditions (0.01 kV/m, 0.01 μ T).	Ambulatory monitoring of electrocardiogram	No effect on heart rate at field strengths < 6 kV/m and 10 μ T.
(Sastre <i>et al.</i> , 1998)	Study 1: 29 men 18-35 yrs	11 men in sham-exposed group. Two intermittent Exposure groups of 9 men each (60 Hz, 1 μ T and 20 μ T).	HRV analyses based on electrocardiogram R- R intervals.	Intermittent exposure at 20 μ T reduced “low band” power compared with sham exposure or 1 μ T*.
	Study 2: 22 men 18-35 yrs	Each man was his own control. 2 sessions: sham and intermittent exposure to 60 Hz, 20 μ T.	Same as above.	Intermittent exposure reduced “low band” power*, and increased “high band” power**, compared with sham exposure Continuous exposure at 20 μ T had no effect on heart rate variability.
	Study 3: 26 men 18-35 yrs	Each man was his own control. 2 sessions: sham and continuous exposure to 60 Hz, 20 μ T.	Same as above.	

HR, heart rate; HRV, heart rate variability

* = $p < 0.05$

** = $p < 0.01$

Table 4.45 Effects of exposure to EMF on melatonin and its metabolite in humans

Reference	Subjects	Magnetic field parameters	End-points	Major results
Laboratory studies				
(Graham <i>et al.</i> , 1996) (2 studies)	Study 1: 33 men 18-35 years	60 Hz, circular polarization 11 men: no-exposure, sham control group 11 men: 60 Hz 1 μ T intermittent exposure 11 men: 60 Hz 20 μ T intermittent exposure (Exposure duration 23:00-07:00 h)	Hourly melatonin (2300-0700)	No overall effect; Men with low basal melatonin had greater suppression in a response to light* and magnetic fields*.
	Study 2: 40 men 18-35 years	60 Hz, circular polarization (23:00-07:00 h) All men sham exposed in one session. All men intermittently exposed to 20 μ T in 2nd session. (Each man his own control).	Hourly melatonin (23:00-07:00)	Effects of exposure no different from sham exposure. No effect in men with low basal melatonin.
(Graham <i>et al.</i> , 1997)	40 men 18-35 years	60 Hz, circular polarization, (23:00-07:00 hrs) All men sham exposed in one session All men continuously exposed to 20 μ T in 2 nd session. (Each man his own control).	Hourly melatonin (23:00-07:00)	Effects of exposure not different from sham exposure. No effect in men with low basal melatonin.
(Selmaoui <i>et al.</i> , 1996b)	32 men 20-30 years	50 Hz; 10 μ T; continuous and intermittent exposure linear and circular polarization; (23:00-08:00) Each subject was his own control	Hourly melatonin, 6-OHMS	Effects of exposure not different from sham exposure.
(Akerstedt <i>et al.</i> , 1997b)	18 men and women 24-49 years	50 Hz, 1 μ T, continuous exposure, linear polarization, (23:00-07:00)	Hourly melatonin	Effects of exposure not different from sham exposure
(Wood <i>et al.</i> , 1997)	30 men 18-49 years	50 Hz, 20 μ T, circularly polarized, sinusoidal and square wave fields, 1.5 - 4.0 h exposures	Periodic melatonin (1800-0700 hrs)	No effect when sinusoidal or square wave exposure examined separately; no effect when exposure occurred at MLT peak time or later at night; early night exposure delayed MLT onset in 1 subject exposed over 5 sessions**.
Environmental studies				
(Wilson <i>et al.</i> , 1990)	32 women 10 men tested at home	Home use of standard (conventional) versus modified AC or DC CPW electric blankets for 8 weeks (0.2 - 0.6 μ T exposure range).	Morning and evening 6-OHMS levels (not creatinine corrected)	No overall effect. 7 of 28 CPW users had decreased 6-OHMS in the last 3-week test period* and showed a rebound effect*.
(Pfluger & Minder, 1996)	108 male electric railway workers	42 controls (50 Hz, 1 μ T); 66 locomotive engineers (16.7 Hz, 20 μ T) Continuous sampling of magnetic field (30 min - 4 h)	Urinary 6-OHMS samples collected in morning and evening (creatinine corrected)	Evening 6-OHMS decreased on work days, but not on leisure days*. No effect on morning 6-OHMS levels. No evidence for dose-response curve.

Table 4.45 (continued)

Reference	Subjects	Magnetic field parameters	End-points	Major results
(Burch <i>et al.</i> , 1998)	142 male utility workers 20-60 years	57 controls (60 Hz, 0.1 μ T) 29 field generation workers (60 Hz, 0.2 μ T) 56 field distribution workers (60 Hz, 0.1 μ T) 72 h EMDEX magnetic field level and light intensity measurements taken.	1 home baseline and 3 workday morning 6-OHMS samples (creatinine corrected)	Workplace: No effects on 6-OHMS of magnetic field intensity, intermittency, or cumulative exposure. At home: Temporally stable magnetic field exposure associated with reduced 6-OHMS*
(Arnetz & Berg, 1996)	47 VDT workers who participated in a 1988 study	Compared 1 day working versus not working in front of VDT. No magnetic field measures taken.	Assay of a.m. and p.m. melatonin samples obtained in earlier study (not creatinine corrected)	Melatonin decreased on work day compared with control day*.
(Kaune <i>et al.</i> , 1997)	203 women (control group in breast cancer study) 20-74 yrs	72-h EMDEX measurement of bedroom magnetic field levels (range 0 - 1.5 μ T) and light intensity. Personal exposure monitoring.	Morning 6-OHMS levels measured on 3 consecutive days, 3 or 6 months apart (creatinine corrected)	As log mean bedroom magnetic field increased, log 6-OHMS levels decreased*. Effect is strongest in summer and in women taking medications which reduce melatonin. No effect on 6-OHMS of wire code, intermittency, personal dosimetry, or light-at-night.

6-OHMS, 6-hydroxymelatonin sulfate; CPW, continuous polymer wire; VDT, visual display terminal

* = $p < 0.05$

** = $p < 0.01$

4.7 *In vitro* and mechanistic studies

Since a very large number of cellular components, cellular processes, and cellular systems can conceivably be affected by EMF, mechanistic studies are essential to interpret and help guide the experimental work. Because evidence from previous theoretical and experimental studies suggested that EMF are unlikely to induce DNA damage directly, most studies have been conducted to examine its effect on the cellular membrane, general and specific gene expression, and signal transduction pathways. More recently, studies specifically addressing the genotoxic effect of exposure to magnetic fields have been pursued.

While some studies were conducted with samples from animals exposed to EMF *in vivo*, most results have come from studies of cultured cells exposed *in vitro*. The great advantage of *in-vitro* exposure is its precision, since the geometry and physical properties of the system can be well controlled.

While a major concern of the possible effects of EMF on public health is cancer, only a small number of *in-vitro* studies were designed to address particular hypotheses generated from previous studies of carcinogenesis. Thus, while EMF have been tested in a number of established assays for genetic toxicity, the effects primarily studied have been non-genotoxic mechanisms of carcinogenesis, including induction of cell proliferation, inhibition of intercellular communication, modulation of cell differentiation, and aberrant control of proto-oncogene expression. These cellular effects and subcellular effects such as active oxygen production and modulation of protein kinase C signal transduction are well-documented activities of non-genotoxic carcinogens such as the phorbol esters.

In this section, the *in vitro* effects of exposure to EMF are documented, including theoretical and physical considerations of mechanisms by which EMF can induce biological effects. The *in vitro* responses considered are mainly genotoxicity, regulation of gene expression, cell signaling and proliferation, and cell differentiation.

4.7.1 Genotoxicity and regulation of gene expression

The interest in assessing the effects of EMF at the cellular level in order to understand the mechanism(s) by which exposure may be harmful and/or beneficial to human health has temporally coincided with a rapid increase in knowledge about regulation of gene expression and the role that specific gene products play in cell replication, proliferation, differentiation, and pathological processes.

4.7.1.1 Genotoxicity

The genotoxic effects of EMF have been extensively reviewed by McCann *et al.* (McCann *et al.*, 1998; McCann *et al.*, 1993).

DNA damage and chromosomal effects

It is generally accepted that ELF EMF do not transfer energy to cells in sufficient amounts to directly damage DNA; however, it is possible that certain cellular processes altered by exposure to ELF EMF, such as free radicals, indirectly affect the structure of DNA. Most investigators have looked for strand breaks and other chromosomal aberrations, including sister chromatid exchange, formation of micronuclei, and/or effects on DNA repair.

Cultured human peripheral blood lymphocytes from volunteers were used to assess the effects of power-frequency sine wave or pulsed magnetic fields on cytogenetic events. Magnetic fields of 1–7.5 mT and exposure durations of 48–72 h produced no significant chromosomal effects (Paile *et al.*, 1995; Rosenthal & Obe, 1989; Scarfi *et al.*, 1994). Simultaneous exposure to an electric field (60 Hz, 30 $\mu\text{A}/\text{cm}^2$) and a magnetic field (0.1 or 0.2 mT) did not cause sister chromatid exchange or chromosomal breaks (Cohen *et al.*, 1986a; Cohen *et al.*, 1986b). In one study (Khalil & Qassem, 1991), however, EMF were found to induce chromosomal aberrations in human lymphocytes. In this study, exposure of human lymphocytes to a pulsed field with a peak magnetic flux density of 1.05 mT for 24–72 h induced a statistically significant, twofold increase in the frequency of chromosomal aberrations and a simultaneous lowering of the mitotic index. In human lymphocytes exposed to a 4.4 kHz pulsed field with a 14 Hz repetition rate, no effect on sister chromatid exchange rate was seen (Garcia-Sagredo *et al.*, 1990). [With only one exception Rosenthal & Obe (1989), positive controls were not used in these studies.]

In another model, human amniotic fluid cells were exposed to a 50 Hz sine-wave field (30 μT rms) for 72 h. They showed a modest but consistent increase in the frequency of total chromosomal aberrations when compared with controls (Nordenson *et al.*, 1992). While higher flux densities (300 μT) did not affect the cells in this manner, intermittent exposure (15 s on–off for 72 h) to the 30 μT field was as effective as continuous exposure in increasing aberration frequencies (Nordenson *et al.*, 1994). In a study to replicate these findings, Galt *et al.* (Galt *et al.*, 1995) reported a nonsignificant decrease in the number of cells with chromosomal aberrations after exposure to 30 μT . [A striking difference between these two investigations was the level of aberrations in the control cells, which was fourfold higher in the study of Galt *et al.*; the authors did not comment on this point. Furthermore, the ambient DC field differed substantially between the two laboratories.] In established cell lines, however, exposure to EMF does not appear to induce chromosomal aberrations (Fairbairn & O'Neill, 1994; Fiorani *et al.*, 1992; Livingston *et al.*, 1991; Reese *et al.*, 1988; Takahashi *et al.*, 1987).

The 'Comet' assay (DNA microelectrophoresis) has been used to detect DNA fragmentation in single cells (Lai & Singh, 1997a; Lai & Singh, 1997c; Singh & Lai, 1998). Increases in both single- and double-strand breaks were reported in brain cells of rats exposed *in vivo* to a 60 Hz field at 0.1–0.5 mT. Radical scavengers like melatonin and *N*-tertbutylphenylnitron counteracted the effects of exposure, suggesting that magnetic fields can affect the levels or lifetimes of certain free radical species (Lai & Singh, 1997c). The authors further suggested that exposure to ELF magnetic fields (60 Hz, 0.5 mT, 2 h) can cross-link DNA and also DNA and proteins, in a manner similar to mitomycin C (Singh & Lai, 1998). [The authors used mitomycin C as a positive control only in human lymphocytes; in addition, the report does not mention ambient DC fields.]

Scarfi *et al.* (Scarfi *et al.*, 1991; Scarfi *et al.*, 1993; Scarfi *et al.*, 1994) were consistently unable to detect an increase in micronuclei in normal cultured human lymphocytes exposed to a 50 Hz pulsed magnetic field or a sinusoidal E field; however, cells from patients with Turner's syndrome showed an 80–100% increase in micronuclei after similar exposure (Scarfi *et al.*, 1997b). After exposure to a 100 Hz magnetic field, the number of micronuclei increased in cultured human lymphocytes (Scarfi *et al.*, 1997a).

Tofani *et al.* (Tofani *et al.*, 1995) found that the DC field is important, since exposure of peripheral lymphocytes to 32 or 50 Hz (75 or 100 μ T) with no DC component was ineffective in inducing micronuclei, whereas cells exposed to the 32 Hz field had a higher incidence of micronuclei when a DC component (42 μ T) was introduced parallel to the AC field. In Chinese hamster V79 cells, however, exposure to pulsed magnetic fields (10 or 100 Hz, 20 or 80 μ T) for 24 h increased 3 H-thymidine incorporation, while exposure to 0.4 mT decreased incorporation (Takahashi *et al.*, 1986). Cadossi *et al.* (Cadossi *et al.*, 1992) using the same assay conditions, reported that lymphocytes from aged donors and from patients with B-cell chronic lymphocytic leukemia responded better to the pulsed magnetic field (2.5 mT, 2 mV PEMF with a 50 Hz repetition rate, 24 or 48 h) than lymphocytes from young healthy donors. Exposure of human T-cell leukemia Jurkat cells to a magnetic field (1.8 mT) bone healing signal reduced 3 H-thymidine incorporation by 50%, whereas a 60 Hz sine wave (0.1 or 0.4 mT) applied for 20 min reduced incorporation by 20–25 % (Nindl *et al.*, 1997). Simko *et al.* (Simko *et al.*, 1998) found increased micronucleus formation in a human squamous-cell carcinoma cell line (SCL II), but not in human amniotic fluid cells, exposed to a 50 Hz magnetic field (0.1–1.0 mT) for 24, 48, or 72 h. The results of most other studies on micronucleus formation have been negative (Lagroye & Poncy, 1997; Livingston *et al.*, 1991), although the latter authors showed micronuclei formation in rat tracheal epithelial cells treated with ionizing radiation (6 Gy) prior to a 50 Hz, 100 μ T field for 24 h, the magnetic field alone had no effect. Very strong static fields (4.7 T) were shown to decrease micronuclei frequency in mitomycin-treated Chinese hamster lung/IU cells (Okonogi *et al.*, 1996).

Several authors have studied the ability of ELF EMF to alter the repair of strand breaks induced by hydrogen peroxide or by radiation. No effects were seen with exposure to either B or E fields (Bersani *et al.*, 1989; Cantoni *et al.*, 1995; Frazier *et al.*, 1990; Whitson *et al.*, 1986).

Mutational changes

Relatively few studies have been reported of the effects of EMF on gene mutation (McCann *et al.*, 1998). As is often the case, the exposure protocols differ widely, and no consistent picture has evolved on possible effects. Exposure to electric and/or magnetic fields at various frequencies did not induce mutation in *Salmonella typhimurium* (Morandi *et al.*, 1996; Nafziger *et al.*, 1993). Similarly, Ager and Radul (Ager & Radul, 1992) found that exposure of yeast cells to a magnetic field (1 mT) alone or in combination with ultraviolet irradiation (2–50 J/m²) had no effect on mutations; and Pakhomova *et al.* (Pakhomova *et al.*, 1998) saw no mutations in *Saccharomyces cerevisiae* after exposure to an ultra-wide bandwidth pulsed field (101–104 kV/m, impulses repeated at 16 or 600 Hz). In contrast, Koana *et al.* (Koana *et al.*, 1997) reported that a strong static field (5 T, 24-h exposure) increased the frequency of somatic recombinations in third-instar larvae of *Drosophila melanogaster*, which was blocked by vitamin E treatment, suggesting involvement of oxygen radicals.

Prior and concurrent treatment of a rat embryo fibroblast cell line carrying the *Escherichia coli lacI* gene with *N*-methyl-*N*-nitrosurea (MNU) or menedione and exposure to a 60 Hz magnetic field (3 mT) for 120 h did not increase the mutation frequency (Suri *et al.*, 1996). The *hprt* gene mutation was induced in human MeWo cells exposed to 50 Hz, 400 mT for 2 h (Miyakoshi *et al.*, 1996). Subsequently, these authors also reported (Miyakoshi *et al.*, 1998) enhanced mutagenicity in a human osteosarcoma cell line, Saos-LP-12, exposed to a 50 Hz, 400 mT magnetic field. When this cell line, which does not carry the *p53* gene, was transfected with an inducible wild-type *p53* gene, the enhanced mutagenicity associated with exposure to EMF was suppressed, suggesting a role for the wild-type *p53* gene in guarding the genome from DNA damage. No marked differences in the mutation spectrum in the *hprt* gene was observed in those cells with or without the *p53* gene after exposure to magnetic fields (Miyakoshi *et al.*, 1998). Nafziger *et al.* (Nafziger *et al.*, 1993), however, did not observe induction of *hprt* mutations in Chinese hamster V79 cells after exposure to a 50 Hz magnetic field at lower field strengths (1 or 10 μ T). An effect of EMF on *hprt* gene mutations was reported in Chinese hamster ovary cells after exposure to ionizing radiation in two laboratories. Exposure to EMF alone did not induce mutations in either study. A dose-related increase in mutation frequency induced by EMF (60 Hz, 0.47–0.7 mT) was reported after pre-exposure to γ -irradiation (2 Gy) (Walleczek *et al.*, 1998). A small increase in mutation rate was also observed when Chinese hamster ovary cells were exposed to EMF (60 Hz, 5 mT) after pre-exposure to X-rays (3 Gy) (Miyakoshi *et al.*, 1998). Similarly, EMF (60 Hz, 400 mT) increased the mutation rate in MeWo cells after prior exposure to X-ray (3 Gy) (Miyakoshi *et al.*, 1996). [A clear effect of magnetic fields on mutation has so far been seen only at field strengths well above those that occur in the environment.]

4.7.1.2 Transcription

Effects on gene expression

Several studies have addressed the general question of whether ELF EMF can affect RNA synthesis, with both positive and negative outcomes. This subject has been reviewed (Lacy-Hulbert *et al.*, 1998).

Effects on gene expression, particularly at the transcriptional level, after exposure to ELF EMF was first investigated by Goodman and coworkers. The main focus of their research was the effect of EMF on *c-myc* mRNA levels in human HL60 cells, although in earlier papers (Goodman *et al.*, 1992; Goodman *et al.*, 1989) they reported increased expression of several specific transcripts (including β -actin, β -tubulin, histone H2B, *c-myc*, and *c-src*) as deduced by dot-blot analysis. Goodman *et al.* (Goodman *et al.*, 1989) found that several types of fields (sinusoidal 60 or 72 Hz; pulsed fields at 1.5, 15, or 72 Hz) at field strengths of 0.38–3.5 mT could increase mRNA levels by two- to threefold after 20 min exposure, as measured by dot-blot analysis. The strongest response was to 60 Hz sinusoidal fields with a 1.5 mT peak B value. In contrast, this group reported later (Goodman *et al.*, 1992) that the most prominent effects appeared after 20 min exposure to a 60 Hz, 5.7 μ T field. Stronger fields or longer exposure times tended to diminish the observed effects. The paper included a report of northern blot analysis to confirm the identity of the investigated transcripts [The group used dot-blot analysis without internal controls for quantification of mRNA levels]. Rao and Henderson (Rao & Henderson, 1996) transfected HL60 cells with a *c-fos* promoter construct upstream of the bacterial *CAT* gene to obtain a reporter gene assay system. The positive control, TPA, increased *CAT* activity by 10–40% above control levels, while a 20-min exposure to a 60 Hz, 6 μ T (rms) field increased the activity by 5–20 % above the control level. [The induction of promoter activity by TPA was rather small.] Increased expression of the large T antigen mRNA and protein in SV40-transformed fibroblasts exposed to a 60 Hz, 8 μ T field for 20 min (the only exposure conditions employed) was reported (Gold *et al.*, 1994).

EMF (pulsed 72 Hz field, 3.5 mT peak value) stimulated 3 H-uridine incorporation, mRNA synthesis, and protein synthesis but not DNA synthesis in the human leukemia cell line CCRF-CEM (Phillips & McChesney, 1991). While exposure for 30 min to 4 h was effective, longer exposure diminished the response. The same cells were used in subsequent studies of transcription of *c-myc*, *c-fos*, *jun*, and *PKC- β* mRNA; nuclear run-off assays showed two- to threefold increases in mRNA transcription after exposure to a 60 Hz, 100 μ T magnetic field for 15, 30, 60, or 120 min. The effects were dependent on time cell density (Phillips *et al.*, 1992). Exposure of CCRF-CEM cells to a pulsed magnetic field (72 Hz, 3.5 mT) induced a modest decrease in *p21-ras* mRNA and protein levels (Phillips *et al.*, 1993).

Possible effects of EMF on the expression of specific genes have been studied by other groups. Lagroye and Poncy (Lagroye & Poncy, 1998) reported that exposure to a 50 Hz,

100 μ T magnetic field for 5 h up-regulated *c-jun* expression in primary and immortalized rat tracheal cells, while expression of *c-fos* increased in the immortalized cells and decreased in the primary culture. Down-regulation of the multi-drug resistance gene *MDR1* mRNA was found after E-field stimulation (10–3000 mV/cm, 60 Hz, 16 h) (Walter *et al.*, 1997). Strong static fields (0.18–0.2 T) were shown to induce *c-fos* transcription in HeLa cells (Hiraoka *et al.*, 1992). In several studies on the effects of 60 Hz fields, however, no effects on transcripts have been seen, including those of *c-myc*, *c-fos*, and *c-jun*, in HL60 cells (Balcer-Kubiczek *et al.*, 1996; Greene *et al.*, 1993), HeLa cells, MCF7 breast cancer cells (Dees *et al.*, 1996; Harrison *et al.*, 1997), and several other human and rodent cell lines (Parker & Winters, 1992). [These studies were performed under more stringent conditions than earlier ones; they included better control conditions and stricter exposure metrics.] In a study on HeLa cells stably transfected with an *HIV-LTR-CAT* construct (Libertin *et al.*, 1994), combined AC and DC fields (10 Hz to 1.6 kHz; 35–70 μ T; plus a 0.17 mT DC field) did not induce reporter gene expression. A 50 Hz (200 or 400 mT) sine-wave field induced expression of a reporter gene containing the human VIP promoter in front of a β -galactosidase gene only when cells were simultaneously treated with forskolin, which activates adenylyl cyclase. These effects were blocked by the PKC inhibitor calphostin C and also by nifedipine and dantrolen, suggesting that the effect is mediated by calcium (Ohtsu *et al.*, 1995).

The effect of EMF on the general transcriptional level has been studied in the yeast *S. cerevisiae* and in cultured human cells (Binniger & Ungvichian, 1997; Woloschak *et al.*, 1998). After exposure of the yeast cells for 15 generations (24 h) to a 60 Hz sinusoidal field at 20 μ T, Binniger and Ungvichian (Binniger & Ungvichian, 1997) found that most of the mRNA (44–67% in four separate experiments) was not affected by exposure, although 26–38% of the investigated mRNA species were increased twofold or more by exposure; 7–18% seemed to be down-regulated by at least 50%. The relatively large variations between experiments are possibly due to the unusually long exposure (several generations), thus reflecting changes in properties that biological materials undergo with time. Another genome-wide approach was adopted by Woloschak *et al.* (Woloschak *et al.*, 1998), who used the so-called differential display reverse transcription–polymerase chain reaction protocol. This procedure allows comparisons of material from two experimental conditions and identification of virtually any change in mRNA pattern. The authors exposed human HeLa cells for 24 h to a 60 Hz, 0.10 mT magnetic field. After analysis of roughly 10% of all transcripts, they found two genes that were specifically induced by exposure. Their identity is unknown. The authors deduced that no more than 20 genes would be affected by their specific exposure regimen.

Effects on c-myc expression

Although a fourfold increase in *c-myc* mRNA was initially found in HL60 cells exposed to various EMF, as measured by dot–blot analysis (Goodman *et al.*, 1989), the magnitude of the increase has since been reported to be only 15% above control levels when analyzed by northern blots and including proper controls after a 20 min, 8 μ T, 60 Hz exposure (Karabakhtsian *et al.*, 1994). In transfected HeLa cells, both endogenous *c-myc* mRNA

and the activity of the reporter gene were increased after exposure to a 60 Hz, 80 μ T magnetic field for 20 min (Lin *et al.*, 1994). An additional group (Liburdy *et al.*, 1993a) has reported a three-fold increase in *c-myc* mRNA levels after exposure of rat thymocytes to 60 Hz (22 mT).

Recently, several groups have tried to reproduce or replicate the findings of Goodman and co-workers on *c-myc* induction by power-frequency magnetic field in HL60 cells. Exposure to 50 Hz sinusoidal fields (10 μ T or 1 mT; 20 min to 72 h) was used by Desjobert *et al.* (Desjobert *et al.*, 1995) and a 60 Hz sine wave (0.57 μ T to 10 mT, 20–60-min exposure by Lacy-Hulbert *et al.* (Lacy-Hulbert *et al.*, 1995), Saffer and Thurston (Saffer & Thurston, 1995), Owen *et al.* (Owen, 1998), and Miyakoshi *et al.* (Miyakoshi *et al.*, 1996). The latter group used only a 5 mT 60 Hz field for 30, 60, or 180 min. None of these studies showed an effect on *c-myc* levels, β -actin level (Lacy-Hulbert *et al.*, 1995), or on any other transcripts as evaluated by the mRNA differential display method (Saffer & Thurston, 1995). In a follow-up study, Goodman and co-workers (Jin *et al.*, 1997), demonstrated that different strains of the HL60 cell line have different responses to the 60 Hz field. Only cells obtained from Columbia University showed increased *c-myc* after exposure, whereas cells from the ATCC were unresponsive. Neither Lacy-Hulbert *et al.* nor Saffer and Thurston used the Columbia University cells; however, Owen *et al.* (Owen, 1998) performed a similar comparison of these cell line variants. They found differences in several characteristics, as did Goodman and colleagues, but could not replicate the finding of changes in *c-myc* after exposure in any of the strains. Owen *et al.* also analyzed the cells in Goodman's laboratory and found no effect of magnetic fields, irrespective of the exposure location.

Stress protein gene transcription

It has been suggested that cells might respond to EMF with changes in transcription and translation of heat-shock proteins, as they do to some other environmental stresses (Goodman *et al.*, 1994a; Lin *et al.*, 1997; Weisbrot *et al.*, 1993). In support of this suggestion, exposure to a magnetic field (60 Hz sine wave, 8 μ T peak B field, 11 μ V/m induced field, 20 min) increased *hsp70* mRNA in cultured human cells (Goodman *et al.*, 1994b). Exposure to EMF (60 Hz sine wave; 0.8, 8, and 80 μ T with an induced E electric field of 1.1 μ V/m, 11 μ V/m, and 110 μ V/m, respectively) had a similar effect on *SSA1* mRNA, corresponding to *hsp70* in *S. cerevisiae* (Weisbrot *et al.*, 1993). Additionally, HL60 cells exposed to 60 Hz, 8 μ T (peak-to-peak) for 20 min showed activation of heat-shock transcription factor (*hsf1*) and subsequent DNA binding (Lin *et al.*, 1997); however, exposure of cultured mouse and human cells to rotating 60 Hz fields (0.1 mT for 24, 48, or 72 h) did not induce *hsp70* mRNA synthesis (Parker & Winters, 1992).

4.7.1.3 Translation and protein synthesis

The effect of EMF on protein synthesis both in general and more specifically has been studied in several laboratories. Increases in protein synthesis were reported in

prokaryotes and eukaryotes after exposure to EMF (Lacy-Hulbert *et al.*, 1998). Only a few studies of the effects of EMF on the synthesis of specific proteins are available. Increased synthesis of some proteins such as IGF II was reported (Fitzsimmons *et al.*, 1992).

4.7.1.4 Summary

Despite the large number of studies of molecular effects in cells exposed to EMF, no consistent picture emerges. The studies differ substantially in their biological approach and the techniques used; even within the same laboratory, some studies could not subsequently be reproduced.

DNA damage and chromosomal effects

The results of studies of primary cultures of peripheral blood cells from volunteers indicate that even quite strong fields, in the millitesla range, do not generally cause chromosomal aberrations; positive results were reported in only one study.

As no consistency was seen in the exposure parameters required for such effects, the observed findings have little predictive value.

Mutations

Mutation is an area of molecular research in which consistency among results appears to be developing. In numerous studies, 48-h exposure to flux densities below approximately 0.1–1 mT have consistently shown no effect on mutagenesis in *Salmonella typhimurium*. As discussed elsewhere, there is little evidence that EMF below 0.1 mT damage DNA or induce cytogenetic damage; these effects are usually associated with mutation. Fields of 400 mT have, however, been reported to enhance mutagenicity at the *HPRT* gene locus in a human cell line after pre-exposure to ionizing radiation. In addition, a 2-h exposure to a 400 mT field enhanced mutagenesis in the absence of ionizing radiation in this same cell line and in a human osteosarcoma cell line. Expression of a regulated p53 transgene in the osteosarcoma cell line suppressed the effect of EMF on mutation. At lower field intensities (0.23–5 mT), exposure was reported by two laboratories to enhance mutagenicity in Chinese hamster ovary cells after exposure to ionizing radiation, and in one laboratory the mutation response was found to depend on the intensity of the field. Finally, in a single study, a static field of 5 T was shown to increase the frequency of somatic recombination in *Drosophila* in a protocol that implicates the involvement of oxygenradicals.

Effects on gene expression and stress response

A few research groups have contributed most of the scientific literature on EMF-related effects on transcription and gene expression. Overall, the results are conflicting, especially with regard to the effects of power-frequency fields. Attempts to replicate the findings of other laboratories have met with little success, although reproducibility has been reported within a single laboratory.

The steady-state mRNA levels of several genes, including proto-oncogenes such as *c-myc*, *c-fos*, and *c-jun*, were reported by a single laboratory to be increased after exposure to EMF. The reports indicated that very low field strengths are effective and that specific time-windows are needed to induce effects. The effect has been seen for several years. Specific studies of replication regarding *c-myc* expression in other laboratories have not been able to confirm this finding. As the reported response was low—a 10–20% increase—replication will be difficult, if this effect is real. It is furthermore unclear whether such small effects on *c-myc* are biologically important for downstream events. The group that reported induction of proto-oncogene expression also tried to follow the specific sequence of events that leads to induction of *hsp70* transcription and translation. Their findings indicate that the primary effect is a stress response to the field, but this is difficult to reconcile with an increase in RNA synthesis and mRNA transcription in general.

4.7.2 Signal transduction and proliferation

Signal transduction occurs in molecular systems at the cell membrane and inside the cell, in which signals from the environment and from other cells are received. These signals regulate intracellular processes, such as metabolic activity, gene expression, differentiation, and cell proliferation. Signal transduction processes are important pathways by which EMF may affect cell function. Membrane signal transduction processes have been an area of particular attention, mainly because the cell membrane presents a substantial barrier to electric fields, especially in the range of field strengths and frequencies present in the environment. Electric fields are attenuated between the external plasma membrane surface of mammalian cells and the interior of the cell by an estimated factor of 10^3 – 10^5 (Polk, 1992b; Polk, 1992c) No significant penetration of information-containing electric signals across the cell membrane can be postulated for the 60 Hz ambient fields encountered in ordinary domestic situations.

Membrane-mediated signal transduction by hormones and other signaling agents involves transmission across the plasma membrane that does not require penetration of the membrane. Signals associated with a conformational change in a membrane protein are propagated across the cell membrane by three well-understood mechanisms: opening and closing of ion channels and resultant current flow; changes in an intrinsic enzymatic

activity of the receptor; and changes in the affinities of the receptor for intracellular proteins, which might have enzymatic activity.

In nearly all cases, the mechanism of signal transduction distal to the receptor involves effects on intracellular pathways due to changes in the ionic composition of the cytosol (e.g. changes in intracellular calcium) or changes in phosphorylation of intracellular proteins (e.g. enzyme activity, enzyme regulators, and factors transcriptional regulatory). Cellular responses to signals are either short-term, with little or no persistence of the effect after removal of the signal, or long-term, involving persistent changes in the function of cells, such as increased or decreased proliferation, changes in gene expression or differentiation, and, in some cases, apoptosis (programmed cell death). The short-term changes are generally mediated by modification of enzyme activity in the cytosol or membrane of the cell. The long-term changes invariably involve alteration of nuclear function, such as transcription, cell division, and cell-cycle regulation.

4.7.2.1 Calcium homeostasis and flux

Numerous experimental investigations have addressed the interaction between EMF and calcium fluxes, because calcium is a principal regulator of processes such as muscle contraction, bone formation, cell attachment, hormone release, nerve impulse transmission, synaptic communication, membrane potential regulation, and cell proliferation. Calcium ions are strictly regulated in all cell types and serve as messengers or effectors of many biological processes (Rasmussen & Barrett, 1984). They also serve as second messengers in excitable and non-excitable cells, where the cytosolic concentration of calcium regulates the activities of a series of molecules, including kinases, phosphatases, phosphodiesterases, cytoskeletal components, and ion channels.

Walleczek and Liburdy (Walleczek & Liburdy, 1990) observed that 60 Hz magnetic fields increased ^{45}Ca influx during concanavalin A-induced signal transduction in lymphocytes. Rat thymocytes were exposed to a 22 mT magnetic field (induced electric field, 1.0 mV/cm) for 60 min at 37 °C in the presence or absence of concanavalin A. In the absence of the mitogen, the cells were unresponsive to the magnetic field: the ^{45}Ca influx was not altered. In its presence, the magnetic field increased the ^{45}Ca influx by 50–200%.

Even though the ion cyclotron resonance mechanism (Liboff *et al.*, 1990) is no longer accepted as a plausible biophysical explanation, a number of experiments were performed under exposure conditions corresponding to the calculated ion cyclotron resonance frequency for calcium, with variable results. For example, some investigators (Liburdy, 1992; Walleczek & Budinger, 1992; Yost & Liburdy, 1992) found alterations when these exposure conditions were combined with stimuli such as mitogens. Parkinson and Hanks (Parkinson & Hanks, 1989), however, saw no changes in cytosolic calcium concentrations with resonant and nonresonant EMF in Balb/c#3T3, L929, V79, or ROS cells.

Lindstrom *et al.* (Lindstrom *et al.*, 1993) showed that application of a 50 Hz 100 μ T magnetic field increased intracellular Ca^{++} signaling in the Jurkat T-cell line, and the effect was similar to that obtained with an anti-CD3 monoclonal antibody, used as a positive control. Additional work by this laboratory showed that exposure to this EMF resulted in a significant increase in inositol 1,4,5-trisphosphate concentration (Korzh-Sleptsova *et al.*, 1995). As chelation of intracellular Ca^{++} did not block the increase, magnetic fields may affect signal transduction events upstream of inositol 1,4,5-triphosphate. Lyle *et al.* (Lyle *et al.*, 1997) failed to replicate these studies on calcium signaling. [Differences in the strain of Jurkat cells may have affected the response.]

It is well established that intracellular calcium concentrations can oscillate in response to an external stimulus (Fewtrell, 1993; Meyer & Stryer, 1991), the period of the oscillations typically being between 1 s and several min. A model based on nonlinear dynamics and the theory of self-sustained (limit cycle) oscillators was developed which shows how a small change in the signal pathway at an early stage can lead to large changes in calcium metabolism in the cell (Eichwald & Kaiser, 1993); however, experimental verification of this model is lacking.

More recent experimental work has taken advantage of technical advances in the study of cell calcium metabolism, including the development of intracellular calcium probes, sensitive imaging procedures, and calcium-selective microelectrodes (Borle, 1990; McLeod, 1992). These studies also involve improved techniques for estimating exposure to EMF.

Walleczek *et al.* (Walleczek, 1995) developed a dual-chamber real-time fluorescence spectroscopy system that allows sham exposure to study the effects of low-level ELF fields. Exposure to a 60 Hz 2 mT magnetic field inducing an electric field of 1.8 mV/m had no effect on calcium influx in cells with a high initial calcium influx rate ($n = 65$), but in cells with a low pre-exposure flux rate, field exposure resulted in a significant increase (3.5%, $n = 88$; $p < 0.001$) in comparison with sham-exposed samples after a single 2-min exposure. The authors concluded that the cellular response to field exposure is strictly dependent on the cell state.

McLeod (McLeod, 1992) studied changes in calcium transient activity in a transformed bone cell line (ROS17/2.8) using a pure electric field exposure system. Aqueorin-loaded cells growing in a monolayer on glass or polystyrene substrates were exposed to 60 Hz electric fields (0.1–10 mV/m). Exposure resulted in a significant, dose-dependent decrease frequency of Ca^{2+} pulses or amplitude. activity that was different for the two substrates. The lowest threshold for a detectable field effect was estimated by the investigators by extrapolation to be approximately 0.4 mV/m for the cells growing on polystyrene. Siskin *et al.* (Siskin, 1998), using a similar approach for measuring calcium but a significantly different exposure system based on magnetic induction, were unable to replicate these effects.

Sontag (Sontag, 1998) used HL-60 cells differentiated into granulocytes to study the effect on cytosolic free calcium of sinusoidal electric fields at selected frequencies between 0 and 100 Hz with the calcium indicator fluo-3. Field strengths of 1-2000 Vpp/m (external field) or 0.1-1000 Vpp/m (in medium) had no significant effect. [As the highest of these intensities would depolarize the cells by more than 10 mV, the sensitivity of this assay to detect intracellular calcium changes is questionable.]

4.7.2.2 Receptor-mediated signaling pathways

Although many early studies on bone cell cultures were performed with complex waveforms, it has since been demonstrated that sine-wave fields can have similar effects. The cellular mechanism of bone stimulation by sine-wave fields appears to be similar to that of pulsed fields. Exposure to a 0.1 mT, 60 Hz sinusoidal magnetic field (Luben, 1993; Luben, 1994) significantly inhibited cAMP accumulation in osteoblasts in response to 1 nM parathyroid hormone. This inhibitory activity was decreased at higher doses of parathyroid hormone, with no significant inhibition at 100 nM or 0.1 μM^{-7} mol/L. Frequency spectrum analysis of the Electro-Biology™ pulsed fields indicated that the most widely used clinical device has a significant component of magnetic field strength in the vicinity of 60 Hz (Polk, 1995). Subsequent experiments with the same 0.1 mT 60 Hz exposure field (Luben, 1994) also showed that exposure for 30 min to 24 h caused translocation of protein kinase C (PKC) to the membrane fraction of bone cells, followed by a progressive down-regulation of PKC activity. Down-regulation of PKC is often seen after treatment of cells with agents such as hormones and phorbol esters which activate it (Kikkawa *et al.*, 1989). It has been known for some time that agents that regulate parathyroid hormone receptor responses in osteoblasts also induce PKC translocation and down-regulation (Abou-Samra *et al.* 1989; Fujimori *et al.*, 1992).

PKC is believed to be the receptor for tumor-promoting phorbol esters (Kikkawa *et al.*, 1989), and several investigators have examined the effects of magnetic fields on PKC. Monti *et al.* (Monti *et al.*, 1991) showed that HL-60 lymphocytes exposed to a 50 Hz, 8 mT magnetic field have increased binding of the PKC-specific phorbol ester PDBu, suggesting that these relatively strong magnetic fields may modify the cellular response to tumor promoters. Similar results were obtained by Holian *et al.* (Holian *et al.*, 1996), who showed that PKC activity in the cytosol of HL-60 human leukemia cells is regulated by exposure to 60 Hz electric fields at 100–1000 mV/cm. The effects of EMF treatment were additive with those of 2 μM TPA.

Miller *et al.* (Miller & Moulder, 1998) used the human promonocytic leukemia cell line U937 to evaluate the hypothesis that exposure to a 60 Hz EMF amplifies the PKC-dependent signal transduction pathway that mediates the activation of NF- κ B or AP-1-dependent reporter gene expression. In comparison with well-understood chemical and biological agents, EMF of 80, 100, or 1300 μT for 0.5-24 h had no effect on the NF- κ B or AP-1 signaling pathway. This finding raises the possibility that the membrane receptor-

linked protein tyrosine kinase signaling pathway operating in B-lineage leukemia cells may be important for the effects of EMF.

Uckun *et al.* (Uckun *et al.*, 1995) also reported that PKC activity is increased in human pre-B leukemia cells exposed to a 60 Hz 100 μ T magnetic field. Moreover, activation of PKC was dependent on the activation of lyn kinase, a tyrosine protein kinase of the *src* family which is known to be involved in proliferation of leukemia cell clones. In recent studies, the same group used the DT-40 chicken lymphoma B-cell model to demonstrate that lyn kinase is essential for phospholipase c- γ 2 activation and inositol 1,4,5-triphosphate turnover stimulated by exposure to 60 Hz, 100 μ T EMF (Dibirdik *et al.*, 1998). In a third paper, this group reported that phospholipase c- γ 2 activation in EMF-stimulated cells in the DT-40 model system is mediated by stimulation of Bruton's tyrosine kinase (Kristupaitis *et al.*, 1998). These three studies provide evidence that a delicate balance of growth regulation in B-lineage lymphoid cells might be altered by EMF.

[The findings of Uckun's group are of interest as they show that EMF affect a well-understood, important signal transduction pathway involved in signaling through the B-cell receptor. Simultaneous, blinded, real and sham exposure was not carried out in the recent studies of Dibirdik *et al.* and Kristupaitis *et al.* since both reports indicate that the unexposed cells were placed in a 'control incubator' with a measured field of 0.8 μ T. This is a critical procedure for quality control. Their observation of apparently robust effects occurring within 15 s of exposure to a 100 μ T 60 Hz field, coupled with the uncertain role of the biological and exposure conditions required for a robust effect, indicate that replication in other laboratories is essential.]

Miller and Furniss (Miller & Furniss, 1998) attempted to replicate the effect of a 100 μ T, 60 Hz EMF on inositol 1,4,5-triphosphate shown by Dibirdik *et al.* and Kristupaitis *et al.*, using the DT40 genetic model obtained directly from the Uckun group and with an experimental design shared between the two laboratories. A rigorous experiment, with blinded sham and field exposure and B-cell receptor-induced signaling as a positive control, showed no effect. [The failure to replicate the findings may be due to a number of reasons. Miller's group presented a detailed protocol for exposure in a well-characterized system and showed no causal effect, whereas Uckun's group showed an apparently robust effect and presented multiple types of evidence for an EMF-induced signaling pathway but without sham exposure.]

4.7.2.3 Cell proliferation

Cell proliferation is a complex process which is under the control of cellular signal transduction pathways. Altered proliferation of cells *in vitro* has been observed in a number of studies, but in none were sham controls used and none have been independently replicated. For example, Rosenthal and Obe (Rosenthal & Obe, 1989) showed a 10–15% increase in cell-cycle progression of human lymphocytes exposed to a

5 mT, 50 Hz field. West *et al.* (West *et al.*, 1994) demonstrated increased colony growth in anchorage-independent JB6 cells after 10–14 days' exposure to a 1.1 mT 60 Hz magnetic field. No effect of the induced electric field was reported. Antonopoulos *et al.* (Antonopoulos *et al.*, 1995) independently confirmed the effects of a 5 mT 50 Hz field reported by Rosenthal and Obe (Rosenthal & Obe, 1989). Using two exposure systems with temperature control, they showed significant acceleration of the cycle of human peripheral lymphocytes. Schimmelpfeng and Dertinger (Schimmelpfeng & Dertinger, 1993) reported a reduction in cell number after exposure of SV40-3T3 cells to a 2 mT, 50 Hz field. In a subsequent study of proliferation, Schimmelpfeng and Dertinger (Schimmelpfeng & Dertinger, 1997) used organ culture dishes with an inner and outer compartment and flow cytometry to demonstrate that the reduction in cell number after a 1h exposure to a 2 mT, 50 Hz field was due to the induced electric field. The peak induced electric field was calculated to be 8–12 mV/m.

In the most recently reported study on proliferation, Katsir *et al.* (Katsir *et al.*, 1998) demonstrated an increase in cell proliferation with exposure over the frequency range of 50–100 Hz and intensity range of 0.1–0.7 mT, as assayed by cell counts, ³H-thymidine incorporation, and MTT. Both frequency- and intensity-dependent responses were observed, with a maximum enhancement of proliferation of 70% seen with exposure to 100 Hz at 0.7 mT ($p < 0.05$). At 50 and 60 Hz, cell proliferation was enhanced by 13% and 26%, respectively. A blinded experimental design was used which included sham–sham studies, although active sham exposure (double-wound coils) was not included.

A potential correlation between cell proliferation and exposure to magnetic fields was described by Liburdy *et al.* (Liburdy *et al.*, 1993b) in human estrogen-responsive breast cancer cells (MCF-7 cell line). These cells grow rapidly in the presence of normal concentrations of estrogens, but their growth rate decreased in the presence of melatonin, a hormone produced by the pineal gland. It has been proposed that disruptions of the normal daily cycle of melatonin synthesis are risk factors for human breast cancer (Stevens, 1987). Melatonin synthesis in whole animals has been shown to be altered by exposure to ELF EMF (Wilson *et al.*, 1990). Liburdy *et al.* confirmed previous studies by Blask (Blask, 1993) that melatonin at a normal physiological concentration (10^{-9} mol/L) can decrease the growth rate of a specific strain of MCF-7 cells; however, application of a 1.2 μ T sinusoidal magnetic field at 60 Hz prevented this action of melatonin. A field of 0.2 μ T had no significant effect, suggesting that a threshold might exist between 0.2 and 1.2 μ T. In more recent work, Liburdy's group extended these findings to demonstrate in experiments similar to those carried out using melatonin that the antiproliferative action of tamoxifen (an anti-cancer drug) is blocked by a 1.2 μ T field (Harland & Liburdy, 1997). They also showed that the effect was due to the magnetic field and not due to the induced electric field.

Two other laboratories replicated the effects of 1.2 μ T fields on inhibition of MCF-7 cell growth by both melatonin and tamoxifen (Blackman *et al.*, 1998; Liburdy & Levine, 1998). Liburdy's group reported similar effects of 1.2 μ T on inhibition by tamoxifen of a second human breast cancer cell line, T47B (Harland *et al.*, 1998) and a human glioma cell

line, SF-757 (Afzal & Liburdy, 1998). [While these results have been replicated, the extremely small effects observed (10–20% growth over 7 d) and the nature of the experimental design raise serious concerns about the robustness of this effect.]

4.7.2.4 Enzyme synthesis and activity

Blank's group has reported effects of VLF electric fields on the Na/K ATPase ion pump in membranes (Blank, 1992; Blank & Soo, 1992b). Electric fields of 30–300 Hz were applied for 15 min to membrane preparations at a current density of 55 $\mu\text{A}/\text{cm}^2$ (1.1 $\mu\text{V}/\text{cm}$); the response was complex, with either increases or decreases in enzyme activity, depending on the concentrations of sodium and potassium ions in the medium. ATPase activity was inhibited by fields when the enzyme was in a medium containing optimal concentrations of activating cations and stimulated when the enzyme activity was reduced by ouabain or by lowering the temperature. Blank estimated that the threshold for effects was an electric field strength of approximately 5 $\mu\text{V}/\text{cm}$ across the membrane, and this threshold was associated with a current density of 8 mA/cm^2 . This threshold value, although low by comparison with ambient electric fields in air near power lines, is much higher than those believed to be induced by environmental exposures to electric fields. The results can be interpreted as indicating that electric fields induce changes in the binding of substrate ions (Na^+ and K^+) to the ion pump at high and low concentrations of the ligands, as in the studies of Liburdy and Luben described above.

Ornithine decarboxylase (ODC) activity is modulated by membrane-mediated signaling events, and its activation during carcinogenesis is associated with the activity of mitogens and tumor-promoting agents of various types. Byus *et al.* (Byus *et al.*, 1987) reported that ODC activity in three cell lines—human lymphoma cells (CEM), mouse myeloma cells (P3), and rat hepatoma (Reuber H35) cells—was increased by up to 500% when they were exposed to a sinusoidal 60 Hz electric field at 10 mV/cm . Increased ODC activity in Reuber H35 cells was detected at fields as low as 0.1 mV/cm . In comparison, phorbol ester at doses associated with tumor promotion activated ODC by more than 1000%. The investigators concluded that electric fields act on the cell membrane, resulting in an effect of signal transduction on ODC activation by mechanisms that were not directly investigated in these or subsequent studies. These findings have been used as a basis for the hypothesis that low electric fields act as a co-promoter with tumor-promoting agents, resulting in more activation of ODC and more growth promotion of carcinogen-induced cells than in the absence of electric fields. Litovitz *et al.* (Litovitz *et al.*, 1991) also reported enhancement of ODC activity in mouse L929 cells by exposure to a 60 Hz magnetic field for 8 h at a strength of 1, 10, or 100 μT . Maximal enhancement of approximately 100% above the control level was produced by 4 h of exposure to a magnetic field at 10 μT .

Effects of EMF on ODC activity have also been reported by other laboratories, although the conditions and signaling agents varied. Mevissen *et al.* (Mevissen *et al.*, 1995) showed that exposure of rats *in vivo* to a 50 Hz, 50 μT field for six weeks doubled the ODC activity in mammary tissue. Valtersson *et al.* (Valtersson *et al.*, 1997) found that both

ODC activity and polyamine levels were increased in the Jurkat human leukemia cell line, but not in the non-leukemic CEM lymphocyte line, after exposure to a 50 Hz, 0.1 mT magnetic field. Little effort was made in these studies to isolate the specific change in membrane receptor mechanisms that resulted in the observed change in ODC activity.

Litovitz *et al.* (Litovitz *et al.*, 1994) and Farrell *et al.* (Farrell *et al.*, 1998) extended their earlier observation of increased ODC activity in mouse L929 cells at 60 Hz, 10 μ T, by showing that an incoherent noise field could block the effect of the coherent 60 Hz field at equal flux density. In contrast, Azadniv *et al.* (Azadniv *et al.*, 1995) showed that a 4h exposure of L929 cells to a 60 Hz 10 μ T magnetic field had no statistically significant effect on ODC activity. Moreover, Cress *et al.* (Cress *et al.*, 1995) failed to show an effect when using the cells, methods, and exposure system of Litovitz' group. [The function generator and power amplifier used in this study were not, however, those used by Litovitz' group.]

4.7.2.5 Apoptosis

Scarfi *et al.* (Scarfi *et al.*, 1991) showed that micronucleus formation in human lymphocytes was not affected by exposure to a pulsed magnetic field of 2.5 mT (peak pulse) at 50 Hz. This field also had no effect on mitomycin C-induced micronucleus formation. This finding was consistent with that of a previous study from the same laboratory (Cossarizza *et al.*, 1989), in which the same pulsed magnetic field produced no change in cell survival or unscheduled DNA synthesis in human lymphocytes with or without treatment with ionizing radiation.

Tofani (Tofani *et al.*, 1995) reported a synergistic effect on micronucleus formation in human peripheral lymphocytes after concurrent exposure to mitomycin C and EMF at a Ca^{++} resonance condition consisting of a 32 Hz 75 μ T AC field with a 42 μ T static field. In these studies, neither a 75 μ T nor a 150 μ T AC field affected micronucleus formation in the absence of mitomycin C or an applied static magnetic field.

Lagroye and Poncy (Lagroye & Poncy, 1997) observed no change in micronucleus formation in a spontaneously transformed tracheal epithelial cell line exposed to EMF alone (50 Hz, 100 μ T, sinusoidal), but when the cells were exposed to EMF plus 6 Gy of ionizing (gamma) radiation, the number of binucleated cells with micronuclei increased by approximately 10% ($p < 0.05$).

Simko *et al.* (Simko *et al.*, 1998) examined micronucleus formation and other apoptotic morphological changes in two human cell lines exposed to 0.1–1.0 mT 50 Hz AC magnetic fields. In the SCLII transformed squamous-cell line, a dose-dependent increase in micronucleus and apoptosis was seen after 48 and 72 h continuous exposure to 50 Hz (0.8 and 1.0 mT). In contrast, in a non-transformed amniotic fluid cell line, no significant changes were noted, suggesting that different cell lines react differently to the same field. In a brief communication, Ismael *et al.* (Ismael *et al.*, 1998) reported use of a specific

assay system for apoptotic cells (TUNEL assay) to observe an increase in apoptosis of mouse thymocytes treated with dexamethasone. The increase was observed only in thymocytes and not in splenic T-cells from animals exposed to a 0.4–1.0 μT 60 Hz magnetic field. The levels of apoptosis in thymocytes and spleen cells from mice exposed to an 8–20 μT DC magnetic field were similar to those in controls.

[None of these recent studies of apoptosis has been replicated. The wide variety of effects, cell lines, and exposure conditions and the relatively qualitative techniques used (e.g. micronucleus counting) cast doubt on any robust effect. Use of more accurate techniques such as the TUNEL and other quantitative assays may result in more definitive answers in the future.]

4.7.2.6 Summary

The body of work on signal transduction suggests that power-frequency EMF, with magnetic fields $\geq 100 \mu\text{T}$ and electric fields $\geq 1 \text{ mV/m}$, are likely to have some effect on a number of signal transduction-related pathways in mammalian cells. Most of the studies, even those that appear to have been performed carefully, were reported from single laboratories, and the results cannot be considered conclusive. Blocking of antiproliferative effects has been replicated at 1.2 μT , but its physiological significance is unknown.

4.7.3 Induction of cytological markers

Cells undergoing embryogenesis, somatic differentiation, and some pathways in carcinogenesis show changes in cytological markers that indicate the expression of lineage-specific genes. These markers include changes in the kinetics of embryonic staging, changes in matrix protein synthesis, changes in cell surface characteristics, changes in cell morphology, and gap-junctional communication.

Changes in the *kinetics of staging* in embryogenesis are a well-accepted measure of coordinated development and can be readily measured in a number of species *in vitro*. A drawback to this assay is that there is little evidence that changes in the onset of these stages result in aberrant development.

Changes in *matrix protein synthesis*, including both extracellular matrix molecules and cell adhesion molecules, are also well-accepted measures of changes in a cell population's differentiated state. Not only does the matrix modulate cell differentiation, but many cell types, particularly those of mesenchymal lineage, can significantly modify the characteristics of the matrix by synthesizing extracellular matrix molecules or matrix metalloproteases. In addition, by changing integrin expression, cells incapable of altering the substrate characteristics can modulate the degree and nature of their attachment to that substrate (Shumaker *et al.*, 1994). Differential adhesion can affect cell associative

preferences in heterogeneous aggregates and is therefore considered to play an important role in malignant invasion (Steinberg & Foty, 1997).

Closely related to the process of cell adhesion and alterations in the extracellular matrix are alterations in *cell surface characteristics*. The glycocalyx serves as the interface between the cell and its environment, and changes in the charge density, enzyme content, or activity of this layer and the distribution of the various glycosaminoglycans are accepted markers of differentiation.

There is accumulating evidence that cell shape is a major determinant of differentiation (Folkman & Moscona, 1978) and is a distinct marker of differentiation in many cell types. Alterations in *cell morphology, size, and orientation* can reflect the cellular response to the extracellular matrix environment but also influence the way in which the cell affects its environment; examples are the orientation of forces in wound contraction and the polarity of a tissue. Mobility is also closely related to orientation and is a commonly used end-point of differentiation.

Intercellular communication has been postulated as a necessary condition for cells to progress through normal differentiation. *Gap-junctional communication* is considered to play a key role in tissue homeostasis, and its disturbance has been associated with various health problems.

4.7.3.1 Embryonic staging

Many studies have been undertaken to assess the developmental effects associated with embryonic exposure to PEMF. The most rigorously designed of these was an international collaboration involving six laboratories in four countries (Berman *et al.*, 1990). Each laboratory used two identical egg incubators equipped to produce a 500-ms pulse of 1 μT with a 2-ms rise-and-fall time. The pulse was repeated at a frequency of 100 Hz. [The induced electric field within the egg can be estimated to have been about 10 $\mu\text{V}/\text{m}$.] Eggs were sham exposed by incubation without energizing the magnetic field coil. Incubated eggs were exposed for 48 h at 37.6–38 °C prior to evaluation for fertility, stage of development, and presence of abnormalities. The evaluations were performed blindly. The principal observation from the combined results of these studies was a 6% increase in the number of abnormal embryos (control, 19%; exposed, 25%; $p < 0.001$); however, significant inter-laboratory differences were observed. No significant effect on embryonic staging was observed. [This study suffers from a small dynamic range of response and inadequate control, given the small flux densities used.]

Zimmerman *et al.* (Zimmerman *et al.*, 1990) investigated the effect of a 60 Hz magnetic flux on the development of sea-urchins. The exposure system consisted of two identical chambers equipped with two pairs of Helmholtz coils 1.5 m in diameter in an orthogonal orientation. The two coil pairs were driven 90° out of phase to obtain rms flux densities up to 500 μT . The geomagnetic field was measured at 43.8 μT ; for sham exposure, the

two pairs of coils were not energized in one system. Fertilized eggs were maintained in 20 ml of seawater at 18 °C in 250-ml beakers [suggesting that the maximum induced rms electric field intensities were approximately 5 mV/m]. The developmental progress of the embryos was assessed by counting the number of cells in the embryo at 10, 16, and 22 h after fertilization. A significant delay ($p < 0.001$) in development was observed, which showed a dose-dependent correlation with flux density. The investigators concluded that the field had caused a temporary delay at the morula stage of development.

Using a similar exposure system, Cameron *et al.* (Cameron, 1993) investigated the effect of a 60 Hz field on mouse embryogenesis. Two-cell-stage mouse embryos were cultured for 36 h after fertilization and then exposed to either a 10 or a 50 μ T flux for 48–68 h at 37 °C. [As the size of the exposure chambers was not reported, the induced electric field intensity cannot be estimated.] The developmental stage was assayed by counting the number of cells in 9–10 embryos under a phase-contrast microscope. Exposure at 10 μ T or 50 μ T significantly delayed development ($p < 0.025$ and 0.01, respectively by binomial test).

Levin and Ernst (Levin & Ernst, 1995) also investigated the effect of exposure to ELF magnetic fields on early development of sea-urchins in a study which spanned the frequency range of DC to 600 kHz. The exposure apparatus consisted of a 10 cm vertically orientated solenoid, 7 cm in diameter, sufficient to permit insertion of a 250 ml beaker, and exposure was to 60 Hz over the rms flux density range of 1.7–8.8 mT [corresponding to a maximum induced rms electric field intensity of 50 mV/m]. The control and exposed samples were held in the same incubator at 12 °C, and the embryos were stirred continuously with thermally isolated stirring motors. By analyzing 200 control and exposed embryos every 15 min, a significant advance in the time of both the first and second cell divisions was observed. Moreover, the degree of advance appeared to be linear with flux density and duration of exposure but to have a complex relationship with the frequency of exposure. A monotonic decrease in efficacy was observed over frequencies ranging from DC to 600 kHz, with a maximum response at DC, suggesting a thermal effect.

In an investigation of chick embryo development, sinusoidal field exposure was used (Veicsteinas *et al.*, 1996). Groups of 210 exposed and sham-exposed (no coil excitation) eggs were incubated for up to 18 d with 2 h on, 22 h off intermittent exposure to a 200 μ T, 50 Hz field [consistent with an induced electric field intensity of about 1 mV/m]. The embryos were examined for developmental stage after 48 h. Immunocytochemical analysis of extracellular components was performed on day 7, and histological examinations on days 7, 12, and 18 of incubation. No difference in developmental progression, extracellular components, or malformations in tissues was observed. In addition, follow-up 90 d after hatching showed no difference between the exposed and unexposed chick populations.

In a recent replication of the chick embryo studies, both pulsed and sinusoidal fields were used (Farrell *et al.*, 1997). A total of 2500 chick embryos were examined in five experimental series spanning five years. The pulsed field exposure comprised a 500-ms

pulse, 100 pulses per second, reaching a maximum flux of 1 μT in 2 ms. The sinusoidal exposure was at 60 Hz, with a peak flux density of 4 μT . [This gives an estimated peak induced electric field intensity of 10 mV/m. No sham exposure appears to have been used.] In four of the five series, a significant increase ($p < 0.01$) in the number of abnormally formed embryos was seen in a blinded fashion after 48 h of continuous exposure. The investigators note, however, that there was also a nearly 10-fold variation in the rate of apparent abnormality in the control samples in the five experimental series, suggesting that there would be no effect by analysis of variance.

4.7.3.2 Matrix synthesis and extracellular interactions

In association with a longstanding interest in the promotion of wound and fracture healing, numerous investigators have addressed the ability of low-frequency magnetic fields to alter extracellular matrix protein synthesis. In two related studies, Murray and Farndale (Farndale & Murray, 1985; Murray & Farndale, 1985) investigated the effect of pulsed-field exposure on collagen production in primary and cultured fibroblasts. Primary chick tendon fibroblasts were exposed in 30-mm culture dishes to a Helmholtz coil pair arrangement producing a 2.2 mT flux at 4 kHz lasting 4.8 ms, with the pulse burst repeated at a 15 Hz rate. [The peak induced fields in the dishes were calculated to be 2.3 V/m. Sham exposure was not incorporated in the experimental design.] Total protein, collagen synthesis, and collagenolytic activity were assayed by radioisotope incorporation after 6 d of exposure (6 h on, 6 h off). Exposure was found to increase collagen production relative to total protein and to induce a significant, two-fold reduction in collagen turnover. The effect of exposure was observed only after the cultures had reached confluency. Similar results were obtained when cultured fibroblasts from rabbit bone-marrow stroma were used. Thermal effects were specifically addressed and dismissed as a confounding factor.

Fitzsimmons *et al.* (Fitzsimmons *et al.*, 1986) reported the results of studies with a capacitively coupled exposure system to stimulate bone matrix formation in tissue culture. Samples maintained in tissue culture were placed within a pair of capacitor plates separated by 2 cm. Tritiated hydroxyproline incorporation in mouse calvaria and tibia was assayed over the last 24 h of a 3 d exposure. Exposure to a 16 Hz electric field at a calculated electric field intensity of 10 $\mu\text{V}/\text{m}$ resulted in a twofold increase in incorporation in the calvaria but no significant change in the tibial preparation.

McLeod *et al.* (McLeod *et al.*, 1987c) also investigated the effect of exposure to electric fields on matrix protein synthesis. Primary bovine fibroblasts were incorporated into three-dimensional collagen gels which, when contracted, permitted transfer to an apparatus in which a controlled current density could be applied through agar bridges. Field intensities of 1 mV/m to 3 V/m were used over a frequency range of 0.1 Hz to 1 Khz. Sham exposure consisted of exposing the cell system in an identical system with no current excitation. Tritiated proline incorporation into extracellular protein was assayed in cultures sustained in serum-free medium and exposed for 12 h. Peak sensitivity of the cell system was found near 10 Hz, with significant inhibition of proline incorporation at 6.5

mV/m rms ($p < 0.02$). Enhanced sensitivity (two-fold increase) of the cell system was seen when the cells were orientated in the direction of the applied electric field.

MacGinitie *et al.* (MacGinitie *et al.*, 1994) investigated field-stimulated matrix synthesis in a cartilage explant model. In this system, 9.5-mm disks of cartilage from the femuropatellar groove of one- to two-week-old calves were maintained in culture for 5–8 d and then exposed to 10–30 mA/cm² at frequencies of 1 Hz to 10 kHz. The explants were maintained in 0.1% defined serum-supplemented medium during exposure. After 12 h of exposure, radiolabelled methionine (a measure of glycosaminoglycan synthesis) was assayed. Peak sensitivity was observed at 100 Hz, with enhanced incorporation at 24 and 30 mA/cm² ($p < 0.05$). No significant increase was observed at 10 mA/cm², a current density associated with an induced electric field intensity on the order of 100 V/m.

The sensitivity of cartilage explants to fields was also evaluated by Liu *et al.* (Liu *et al.*, 1996), who exposed 16-d-old chick embryo sternal cartilage explants to 30-ms pulse bursts (pulse rate, 4 kHz) repeated at 1.5 Hz for 3 h/d for 2 d. Exposure was given from a Helmholtz coil pair (14 cm in diameter), permitting a peak flux density of 100 μ T with a rise time of 230 μ s and fall time of 30 μ s. For sham exposure, the coils in a similar system were not energized. Glycosaminoglycan production was assayed by ³⁵S incorporation. The exposed explants showed a 21% increase in glycosaminoglycan content ($p < 0.05$) and, correspondingly, a 30% decrease in glycosaminoglycan released into the medium ($p < 0.02$). Exposure was also found to significantly decrease the amount of newly synthesized glycosaminoglycan (76%, $p < 0.001$), leading the investigators to conclude that the exposure also significantly suppressed pre-existing glycosaminoglycan degradation in the explants.

Rodemann *et al.* (Rodemann *et al.*, 1989) reported dramatic increases in protean synthesis in fibroblasts in response to exposure to a 6 mT, 20 Hz magnetic field. Normal human fibroblast cell lines (HH-8 and WI38) and virally transformed fibroblasts (WI385V40) were exposed twice a day for 6 h in a water-cooled solenoid exposure system. Control cultures were maintained in a separate incubator. S³⁵-Methionine incorporation, ³H-proline incorporation, total protein, and the mitotic index were assayed. After 21 d of exposure, a 5- to 13-fold increase in total protein synthesis was observed, accompanied by a significant ($p < 0.05$) increase in collagen synthesis and a shift in the mitotic index. The authors concluded that field exposure induced differentiation in these cell lines. [The lack of a sham-exposed group in a system that required water cooling to maintain the incubation temperature raises concerns about the reproducibility of these studies.]

4.7.3.3 Cell surface markers

Interest in the effects of pulsed magnetic fields has led to numerous studies of phenotypic changes in exposed cell populations. Most cell types have a distinct coat (glycocalyx) which presents a highly negatively charged surface to the environment. Smith *et al.* (Smith *et al.*, 1991a) investigated the effect of exposure to PEMF on this cell coat by exposing a

monocyte-like, non-adherent, mammalian cell line (U937) to a 25 Hz pulse-burst field from a Helmholtz coil pair (7.5 cm radius). A peak flux density of 0.63 mT were used, with a rise time of 200 μ s and a fall time of 20 μ s. [The induced electric field intensity at the periphery of the culture vessel was estimated at 160 mV/m.] For sham exposure, the Helmholtz coils were not energized. Surface charge density was assayed by partition chromatography. Cells exposed for 48 h had a significantly higher partition coefficient than control cells ($p < 0.03$), consistent with an increase in the negative surface charge density on the cells. In the context of previous experiments undertaken by this group, the investigators concluded that the observed effect was due to the induced electric field.

Differentiation of bone cells is commonly characterized by an abrupt rise in the activity of alkaline phosphatase, an ectoenzyme believed to be associated with the mineralization process. McLeod *et al.* (McLeod & Guilak, 1993) investigated the effect of field exposure, from three identical solenoid systems installed in a single incubator, on alkaline phosphatase activity in a rat osteosarcoma cell line (ROS-17/2.8). Bifilar winding of the solenoids permitted excitation of the sham-exposed samples, and a third unexcited coil system was used as the control. The tissue culture dishes were exposed for 72 h to a rms flux density of 1.8 mT at 30 Hz [sufficient to induce a maximum electric field of 600 μ V/m]. Cells were maintained in a normal growth medium with 10% serum, and enzyme activity was assayed from the conversion of *para*-nitrophenylphosphate to *para*-nitrophenol, which was quantified spectrophotometrically. While no effect on enzyme activity was found in exposed cell populations plated sparsely, a doubling of activity ($p < 0.001$) was observed for cells plated densely (3000, or use 3×10^4 cells/cm²) as compared with sham-exposed samples. As these results were associated with a significant depression in cell numbers in the exposed population, the investigators concluded that the normal differentiation response of these cells accelerates as they attain confluency.

Neural cell adhesion molecules are associated with neuronal differentiation. Horton *et al.* (Horton, 1993) investigated the ability of a sinusoidal flux to affect the onset of expression of these molecules in rat pheochromocytoma cells (PC12, ATCC), a well-investigated neuronal differentiation model. Field exposure was accomplished from a Helmholtz coil pair (30 cm diameter) to produce a vertical field with a peak–peak flux density of 40 μ T at 16 Hz. A DC magnetic flux was imposed at 20 μ T, colinear with the applied AC flux. [The estimated induced electric field intensity would be 50 μ V/m. Sham exposure conditions were not reported.] Cells were exposed to the field for up to 72 h while maintained in a low serum (1%) medium in T-75 flasks treated with polylysine or polyornithine. Neural cell adhesion molecule expression was assayed by monoclonal antibody labeling and immunoprecipitation. A transient effect of field exposure was observed, as neural cell adhesion molecule expression was found to be significantly elevated at 24 h but not at 72 h. Moreover, the effect was observed only in cultures exposed for 30 min/d and not in those exposed continuously.

Kula and Drozd (Kula, 1996) investigated alterations in the character of the cell coat of fibroblasts caused by field exposure. Balb/c mouse fibroblasts maintained in 5% heat-inactivated serum in 43-cm³ flasks were exposed to a 50 Hz, 20 mT flux from a solenoid

coil; for sham exposure, a similar apparatus was used which was not energized. [The estimated induced electric field intensity would be 100 mV/m.] The length of exposure ranged from 2 to 64 min/d from day 5 to day 8 of culture. Glycosaminoglycan distribution was assayed in the cells, the medium, and cell coats by ^{35}S incorporation. Rapid changes in the distribution of glycosaminoglycans in the cell coat were observed. ^{35}S incorporation into heparin sulfate was found to decrease by two-thirds after exposure for only 16 min/d, although longer exposure had little additional effect. Conversely, ^{35}S incorporation into chondroitin sulfate nearly doubled with similar lengths of exposure. Control exposure with static magnetic fields of up to 0.5 T showed no effect.

McLeod *et al.* (McLeod, 1998) used the upregulation of alkaline phosphatase activity in differentiating bone cells to determine the dose–response characteristics of cells to an ELF (30 Hz) sinusoidal field. A non-transformed bone-cell line which undergoes terminal differentiation (MC-3T3-E1) was plated into confluent culture and maintained for 4 d in a normal growth medium with 10% serum. These cultures were then exposed to fields from a solenoidal apparatus, which provides an active sham exposure for comparison. Exposure at 2.5 mT resulted in a non-uniform electric field distribution at the cell monolayer surface, varying from approximately 100 to 6000 $\mu\text{V}/\text{m}$ peak. Alkaline phosphatase activity was then assayed *in situ* at periods of 4–64 h with an optical scanning technique which allows spatial mapping of the overall cell response. Alkaline phosphatase distribution was changed in comparison with that in the sham-exposed samples within 16 h, reflecting suppression of activity correlated to the intensity of the induced electric field. By 64 h of exposure, a uniform 25% suppression of alkaline phosphatase activity was observed across the culture dish. These investigators concluded that the cellular response depends on the magnitude of the induced electric field with a threshold intensity in the range of 100 $\mu\text{V}/\text{m}$.

4.7.3.4 Matrix interactions: Adhesion, morphology, and motility

In a series of investigations, Blackman *et al.* (Blackman *et al.*, 1993a; Blackman *et al.*, 1993b; Blackman *et al.*, 1994; Blackman *et al.*, 1998) studied the effect of ELF EMF on neurite outgrowth in a well-developed model of neuronal differentiation. PC-12 cells were primed for growth by plating them on collagen-coated dishes and were maintained on growth medium with 15% serum for one week; they were then replated, and nerve growth factor (5 ng/ml) was added to initiate differentiation. The cells were exposed in a Helmholtz coil pair to produce either a uniform flux of 0–30 μT or a non-uniform flux of 0–50 μT , in order to obtain data for determining a dose–response relationship in a single experiment. Sham exposure was not undertaken, but concurrent control samples were placed in an adjacent magnetically shielded enclosure. The percentage of cells undergoing differentiation was assayed by counting all cells in randomly selected areas in which neurite growth was greater than the cell body length. Blackman *et al.* (Blackman *et al.*, 1993b) observed suppression of neurite outgrowth (normally about 60% of the cells), with maximal inhibition of approximately 20% after 22 h of exposure to a 50 Hz magnetic field. A threshold-like response in neurite outgrowth was observed, with a transition in the range of 5–10 μT ; higher flux densities induced no additional inhibition. In additional

experiments, uniform suppression was observed in cells in dishes of different sizes resulting in induced electric field intensities of 3.7–45 $\mu\text{V}/\text{m}$, for an applied flux density of 7.9 μT , suggesting that the observed effects were strictly dependent on the magnetic field.

In a subsequent experiment with identical exposure conditions but using the PC-12D cell line, Blackman *et al.* (Blackman *et al.*, 1993a) showed that exposure to a 50 Hz magnetic field enhanced neurite outgrowth by more than two-fold (maximum, 55%) in the absence of nerve growth factor. This effect was also found to be dependent on the magnetic flux density and not on the induced electric field intensity, 1–10 $\mu\text{V}/\text{m}$. Blackman (Blackman, 1994) then investigated the response of the PC-12 cell line to flux densities as high as 50 μT with a nerve growth factor concentration of 50 ng/ml to achieve 100% neurite outgrowth in the absence of fields. Exposure of the cells at 45 Hz had no effect up to flux densities of 5 μT , but outgrowth was inhibited at flux densities of 5–30 μT , with a maximum inhibition of up to 60%. With flux densities greater than 30 μT , the efficacy of the field to inhibit neurite outgrowth appeared to be diminished. Blackman *et al.* (Blackman *et al.*, 1998) recently replicated these effects in a blinded fashion [although sham exposure was not incorporated in the experimental design].

A trial to replicate the findings of Blackman *et al.* was undertaken at the Oak Ridge National Laboratory (Griffin *et al.*, 1998). Populations of PC-12 cells previously primed by treatment with nerve growth factor were treated with graded doses of this factor alone (2.5 mg/ml) or combined with EMF (2.38 mT at 45 Hz plus 3.66 mT DC). Appropriate sham controls were included. No significant difference in neurite outgrowth was observed. Different nerve growth factor-primed populations showed differential response to challenge with the factor.

Greenebaum *et al.* (Greenebaum *et al.*, 1996) reported the effects of exposure to pulsed fields on neurite outgrowth. Chick dorsal root ganglia were isolated from 6 d-l d chick embryos and placed in 60-mm Primaria culture dishes. Neurite outgrowth was initiated by treatment with 50–100 ng/ml nerve growth factor, and the cells were exposed to fields from a Helmholtz coil pair, which produced a 4.0 mT flux pulse with a 200 μs rise time and a 20 μs fall time. [The peak induced electric field intensity at the edge of the culture dish was estimated to be 3 V/m.] A series of 22 pulses in 4.8 ms were repeated at a rate of 15 or 25 Hz. Exposure lasted 18 h, and the cells were then left undisturbed for an additional 6 h before fixation and assessment. Controls samples were held in a similar incubator with unenergized coils. Neurite outgrowth was determined by the length of the growth process from the dorsal root ganglion body. In addition, the positions of the ganglia within the dish and the angular orientation of the growth processes were recorded. In their study of 808 ganglia, the authors reported a high level of inter-experiment variation but were able to identify a significant increase in neurite growth in the field-exposed population that was independent of nerve growth factor concentration. Moreover, field exposure led to greater directional growth. No dependence on induced electric field intensity or frequency was identified.

Spadinger *et al.* (Spadinger *et al.*, 1995) investigated motility and morphological changes in cells during field exposure, using an automated tracking system to measure and record the field-induced changes. NIH-3T3 fibroblasts were maintained in normal growth medium with 10% serum and exposed in 6-cm petri dishes. They were exposed to vertical magnetic fields in the frequency range of 10–1000 Hz, at rms flux densities of 10–800 μT , from a short solenoid coil encased in plastic. [No sham exposure was performed.] No DC field was applied, but the geomagnetic field was 29 μT . [The induced electric field intensity at 60 Hz for a 100 μT flux was calculated to be 0.4 mV/m.] Motility was assayed as cell speed, direction, and persistence, and the morphological measurements included cell area and circularity. These assays were performed during 3–4-h field exposures interspersed with periods of no exposure. The investigators found no evidence of significant changes in motility or morphology that could be attributed to the applied magnetic field.

Osteoclast formation is a multistep process involving extensive cell–matrix and cell–cell interactions, in that cell migration, aggregation, and fusion are required. Rubin *et al.* (Rubin *et al.*, 1996) investigated the effect of exposure to ELF fields on osteoclast formation in a mixed murine marrow culture system. Marrow cells were obtained from the femurs and tibiae of 4–8-week-old male C57Bl/6 mice and plated on chamber slides with medium and vitamin D to promote osteoclast recruitment. Exposure was begun immediately with the solenoid exposure system described by McLeod *et al.* (McLeod & Guilak, 1993), which provides matched field and sham exposure. The cultures were exposed for 8 d to 30- and 60 Hz fluxes of 1.8 mT [corresponding to an induced rms electric field intensity of 600 $\mu\text{V}/\text{m}$ at 30 Hz]. Osteoclast recruitment was assayed by counting all multinucleated, tartrate-resistant, acid phosphatase-positive cells in each 0.9-cm² culture well. The counts were performed in a blinded fashion. A 22% reduction ($p < 0.0001$) in osteoclast number was found with exposure to 60 Hz and a 28% reduction with 30 Hz. The investigators concluded that the fields may affect the pool of proliferating precursor cells.

Lee and McLeod (Lee & McLeod, 1998) reported the results of a study of the morphological adaptation of osteoblast-like cells (MC-3T3-E1) to a 60 Hz field. Cells maintained in culture medium with 10% serum were exposed for 24 h to fields from a solenoid exposure system (McLeod & Guilak, 1993), with a 0.7 mT rms flux density, sufficient to induce a 0.5-mV/m electric field intensity in the culture wells. Cell length, width, area, perimeter, circularity, and angular orientation were calculated from digitized phase-contrast images of the cells with commercial image-analysis software. As reported by Spadinger *et al.* (Spadinger *et al.*, 1995), no significant effect of exposure could be identified when the cell measurements were pooled. When the morphological measurements were analyzed with respect to the orientation of the cells (angular orientation with respect to the induced electric field vector), however, the cells orientated parallel to the induced electric field were found to be significantly longer, with larger areas and perimeters, and more spindle shaped ($p < 0.001$). The investigators concluded that these effects were due to the induced electric field rather than the magnetic field.

4.7.3.5 Cell–cell communication and gap junctions

Alterations in gap-junctional coupling provide two distinct views of the interactions of EMF with cells and tissues. First, gap junctionally coupled cells theoretically interact differently from isolated cells with induced electric currents. Second, gap-junctional competence can serve as an assay of cell–cell communication, a factor considered to be essential in the normal development and function of tissue.

Ubeda *et al.* (Ubeda *et al.*, 1995) investigated changes in gap-junctional competence in dye-coupling experiments. C3H 10T1/2 cells were plated sparsely onto tissue culture dishes [size not reported] and allowed to proliferate for 18 d until reaching confluence. Melatonin was then added to the medium at a concentration of 0.1 μ M, and the cells were allowed to incubate for another 27 h. At the end of this incubation period, they were exposed for 30 min to a magnetic field of 50 Hz at 1.6 mT from a Helmholtz coil pair. Controls were sham exposed by not energizing the coils. A subset of the cells in each dish was then loaded with Lucifer yellow dye by a single scrape across the culture dish, and transfer of the dye to adjacent cells was determined by counting fluorescently labeled cells. Exposure to the field blocked the up-regulation of coupling caused by the melatonin treatment.

Conversely, Schimmelpfeng *et al.* (Schimmelpfeng *et al.*, 1995) showed in dye microinjection studies with NIH 3T3 cells that a 50 Hz field could up-regulate intercellular coupling. NIH 3T3 fibroblasts which had obtained a monolayer density of $1-3 \times 10^5$ cells/cm² and aggregates of cells 200–400 μ m in diameter were exposed in 60-mm culture dishes to a sinusoidal 50 Hz field at 2 mT by placing the dishes within the air gap of an iron core electromagnet. [The maximum induced electric field intensity can be calculated to be approximately 10 mV/m.] Control cultures were placed in the same incubator at a sufficient distance from the electromagnet that the flux densities were less than 2–3 μ T. After exposure, three to nine cells were assayed for gap-junctional coupling by microinjection with Lucifer yellow. The dye that had spread into neighboring cells was evaluated by counting fluorescent cells 2 min after the injection. Exposure to the field for 5 min was reported to cause a 1.6-fold increase in the average number of coupled cells in the monolayer configuration. Coupling of cells in aggregates was not readily quantified. [Four independent experiments with three to nine cells per experiment provides a questionable statistical basis for comparison.]

Vander Molen (Vander Molen, 1997) reported a series of experiments designed to test the altered sensitivity of a cell population to EMF in the absence of gap-junctional coupling. An osteosarcoma cell line (ROS 17/2.8) was transfected with anti-sense *connexin-43* to yield a cell line that was intercellular communication-deficient. Communication-competent and -incompetent cells at similar confluent densities were then exposed to a 1.8 mT rms flux at 30 Hz [sufficient to induce a 600 μ V/m electric field intensity in the culture wells] for up to 72 h from the exposure system of McLeod *et al.* (McLeod & Guilak, 1993). Cell proliferation and alkaline phosphatase activity were assayed. The communication-competent and -incompetent cell lines had similar sensitivity to EMF exposure. These

results were confirmed by exposing sparsely plated cell populations (precluding significant numbers of gap-junctional couplings). The investigators conclude that gap-junctional coupling does not enhance cell sensitivity to EMF.

Griffin *et al.* (Griffin *et al.*, 1998) examined the effects of EMF on the inhibition of gap-junctional communication by chloral hydrate. Clone 9 rat liver cells were treated with 1.5 mmol/L of chloral hydrate for 24 h; they were then left for 30 min for CO₂ and temperature to reach equilibrium and then treated with EMF for 30 min. After exposure to a combined field of 2.38 mT at 45 Hz and 3.66 mT DC, cell monolayers were assayed for dye transfer by monolayer assay techniques. Mezerein was used as a positive control, and sham-exposed controls were available. No significant effects of EMF on dye transfer were observed.

4.7.3.6 Summary

Patterns in cytological responses

The results of the studies described in this section do not show a clear pattern of effects of EMF on cytological markers. Two of the studies on development showed no effect of exposure to fields, and two had questionable protocols; the two remaining studies show a significant effect of exposure, with a delay in the kinetics of progression of embryogenesis. The delays were achieved, however, only after extended exposure (10–70 h) to 50–500 μ T, inducing electric field intensities of 0.5–5 mV/m. In none of these studies was an active sham-exposure system used, as is now standard in research on EMF sponsored by the NIEHS.

The results of studies on alterations in extracellular matrix synthesis are interesting, for three reasons. First, they include two investigations of only electric fields, which established remarkably low-intensity thresholds (10 μ V/m and 6 mV/m). Second, a reasonable level of correlation is seen between dose and the differentiated state of the cells. The lowest reported threshold (10 μ V/m) was observed for differentiating calvaria, while the highest (100 V/m) was seen for fully differentiated articular cartilage. Cultures at intermediate stages of differentiation (primary cells, cell lines, and embryonic sternal cartilage) had intermediate sensitivity to exposure to fields. Each of these experiments involved long durations of exposure, ranging from a minimum of 12 h to 21 d. Third, it should be noted that none of the exposure systems incorporated an active sham design.

Several important observations can be made on the basis of the results of the studies of cell surface markers. In this series, an active sham-exposure system, calibrated according to NIEHS guidelines, was used, and significant cellular responses were observed in comparison with cells exposed to the active sham. In addition, while high flux densities that give rise to high-intensity induced electric fields were reported to alter cellular activity, two investigations with significantly different flux densities (40 μ T and 2.5 mT) but inducing similar electric field intensities (50 μ V/m and 100 μ V/m) showed cellular

effects. Perhaps of equal interest, the field frequencies used (16 and 30 Hz) and exposure durations required (30 and 240 min) were similar in these two studies. Moreover, both cell systems (PC-12 and MC-3T3-E1) were exposed during well-established stages of differentiation. A critical observation in two of the studies was that the induced electric field was the active agent.

Similar observations were made in studies of cell morphology. In a terminally differentiating osteoclast model, with active sham exposure, an 8-d exposure to a 1.8 mT, 30 Hz magnetic flux, inducing a 0.6-mV/m electric field, resulted in a significant delay. Consistent with this observation were the morphological changes observed after a 24-h exposure to a 60 Hz, 0.7 mT flux (inducing a 0.5-mV/m electric field), whereas no significant morphological changes were observed with a 60 Hz, 0.1 mT flux applied for 3 h. Flux magnitudes and induced electric field intensities smaller than these induced differential responses, while values well above these consistently produced robust responses.

Few studies have been reported of the effect of EMF on gap-junctional communication, and, of those studies that have been completed, fewer have been reported fully. The two studies reported here provide little or no support for a role of gap junctions in cellular responses to EMF.

Threshold field intensities and required exposure times

Exposure to EMF can be expressed either as induced electric field intensity or imposed magnetic flux density. Studies of pure electric fields showed that only ELF fields can affect cytological responses, with a required threshold intensity in the range of 0.1 mV/m plus or minus one order of magnitude. This threshold is consistent with those found in several experiments on magnetic induction. Moreover, no response has been found with exposure shorter than 30 min, and most reported cellular responses require exposure of tens of hours. Finally, the threshold field intensity with exposure to 10–100 Hz appears to be lower than that for broader-spectrum or higher-frequency exposure.

The patterns associated with magnetic fluxes are more difficult to identify. Flux densities ranging from 1 μ T to 2 mT have been reported as threshold values, although the lowest are associated with stimuli with a higher frequency content. Assuming an electric field threshold near 0.1 mV/m, it is difficult to separate the effects of magnetic flux from those of electric fields when the induced electric fields exceed this level. Only a few studies reported cytological responses to induced electric fields below 0.01 mV/m, and these observations have not been replicated.

4.7.4 Summary

In-vitro experiments permit the testing of potentially toxic exposure under controlled conditions, typically at doses well above those encountered in the environment. Studies of the genotoxic effect of such exposure and effects on cell proliferation, alteration of signal transduction pathways, and modification of differentiation processes can serve to identify agents with potential carcinogenic effects or effects on other health end-points. This toxicological approach may be applied to EMF, although careful consideration must be given to the range over which the ‘dose’ or intensity of EMF is varied; unlike many chemical agents, EMF may have different mechanisms of field–cell coupling over different ranges of field intensity.

The generally accepted theoretical limits for effects of EMF are one to two orders of magnitude lower than they were a decade ago. The reasons for this change are that new mechanisms have been considered that were not studied in detail previously and that slightly more realistic biological models have been constructed. There is no controversy about the theoretical basis and experimental evidence for biological effects at magnetic flux densities greater than 0.1 mT or internal electric field strengths greater than approximately 1 mV/m. Similarly, there is general agreement about the lack of theoretical models and experimental evidence for effects at magnetic flux densities of less than 0.1 μ T, and theoretical models for effects at densities less than 0.1 mT, and particularly less than 5 μ T, are controversial. It is important to note that most of the theoretical results reported to date are based on single-cell models. Realistic modeling of temporal and spatial averaging across functional groups of cells (e.g. synchronized neurons) is a newly developing area of research, which may serve to expand the range of physical mechanisms of interaction. Existing models and theoretical thresholds are only as good as the biological data used to construct them; advances in biology and biochemistry can therefore be expected to serve as a basis for advances in our understanding of the mechanisms of interactions with EMF.

Three critical factors were considered in evaluating the contribution that *in-vitro* research can make to our understanding of the potential effect of EMF on human health: whether an observed (positive or negative) response has been independently validated, whether there is a demonstrated physical mechanism for the response at the field intensities used, and whether the end-points evaluated are widely considered to be predictive of potential health effects.

A series of recent (1996–98) studies demonstrated the effects of fields on gene mutations. Studies of ELF exposure at flux densities below 0.1 mT have consistently shown no effect on mutation rates; however, exposure to 0.2–400 mT reproducibly and significantly enhanced the mutation rate after X-ray or gamma-ray initiation. Moreover, exposure to 400 mT increased the number of mutations in the absence of ionizing radiation in two human cell lines. Thus, multiple, self-consistent reports demonstrate a dose-dependent effect on a process or end-point commonly considered to be associated with

carcinogenesis. Importantly, the flux densities used in all of these studies (≥ 0.1 mT) are within the range of a single physical transduction mechanism, specifically magneto-chemical transduction. The potential for magneto-chemical effects at flux densities greater than 0.1 mT has been firmly established in both theoretical analyses and biochemical investigations.

In addition to these reports on genotoxicity, numerous well-programmed studies have shown strong effects on other end-points commonly associated with carcinogenic agents. These include significantly increased cell proliferation, disruption of signal transduction pathways, and inhibition of differentiation, all of these effects being seen at field levels ≥ 0.1 mT. These investigations were also performed at sufficiently high intensities that magneto-chemical transduction is a plausible mechanism of field–cell transduction, although this does not preclude other mechanisms of interaction. Indeed, several well-controlled studies of physical transduction have clearly demonstrated that the induced electric field can alter cell behavior. In addition to these studies, a large number of well-performed studies have also shown biological effects of EMF that are not associated with cancer end-points, suggesting that exposure may affect other disease end-points.

A limited number of well-performed studies provide moderate evidence for mechanistically plausible effects of EMF greater than 0.1mT *in vitro* at end-points generally regarded as reflecting the action of toxic agents.

[This conclusion was supported by 27 Working Group members; there were 2 abstentions.]

There is weak evidence for an effect of fields lower than approximately 0.1mT.

[This conclusion was supported by 26 Working Group members; there were 3 abstentions.]

The potential role of magneto-chemical processes in the coupling of ELF fields to biological systems suggests that extension of both theoretical and experimental studies of intensity regimes below 0.1 mT should be conducted.

4.8 Biophysics of interactions of ELF EMF with biological systems

The fundamentals of the interactions of EMF with matter were elucidated over a century ago and succinctly stated as the well-known Maxwell equations. Years of successful application of these principles for practical advances has left little doubt about our ability to understand and predict electromagnetic phenomena when the details of the system and fields are completely described. Application of these principles to biological systems, however, is very difficult because of the extreme complexity, dynamic nature, and

multiple levels of organization in living organisms. In addition to their structural and biochemical complexity, biological systems are also electrically very complex and have widely ranging conductivities and dielectric properties.

The difficulties encountered in applying electromagnetic theory to the enormous number of potential interaction sites has slowed progress in understanding the possible biological and health effects of EMF. Knowledge of the mechanisms and sites of interaction could be used to identify appropriate dose metrics, to predict dose–response characteristics, to design better experiments, and to assist in determining whether harmful effects are likely at specific levels of exposure. The impetus for developing such an understanding is clear.

Several physical interaction mechanisms have been proposed to explain the possible biological effects of EMF. Most are based on the well-known electromagnetic interactions with inanimate materials that can be observed experimentally in the laboratory at sufficiently high electric or magnetic field strengths. The controversy surrounding the application of these mechanisms to explain the biological effects of environmental exposure to EMF arises for two reasons. First, the field strengths and resulting forces associated with these exposures are very small. Second, the weak signals produced by field exposure must compete with the noisy background of endogenous electric fields and normal thermal fluctuations.

An additional complication in evaluating interaction mechanisms is the complex cascade of information processing that is involved in normal cell physiology. Physical theory focuses mainly on the first step in the detection of fields: conversion of energy from the field into physical or biochemical changes. Measurable biological effects may well occur far downstream from such interactions, thereby obscuring characteristics such as dose–response that are important for identifying the physical basis of the initial interaction.

The research discussed in this section is useful for addressing four essential questions:

1. What are the mechanisms by which EMF interact with biological systems?
2. At what levels of exposure are effects due to these mechanisms plausible?
3. What experimental evidence exists in support of these mechanisms?
4. Do these mechanisms have implications for the interpretation of in-vivo and epidemiological results?

It is important that a given study clearly state which of the above questions is being addressed. Studies that address only theoretical signal-to-noise, for example, can be used to answer question 2 but not the other questions. Because of the complexity of biological structure and function, it can be argued that the presently available theoretical models are

insufficient to predict or exclude the possibility of biological effects at specific levels of exposure. The rationale for this argument is that detailed knowledge of local noise environments, amplification, and specificity arising from spatial coherence of the field, dynamic processes (e.g. frequency encoding of biological signals), and other factors is not available. Only when every potential interaction site has been evaluated can the possibility of such effects be logically excluded.

Nevertheless, the reasonableness of a health concern is one of the first criteria for deciding how much attention should be given to it. The results of epidemiological studies, for example, are often evaluated in terms of Hill's criteria, one of which is the plausibility of a suggested causal relationship. Epidemiological studies form a large fraction of the basis for concern about exposure to EMF, and interpretation of their results requires a decision about whether there is a plausible underlying mechanism of interaction with EMF that could be responsible for the reported results. The current accumulated body of theoretical work provides more detailed guidance for experimentalists about the plausibility of effects than was available a few years ago. Although differences in findings persist, there is general agreement about the plausibility of effects at some levels of exposure, agreement about the lack of explanatory theoretical bases at other levels of exposure, and controversy about the explanations for effects at intermediate levels.

The need for a theoretical mechanism would be reduced if identical or similar experimental results *in vitro* or *in vivo* were available from many laboratories. The lack of such experimental support increases the role of theory in addressing questions of plausibility. Thus, purely theoretical investigations of interaction mechanisms are perhaps more relevant in evaluating the biological effects of EMF than they would be in disciplines in which robust experimental results are abundant. One problem in research on EMF is the complexity of the exposure environment, as described in section 2. Unless biologically relevant exposure parameters are identified, biologists must search a massive range of exposure parameters with few guiding principles.

Few experimental studies are available of the biological effects of EMF at the field strengths commonly associated with residential exposure ($< 0.5 \mu\text{T}$). The increased risks suggested by most epidemiological studies of EMF at these strengths are far too small to be observed *in vivo*. It is uncertain that the biological changes associated with the small increased risks (e.g. one additional case of childhood leukemia per 10 000 exposed children) could be observed as measurable changes *in vitro*.

Some attempts have been made to test the proposed mechanisms of EMF interactions experimentally. The papers that are considered in this section directly address questions 1 and 3 above. Although in-vitro results do not provide definitive evidence for human health effects, they can provide critical information on important exposure metrics and on intermediate end-points that may guide the search for health effects.

4.8.1 Biologically important interactions at the molecular level

Early attempts to explain the biological effects of EMF focused on simple application of electromagnetic theory to calculate the forces on biological molecules and the energies transferred to them by weak EMF. The extremely small magnitude of these interactions led many investigators to conclude that they would not occur at normally encountered field strengths. More recent theoretical analyses have demonstrated that spatial and temporal averaging processes (e.g. arrays of ion channels, synchronized cell populations, multiple receptors, and charged species on cell membranes) substantially reduce the predicted detection thresholds.

4.8.1.1 Forces and torques on ions and molecules

When the original ion (or electron) velocity is due to an electric field E_0 (which could be endogenous), it can be expressed in terms of the electrical mobility μ_e as $v = \mu_e E_0$. The transverse force resulting from application of a magnetic field would then be $E_T = (F/q) = v \times B$ and the ratio

$$\frac{E_T}{E_0} = \mu_e B \quad \text{Eq. 4.1}$$

Since the mobility of ions in biological fluids (Pethig, 1979) is on the order of $10^{-7} \text{ m}^2/\text{V s}$, this ratio would be $\leq 10^{-11}$ for $B \leq 10^{-4} \text{ T}$. The value of μ_e for electrons inside DNA (Arkin *et al.*, 1996; Meade & Kayyem, 1995; Murphy *et al.*, 1993; Stemp *et al.*, 1995) or inside mitochondrial membranes (Nicholls, 1982) is not yet known.

When an electric field is alternating, the dipole moments p of molecules due to displacement of counter-ions are not lined up with the applied electric field (owing to finite surface conductivity and resulting time delays), and consequently a torque is produced that gives rise to continuous rotation (Fuhr *et al.*, 1986; Pohl, 1983). The electric fields necessary to sustain this rotation, even in water (where the opposing viscosity is only $\eta = 10^{-3} \text{ N s/m}^2$), however, is several kilovolts per meter inside the fluid. This viscous torque opposing the rotation is given by Stokes' law for a sphere of radius a by

$$T = 8\pi\eta a^3 \dot{\theta} \quad \text{Eq. 4.2}$$

where $\dot{\theta}$ is the angular velocity. On individual protein molecules after folding, the quasi-permanent electric charge distribution is nearly symmetrical. Most protein molecules have therefore a relatively small net dipole moment, considering their large size (Takashima, 1989). Typical values of p are in the range of 500 Debye units ($500 \times 1.6 \times 10^{-29} = 8 \times 10^{-27} \text{ C m}$), but can be larger for very large molecules. The torque exerted on such a protein

molecule by the 2.5 V/m electric field inside the membrane of a 20 μm cell, which is produced by a 10^{-3} V/m electric field in the fluid outside the cell, would then be 2×10^{-26} N m. By comparison, the value of the endogenous torque measured on the ‘ γ ’ subunit of the mitochondrial F_1 ATPase, which receives energy from ATP hydrolysis, is 4.5×10^{-20} N m (Noji *et al.*, 1997). Relatively large torques can be exerted even by magnetic fields less than 10^{-4} T on particles, including some of endogenous origin, with high magnetic permeability (Adair, 1993; Frankel, 1986; Kirschvink, 1992a; Polk & Wu, 1994). This mechanism is discussed below.

4.8.1.2 Perturbation of chemical reactions

The energy of the weakest, transitory, but nevertheless biologically very important chemical bond—that due to Van der Waals’ forces—is about 1 kcal/mol (corresponding, on a per particle basis, to $1.62 k_B\tau$, where k_B is Boltzmann’s constant and $\tau = 310$ °K) (Stryer, 1989). The energies W_e and W_m shown on Figure 4.2 are given per unit volume. The volume of an enzyme molecule with a molecular mass of 10^6 (Price & Stevens, 1989) and a density of 1.7×10^3 kg/m³ (Stryer, 1989) is 10^{-24} m³. Over this volume, the electric energy in a medium with relative dielectric constant $\epsilon_r \sim 10$ (as inside a cell membrane) would be about 3×10^{-34} J $\leq 10^{-13} k_B\tau$ for a 2.5 V/m electric field. Such a field would be produced inside the 6 nm thick cell membrane of a 20 μm diameter cell by a 10^{-3} V/m external field. The magnetic energy over the same volume due to a 10^{-4} T magnetic field in a material with the magnetic permeability of free space would be 4×10^{-27} J $\sim 10^{-6} k_B\tau$.

The assumption that the electric field within very complex biological structures is uniform is, of course, highly unrealistic. Furthermore, the maximum potential energy pE of the electric dipole with volume v in a field E is considerably larger than the available electric energy obtained by the product $W_e v$. The fixed charge distribution of the dipolar molecule would modify the electric field in its vicinity by inducing charges on the interface of the surrounding dielectric (Coelho, 1979), the resulting energy W_r depending very much on the shape of the molecule and the electrical characteristics of the surrounding (probably inhomogeneous and anisotropic) structure. The enzyme molecule considered here (of molecular mass 10^6) might have a dipole moment of 2000 Debye units (3.2×10^{-26} C m), giving a maximum value for the alignment energy pE of 8×10^{-26} J $\sim 1.9 \times 10^{-5} k_B\tau$. Thus, the potential energy due to an applied 10^{-3} V/m field (leading to 2.5 V/m in the membrane) can be specified only as $10^{-13} k_B\tau \leq W \leq 10^{-5} k_B\tau$ in the absence of detailed knowledge of its environment and assuming that the electric field in the membrane is uniform.

All of the general considerations and numerical examples given above strongly suggest that the small electric and magnetic fields of interest here cannot be expected to supply, by themselves, the energies necessary for chemical changes (Valberg *et al.*, 1997). Even very small fields, however, might act as control signals to modify processes that depend on metabolically supplied energy, analogous to the extremely weak radio signals, such as those transmitted over thousands of miles, that control locally supplied energy which

powers a loud-speaker or large-screen television set. The exact nature of biological signal processing systems and their susceptibility to control by time-varying EMF is thus of particular interest.

4.8.1.3 Temporal averaging and time-dependent processes

Life processes depend, of course, on the quantities of chemical substances that are processed; they also depend on reaction velocities and the periods over which those processes are completed. Many biological systems contain complex feedback loops and sequences, in which very small changes at one point can ultimately lead to very large changes further along the communication chain. Prime candidates for the investigation of sensitivity to EMF are the signal processing structures: receptors on cell surfaces and inter- and intracellular messenger processes. Probably equally important are the biological 'amplifier control elements', e.g. enzymes, particularly when they also are part of signal processing systems, as in some cell surface receptors. Unfortunately, there is incomplete knowledge about the intracellular events that transform receptor-mediated signals into cell behavioral responses (Lauffenburger & Linderman, 1993); more information is available about very early signal generation, which occurs immediately after receptor or ligand binding. These early signals are more closely associated with short time-scale responses, such as secretion and the release of certain cell products such as cyclic AMP, histamine, and antibodies than long time-scale behavior, for example cell migration and proliferation. For EMF fields, however, which may be active continuously over long periods, long-term biological signaling is likely to be even more important than short-term behavior.

Surface receptors fall into three classes (Lauffenburger & Linderman, 1993): those that act as ion channels, those that interact with G proteins to produce second-messenger molecules, and those that act as enzymes. Some experimental evidence indicates the second group (Luben, 1993) and the third group (Blank, 1992) are of particular interest for the effects of electric fields. Since the receptors of these two groups are quite different from ordinary ion channels, caution must be exercised in generalizing information about the electrical behavior of receptors obtained by analysis of ion channels.

Time scales that are susceptible to intervention from alternating signals are listed in Table 4.46 (Stryer, 1989), which shows the maximum turnover of some enzymes. "The turnover number of an enzyme is the number of substrate molecules converted into product by an enzyme molecule in a unit time when the enzyme is fully saturated with substrate". It is obvious that the turnover rates of some enzymes are well within the frequency range of interest in the present context, which is < 100 Hz.

Finally, in considering the possible nature of biological signals, it is essential to recognize that both frequency modulation and amplitude modulation or pulse code modulation may be involved. Oscillations in electrical potential (Jagadeesh *et al.*, 1992)) and in the quantities of calcium and other ions have been observed in many biological systems (Berridge & Galione, 1988), as illustrated in Table 4.47 (Berridge, 1989; Lauffenburger &

Linderman, 1993). Berridge (Berridge, 1989) suggested that some physiological processes are under frequency-dependent rather than amplitude-dependent control. After reviewing reports on this subject and applicable mathematical models (Goldbeter *et al.*, 1990; Meyer & Stryer, 1991), Lauffenburger and Linderman (Lauffenburger & Linderman, 1993) concluded “that oscillations in receptor-generated second messenger systems may indeed be capable of regulating cell behavioral response in a frequency-dependent manner”. It is also worth noting that the amplitude of the observed Ca⁺⁺ oscillations is not significantly affected by ligand concentration; furthermore, the observed oscillations (‘spiking’) are clearly a non-linear phenomenon which requires models of non-linear processes for its analysis and for possible effects of even small fields (Eichwald & Kaiser, 1993).

4.8.2 Comparison of changes induced by EMF and competing physical processes

The general approach for determining the minimum fields theoretically capable of causing biological effects is a comparison of changes induced by the fields and by other naturally occurring energies and forces.

4.8.2.1 Comparison with the geomagnetic field

A representative value of the Earth’s magnetic field over continental USA is 0.45×10^{-4} T. Bennett (Bennett, 1994) stated that this value is “about 200 times that from typical distribution lines...sudden fluctuations often exceeding 100 mG [10^{-5} T] are correlated with unusual solar activity”. The second part of the statement is incorrect, since even peak variations in very large geomagnetic storms at mid-latitudes rarely exceed 5×10^{-7} T (Garland, 1971). In addition, changes of that magnitude take several hours, so that induced electric fields are very much smaller than that produced by a power-frequency field, which varies 60 times per second over the same amplitude. The first part of the statement refers to a static field, which does not induce any electric field or current, although it can modify the effects of alternating magnetic or electric fields, as suggested by equations (a) and (c) in Figure 4.2 or by its influence on electron spin. Uniform linear motion of a body through a constant static magnetic field also does not induce an electric current, since the total magnetic flux through any closed contour does not change. Only tumbling motion, such as by somersaults, or rapid bending (changing the angle between a cross-sectional area and the direction of the magnetic field vector) would change the total induced voltage

$\oint \mathbf{E} \cdot d\mathbf{l}$ and produce current flow.

4.8.2.2 Comparison with endogenous electric fields

It has been suggested that an induced 10^{-3} V/m 60 Hz electric field is unlikely to affect human biology, because naturally occurring electric fields from electroencephalographic,

electrocardiographic, and other bioelectric sources are about 10^6 times stronger and imprecisely the same frequency range (Foster, 1992). Electric fields and current densities due to heart electrical activity ('electrocardiographic') have been calculated using an anatomical model based on magnetic resonance imaging with a volume resolution ($1.974 \times 1.974 \times 3.0$ mm) that is reasonably adequate for predicting fields at various body points (Hart & Gandhi, 1997). The results (Table 4.48) show that above 40 Hz the resulting average endogenous fields are well below 10^{-3} V/m, except in the vicinity of the heart. Recent measurements of the spectrum of endogenous fields confirm these results (Miller & Creim, 1997).

4.8.2.3 Comparison with thermal noise

Thermal noise, present in all physical systems, is an important factor in limiting the detection of weak signals. To the extent that the transmembrane channels of a cell are in thermal equilibrium with their environment, the mean square thermal noise \bar{V}_n^2 in such channels, considered as a simple resistor, would be the 'Johnson' noise given by

$$\bar{V}_n^2 = 4 k_B \tau R \delta f \quad \text{Eq. 4.3}$$

where R is the channel resistance and δf its bandwidth for electrical signal transmission. As a first approximation, V_n could be considered the 'transmembrane potential', which would have to be measured far enough into the conducting fluid that surrounds the cell that its entire surface could be considered as at the same potential. If this is done, the resistance R in equation 4.3 is the mean membrane resistance of a membrane that is assumed to be homogeneous, and δf becomes the bandwidth of a circuit in which the entire cell membrane is considered to be a single resistor in parallel with the membrane capacitance C . Subject to these assumptions, by which the cell membrane becomes a low-pass filter,

$$\delta f = \frac{1}{4RC} \quad \text{Eq. 4.4}$$

and

$$\bar{V}_n^2 = \frac{k_B \tau}{C} \quad \text{Eq. 4.5}$$

Since

$$RC = \frac{\epsilon_0 \epsilon_r}{\sigma} \quad \text{Eq. 4.6}$$

where ϵ_r is the relative dielectric constant of membrane ≈ 6 according to Takashima (Takashima, 1989) and Pethig (Pethig, 1979).

$$\delta f = \frac{1}{4RC} = \frac{\sigma}{4\epsilon_0\epsilon_r} \quad \text{Eq. 4.7}$$

The values given by Pethig (Pethig, 1979) and Barnes (Barnes, 1986; Barnes, 1996) for cell membrane conductivity vary between 10^{-5} and 10^{-9} S/m, leading to the estimate

$$4.5 \text{ Hz} \leq \delta f \leq 45 \text{ kHz} \quad \text{Eq. 4.8}$$

The actual bandwidth for both noise and signal depends, however, on the source resistance R_s (e.g. the resistance to current flow in the extracellular medium and cytoplasm) in series with the hypothetical RC parallel combination. With $R_s \rightarrow 0$, $\delta f \rightarrow \infty$ and $[V(f)/V(f=0)] = 1$ for any f , while with $R_s \gg R$, $[V(f)/V(f=0)] = 0.53$ at $f = 1/(4RC)$. When $R_s \approx R$, this ratio is 0.78. A more reasonable circuit model, in view of the ‘access resistance’ of ion channels, is discussed further on in this section. Weaver and Astumian (1990) evaluated the thermal noise limit on the response of living cells, mainly on the basis of the assumptions leading to equation 4.5. For a spherical cell with a radius of 10 μm , they obtained $\bar{V}_n = 2.8 \times 10^{-5}$ V. [Since they used $\epsilon_r \approx 2$ rather than the probably more appropriate $\epsilon_r \approx 6$, a better value might be 1.6×10^{-5} V, but the assumptions leading to equation 4.5 are so radical that the value of V_n can be considered only a rough estimate.] Relating the transmembrane voltage V on a spherical cell of radius r to the applied field E (Foster & Schwan, 1986),

$$V = 1.5 E r \quad \text{Eq. 4.9}$$

they obtain a value for the minimum detectable electric field $E \approx 2$ V/m for the prototype cell with $r = 10 \mu\text{m}$. They then considered elongated cylindrical cells (radius r , length L) and found

$$E_{\min} = \frac{2\sqrt{2}A}{r^{1/2}L^{3/2}} \quad \text{Eq. 4.10}$$

where A , obtained from equation 4.3, including effects of signal frequency and membrane conductivity. In evaluating V_n they used $10^{-7} \leq \sigma < 10^{-5}$ S/m and rather arbitrarily selected values of $\delta f \approx 10$ Hz or 100 Hz for the noise bandwidth. They then pointed out that ‘if a cellular mechanism for signal averaging exists’, the signal-to-noise ratio would improve by the square root of the number N of signal cycles during an exposure time T , or by \sqrt{fT} (since the signal would be added in proportion to $N = fT$ while the incoherent noise would be added as \sqrt{N}). With time averaging over 4.3×10^4 s = 12 h, and a $\Delta f = 10$ Hz, they obtained a theoretical limit for bovine fibroblasts ($L = 150 \mu\text{m}$) of only 4×10^{-5} V/m at 100 Hz. Using a bandwidth of 10 Hz, they concluded that their estimates indicated that

“concerns related to possible biological effects due to very weak environmental electric fields cannot be dismissed on the grounds of being swamped by thermal fluctuations”. Applying similar thermal noise considerations to molecules in solution, they came to the important conclusion that “membrane constituents should be much better detectors of an applied (electric) field than isolated molecules in solution”.

Gailey (Gailey, 1996) pointed out that current flowing through a channel must also pass through cytoplasm on one side and the glycocalyx at the cell surface. In this “access resistance of the channel” (Hille, 1992), R_H enters as resistances (R_A, R_B) between adjacent channels in the circuit representation of multiple channels illustrated by Figure 4.1 (Gailey, 1996). Gailey (Gailey, 1996) showed that a reasonable approximation of the net resistance between the mouths of any two channels is given by twice R_H as defined by Hille (Hille, 1992),

$$R_H = \frac{1}{4a\sigma} \quad \text{Eq. 4.11}$$

where $a \approx$ radius of channel mouth and σ is the conductivity of cytoplasm. From Figure 4.1, it is clear that the noise voltage V_1 across the first channel depends not only on its own noise voltage V_{G1} but also on the noise voltages in all the other resistances. Since R_{G1} is not directly in parallel with the other resistors, however, it cannot be assumed that the noise in the different resistors is correlated. Gailey (Gailey, 1996) evaluated a general expression for the normalized correlation or coherence, $\gamma(V_j, V_k)$, between the thermal noise in any two open ion channels, which depends on the total number of channels. The results of this calculation are given in Figure 4.2, which indicates that γ for typical channel parameters can be as low as 0.002 when the number of channels reaches 7×10^4 . The noise voltages for this result were obtained from equation 4.3 using $\delta f = 100$ Hz, a value of $6.5 \times 10^9 \Omega$ for channel resistance, and $3.3 \times 10^9 \Omega$ for access resistance. If voltage from an external coherent source is applied to the combination of N ion channels, the voltages across all channels due to that source will remain coherent. This result is significant, however, only for open channels when R_G is not very much larger than the access resistances R_A and R_B . For closed channels, i.e. when $R_G \gg R_{A,B}$, the correlation coefficient γ approaches 1, even for a large number of channels.

If a voltage from an external coherent source is applied to a cell with N_1 open ion channels and N_2 closed channels, the applied voltages will be coherent across all channels, while the noise voltages will be coherent only across the N_2 closed channels and virtually incoherent across the N_1 open channels. Individual channels open and close randomly. The closing and opening rate constants, α and β , for exponential probability functions for the sojourns in these states have been determined experimentally. The reciprocals are the mean open time ($1/\alpha$) and mean closed time ($1/\beta$). The dependence of these constants on applied voltage V_m is generally non-linear; however, for small values of V_m the

dependence can be characterized by slopes M_α and M_β . If α_0 and β_0 are the rate constants before the perturbing signal, one can write (Gailey, 1996)

$$\alpha(V_m) = \alpha_0 + M_\alpha V_m \quad \text{Eq. 4.12}$$

$$\beta(V_m) = \beta_0 + M_\beta V_m \quad \text{Eq. 4.13}$$

Since the mean number of open channels N_0 is related to the total number of channels by

$$N_0 = \frac{\beta}{\alpha + \beta} N \quad \text{Eq. 4.14}$$

it is possible to compute N_0 as a function of the perturbing potential V_m from equations 4.12–4.14. Thermal noise voltages are practically incoherent across the open channels, as illustrated in Figure 4.2, and therefore add as $\sqrt{N_0}$, while the applied voltage adds as N_0 . This differential effect is not the case for closed channels. It can then be shown (Gailey, 1996) that the signal-to-noise ratio will improve by a factor of

$$\delta\left(\frac{S}{N}\right) = \frac{M_\beta \alpha_0 - M_\alpha \beta_0}{M_\beta \alpha_0 - M_\alpha \beta_0 \gamma - \frac{\beta_0 M_\alpha}{\sqrt{N_0}}} \quad \text{Eq. 4.15}$$

where the signs of the slopes M_α and M_β are generally opposite. Also, for $N_0 \approx 10^4$ or larger, the denominator of equation 4.15 reduces to $M_\beta \alpha_0$. This improvement factor is shown in Figure 4.3 for $\alpha_0 = \beta_0$. When the slopes M_α and M_β are equal in magnitude but have opposite signs, the improvement factor due to noise incoherence is only about 2; however, when $M_\alpha \gg M_\beta$ (with $\gamma \rightarrow 0$ and $N \rightarrow \infty$), the value of $\delta(S/N)$ can approach 100.

4.8.2.4 Comparison with shot and 1/f noise

Biological processes experience not only thermal noise but also ‘shot noise’ and 1/f noise. Shot noise is the fluctuation of a variable, such as ion current, due to its discreteness (e.g. individual charges that make up the ion current) or ‘granularity’. While the inevitable graininess of the environment (through collisions) appears through $k_B \tau$, the graininess of the variable itself shows up as a separate source of noise and appears only when a system is not in thermal equilibrium with its environment and significant energy is passing into or from the system (MacDonald, 1962). Shot noise can generally be described by the Poisson probability distribution, where the standard deviation, $\sqrt{\sigma}$, is proportional to the mean value of the variable (e.g. current through a membrane channel).

$1/f$ noise is noise that, when described according its spectrum, increases with decreasing frequency as $1/f^\alpha$. This noise, which appears in a great variety of macroscopic and microscopic systems, was thought to arise at cell membranes by flow of ion current through an orifice (Verveen & DeFelice, 1974); however, recent analytical work and analysis of available data indicate that $1/f$ noise in biological membranes is not an inherent property of ion transport but is produced by random switching of channels between their different states (Bezrukov, 1996).

The voltage noise spectra of a frog node of Ranvier shown in Figure 4.4 indicate that total noise depends strongly on the value of the (quasi-static) membrane potential and that $1/f$ noise must be a major component of total membrane noise. Verveen and Derksen (Verveen & DeFelice, 1968) concluded that $1/f$ is the largest source of noise at the cell membrane below 160 Hz. Barnes (Barnes, 1986) estimated that $1/f$ noise and shot noise in a bandwidth of 1 Hz at 1 Hz in the frog node of Ranvier is 10^3 times greater than thermal noise; this would translate to a ratio of about 16.7 at 60 Hz.

Astumian *et al.* (Astumian *et al.*, 1995) and Weaver *et al.* (Weaver *et al.*, 1998) considered a situation in which the “noise drift across a cell membrane is equal to the square root of the number of molecules passing through the membrane plus the number absorbed”, i.e. the typical Poisson process of shot noise. For membrane channels, calculation gives a time of about 1 h to reach $(S/N) = 1$ when the electric field E_0 in the medium surrounding a cell with 100 μm radius is 0.1 V/m. The principle limitation of this analysis is the assumption that only deviations in the total quantity of accumulated substance greater than noise in that parameter can be detected. No role is assigned to recognition by any part of the complex cell signaling system of changes in the velocity of substance accumulation or regular periodic changes in that velocity.

Minimum detection limits for ensembles of voltage-gated ion channels were analyzed theoretically by Gailey (Gailey, 1996) with a two-state model for channel gating. The stochastic gating of ion channels is a form of shot noise. Gailey compared the net change in charge transferred over some period of time due to a small perturbing membrane potential to the expected fluctuations in charge transferred due to stochastic channel activity. The model predicts that a 1 μV induced membrane potential can be detected after a few milliseconds by an ensemble of 10^8 ion channels. Because most cell types have fewer than this number of channels, the model suggests that single cells are unlikely to detect signals of this magnitude; however, groups of synchronized cells, such as those that occur in the central nervous system, may be able to detect such signals.

4.8.2.5 Magnitude of competing thermal effects

Weaver *et al.* (Weaver *et al.*, 1997) suggested that molecular changes due to temperature variations within biological systems are larger than those expected from weak exposure to EMF. This statement was based on their evaluation of the temperature dependence of the chemical rate constants, k , given by Arrhenius' equation

$$k = Ae^{-\frac{U}{k_B\tau}} \quad \text{Eq. 4.16}$$

and, apparently, the assumption that electric or magnetic fields could affect a chemical reaction (or ‘molecular flow’) only by changing the activation energy U .

Before discussing either the pertinent numerical results or the assumptions that were apparently made, equation 4.16 must be discussed in some detail. The energy U represents the barrier between reactants and product. In deriving equation 4.16, it is assumed that reactions proceed slowly enough that thermal equilibrium between reactants and the transition state is maintained at all times at the level of the energy barrier. Since the equation is derived from thermodynamics, it describes only the average properties of a system and not individual molecular changes. The constant A is given approximately by Wojciechowski (Wojciechowski, 1975) and Price and Dwek (Price & Dwek, 1984) as

$$A = \frac{k_B\tau}{h} s \quad \text{Eq. 4.17}$$

where h is Planck’s constant and s is a steric factor, which can be derived from statistical mechanics and has values between 1 (atom-to-atom reaction) and 10^{-5} (two non-linear molecules) (Wojciechowski, 1975). At the physiological temperature $\tau = 310$ °K, the value of the ratio $(k_B\tau)/h$ is $6.5 \times 10^{12}/s$.

The rate constant k is related to the time rate of change of product formation from reactants $[C]$ and $[D]$ (where the square brackets indicate concentration) by

$$\frac{d[P]}{dt} = k[C]^c[D]^d \quad \text{Eq. 4.18}$$

where the order of the reaction is indicated by the exponents c and d . The total order of a reaction is indicated by the sum of c and d ; a reaction that is of ‘second order’ with respect to the reactant C will obviously proceed much faster than a reaction that is of first order ($c = 1$). The exponents c and d are experimental quantities, which can be zero or have either integral or non-integral values. In a single-step reaction (called an ‘elementary reaction’), the order of the reaction is equal to its ‘molecularity’, i.e. the number of molecules that must collide for the reaction to take place. When the exponents in an experimental rate law are not equal to the coefficients of the chemical balance equation (e.g. $2C \rightleftharpoons D + E$), the total reaction must generally occur in a sequence of steps. If they are equal, the reaction may occur in a single step, but this is not necessarily the case (Freifelder, 1985). In complex biological systems, the order of a reaction can change during its course (Johnson *et al.*, 1974).

It will become apparent from the discussions in the next section that electric or magnetic fields could affect both the steric factor in equation 4.17 and the effective concentration of reactants which can interact. Thus, any calculation that shows that the effect on product formation (equation 4.18) due to a small voltage which modifies U in equation 4.16 is smaller than that caused by a temperature change $\Delta\tau$ in equation 4.16 cannot be generalized, as Weaver *et al.* (Weaver *et al.*, 1997), to assume that molecular changes due to temperature variations within biological systems are larger than those expected from weak exposure to EMF.

It should also be noted that the important chemical reactions in mammals that involve enzymes have overall rate constants that encompass the rate constants of several intermediate reactions, so that the overall reaction rate cannot necessarily be described by equation 4.16 (Price & Stevens, 1989).

4.8.3 Proposed physical mechanisms

4.8.3.1 Effects of electric fields on cell surface structures and cell attachment

(a) Polarization forces

Polarization forces have been proposed as a possible physical mechanism of the interactions between fields and cells. It has been suggested that the pronounced sensitivity of cells to low frequencies is related to the very large increase in dielectric permittivity with decreasing frequency of living tissue (Foster & Schwan, 1986). The interface of the cell with its environment is a highly charged coat, or glycocalyx, and in the presence of VLF electric fields an ion diffusion cloud develops within the glycocalyx to compensate for depletion of the co-ion species in this region (Chew, 1984). ELF excitation of this cloud is also likely to affect adjacent cells (Polk, 1992a). While the microscopic relative dielectric permittivity of the glycocalyx region remains small (< 100), the large dielectric enhancement at the macroscopic level produces a substantial force on the macroscopic collection of fixed charges on the cell surface and in the glycocalyx (McLeod *et al.*, 1993b). The large dielectric enhancement at the macroscopic level is the large polarization per unit volume of the bulk tissue, which is due to counter-ion displacement on cell surfaces when an electric field is applied (Pethig, 1979). Thus, the gradient ($\nabla\epsilon$) of the dielectric constant in the glycocalyx region is due to the cell's location within a dielectric environment created by other, adjacent cells.

The Kelvin polarization force density F_v can be derived from equation (E) on Figure 2.3. Thus, in a material with N dipoles per unit volume, each having a dipole moment p , the polarization or dipole moment per unit volume $P = Np$ and $F_v = P \cdot \nabla E$ (Haus & Melcher, 1989). For non-uniform fields and non-uniform dielectrics, this can be generalized by stress tensor formalism (Stratton, 1941) to

$$F_v = (-1/2) E^2 \nabla \epsilon \quad \text{Eq. 4.19}$$

This expression is the starting point for an explanation of at least some of the electrical forces that must be acting at the cellular level. McLeod *et al.* (McLeod *et al.*, 1993b), using, apparently, the vector identity

$$\nabla(\mathbf{P} \cdot \mathbf{E}) = (\mathbf{P} \cdot \nabla)\mathbf{E} + (\mathbf{E} \cdot \nabla)\mathbf{P} + \mathbf{P} \times (\nabla \times \mathbf{E}) + \mathbf{E} \times (\nabla \times \mathbf{P}) \quad \text{Eq. 4.20}$$

considered only the purely electrostatic case, when $\nabla \times E = 0$ and $\nabla \times P = 0$, rather than $\nabla \times E = -(\partial B/\partial t)$, and then estimated

$$F_v = \frac{\epsilon_x - \epsilon_m}{\Delta} \epsilon_0 E_t^2 \text{ Nm}^{-3} \quad \text{Eq. 4.21}$$

where Δ is the thickness of the boundary layer and ϵ_m its relative dielectric permittivity, while ϵ_x is the relative dielectric permittivity of the external medium; E_t is the tangential electric field. The pressure, F_A , at the boundary layer of area A will then be $(F_v A \Delta)/A$ or

$$F_A \approx (\epsilon_x - \epsilon_m) \epsilon_0 E_t^2 \text{ Nm}^{-2} \quad \text{Eq. 4.22}$$

If one uses for ELF (Foster & Schwan, 1986) $\epsilon_x \epsilon_0 \approx 10^{-4}$ F/m and $\epsilon_m \epsilon_0 \approx 10^{-9}$ F/m, one obtains $F_A = 10^{-6}$ N/m² if the applied electric field is as large as 0.1 V/m. This is only slightly lower than the sound pressure at the threshold of hearing, of about 2×10^{-6} N/m² (Beranek, 1954), which might suggest that the effect is physiologically significant at this field intensity.

Since the effect is proportional to the square of the applied field, a sinusoidally time-varying field would give a time average of $E_0^2/2$, where E_0 is the peak value of the sinusoidal field. Therefore, the resulting pressure would act continuously while the field is applied. McLeod *et al.* (McLeod *et al.*, 1993b) suggested that this temporal integration might be responsible for the effects of low-intensity fields. They also pointed out that the pressure variation at constant frequency could excite or enhance the natural mechanical vibration frequencies of some cellular structures. Furthermore, the same small pressure applied simultaneously at the boundaries of many cells could have effects on organs or organ cultures *in vitro*.

Support for the importance of boundary layer pressure is provided by the findings that modulation of bone-cell function by electric fields is dependent on the density (McLeod *et al.*, 1993a) and that the effects of fields below 100 Hz reach a peak near 30 Hz (McLeod *et al.*, 1987c). Many of the effects seen *in vitro* in cells that involve neither electric nor magnetic fields are, however, also dependent on cell density.

(b) *Coulombic forces*

Otter *et al.* (Otter *et al.*, 1998) suggested that the component of the electric field perpendicular to the cell in the glycocalyx is sufficiently large to affect cytoskeletal polymerization by the mechanism known as the Brownian ratchet (Peskin *et al.*, 1993). The Brownian ratchet has been proposed as a means by which the cell rectifies the thermal motion of its membrane to permit it to extend cytoplasmic processes. It has also been shown that addition of a weak, homogeneous force F in combination with square-wave modulation can cause particles of slightly different size to move in opposite directions. The synergetic change in velocity caused by F can be much greater than the drift velocity that would be caused by F alone (Tarlle & Astumian, 1998).

Otter *et al.* (Otter *et al.*, 1998) suggested that small imposed oscillations of the membrane add to the local thermal motion and enhance the ability of actin monomers to diffuse into the space between the actin microfilament ends and the cell membrane. Atomic force microscopy has been used to show that 1.2 nm oscillatory deflections of the cell membrane can result in 1000-nm deformations of the cell surface (20–25% of the original cell height) over 90 s when the frequency of oscillation is 15 Hz. Oscillation at lower (1.5 Hz) or higher (150 Hz) frequencies produces smaller deformations, indicating a strong frequency dependence of this rectification mechanism.

The force imposed by the atomic force microscopy cantilever in these experiments is estimated to be on the order of 0.1 pN. The surface charge density of the cell surface coat (glycocalyx) has been estimated to be between 0.001 and 0.2 C m⁻² (Bongrad, 1988; Lakshminarayanaiah, 1984; Pethig, 1979). With the largest of these values, an electric field of 10⁻³ V/m would exert a force per unit area of $\rho E = 10^{-4}$ N/m². Thus, the force on the membrane of a cell 10 μ m wide by 100 μ m long would be roughly 0.1 pN, similar to the force shown to cause dramatic cell distortion by atomic force microscopy perturbation of the cell surface (Otter *et al.*, 1998).

To obtain a similar pressure from polarization forces, a much larger electric field, 0.1 V/m, was required. Provided that the estimate of unbalanced charge density at the cell surface is correct, the force due to the perpendicular component of the electric field appears to have a greater effect on receptors than the combination of dielectric gradient and tangential field. It is difficult, however, to believe that electric fields much smaller than 10⁻⁴ V/m affect cells through pressure effects at the boundary layer, unless the charged protein molecules are particularly sensitive to stimuli at a particular frequency. Simultaneous, coherent pressure on many receptors and alternating pressure continued for a long time could also increase very small pressure effects above the ‘noise’ produced by random motion of adjacent cells.

(c) *Effects of induced charge on cells*

Possibly as significant as the ‘push–pull’ (i.e. alternating positive and negative) pressure due to the interaction of a sinusoidally time-varying electric field with the permanent surface charge on a cell is the interaction with the time-varying component, ρ' , of that charge density, which itself depends on the applied field. ρ' can be expressed in terms of the component of the applied electric field, E^\perp , that is perpendicular to the cell surface. For a long cylindrical cell of radius r , it is (Polk, 1990; Polk, 1992c).

$$\rho' = \frac{e^2 n_0 r}{k \tau (1 + j\omega / f_r)} E^\perp \quad \text{Eq. 4.23}$$

At frequencies ($\omega/2\pi$) well below the relaxation frequency f_r , the term $j\omega / f_r$ is negligible. If e is the elementary charge 1.6×10^{-19} C, $n_0 = 2 \times 10^{17}/\text{m}^2$ as before, $r = 10^{-5}$ m, and $k_B\tau = 4.28 \times 10^{-21}$ J at 37°C , one obtains $\rho' = 1.2 \times 10^{-5} E^\perp$ C/m². If $E^\perp = E_0 \cos \omega t$, the pressure $\rho' E^\perp$ will be proportional to $E_0^2 \cos^2 \omega t$, and its unidirectional time average will be $F'_A = 6 \times 10^{-6} E_0^2$ N/m². For $E_0 = 10^{-4}$ V/m, one obtains $F'_A = 6 \times 10^{-13}$ N/m².

(d) *Induced surface charge on cell matrix or substrate*

In addition to inducing charge at the cell surface, an electric field within a tissue induces a surface charge on the extracellular matrix or other growth substrate. This induced charge can have a robust effect on processes such as protein absorption and cell adhesion, as cell matrices and substrates typically have a low fixed charge density. Recent work has shown that induced charge densities on growth substrates on the order of $0.1\text{--}1.0 \mu\text{C}/\text{m}^2$ can significantly affect cell growth and morphology through this induced surface charge mechanism (McLeod, 1998).

4.8.3.2 Cyclotron resonance and ion parametric resonance

As a consequence of Lorentz' force $F = q(v \times B)$, equation (a) on Figure 4.2, a charge q of mass m which moves at velocity v in a constant (static) magnetic flux density B_s will follow, in a vacuum, a circular path of radius R_c

$$R_c = \frac{vm}{qB_s} \quad \text{Eq. 4.24}$$

The angular velocity ω_c and cyclotron frequency f_c will be given by

$$\omega_c = 2\pi f_c = \frac{qB_s}{m} \quad \text{Eq. 4.25}$$

If an electric field is applied as in a cyclotron (Sears *et al.*, 1976) or induced by an alternating magnetic field, $B = B_0 \cos \omega_c t$, that has the same direction as B_s , the tangential velocity v of the charge will increase, as will correspondingly its orbital radius R_c . It has been noted that the cyclotron frequencies, $f_c = \omega_c/2\pi$, of many physiologically important ions fall below 100 Hz in the geomagnetic field ($\approx 50 \mu\text{T}$ depending on latitude). For example, $f_c = 38.4 \text{ Hz}$ for the $^{40}\text{Ca}^{++}$ ion at $50 \mu\text{T}$. Chiabrera *et al.* (Chiabrera *et al.*, 1985) and Liboff *et al.* (Liboff, 1985) therefore proposed various mechanisms which require cyclotron motion of ions along circular or helical paths, either in transmembrane channels or at receptors on the cell surface. It has been pointed out (Durney *et al.*, 1988; Halle, 1988; Sandweiss, 1990), however, that such motion is impossible in the dense, collision-dominated fluids of biological materials. Furthermore, ions in biological fluids are normally hydrated, and the frequency given by equation 4.25 would depend on the number of water molecules (and their total mass) in the hydration sheath of each ion (Koryta, 1982).

Despite the apparent implausibility of cyclotron resonance as a mechanism for interactions between magnetic fields and biological systems, many experiments have shown a response to combinations of static and alternating magnetic fields, which reaches, in different systems, either a maximum or minimum at the frequency f_c given by equation 4.25 for various physiologically important ions. Some attempts to replicate the results independently in different laboratories have failed while others have been successful (Table 4.5).

(a) *Lednev model*

A refinement of the cyclotron resonance model is provided by a theory proposed by Lednev (Lednev, 1991; Lednev, 1993; Lednev, 1994), which pertains to effects that would affect transport through ion channels only indirectly. It is based on the idea that an ion weakly bound within a protein, notably Ca^{++} within calmodulin, can be modeled as a charged oscillator. The oscillations are metabolically excited and are at infrared frequencies. An ambient, steady (DC) magnetic field, B_s , such as that of the Earth, would cause Zeeman splitting (Haken & Wolf, 1984) of each vibrational level into two levels, ω_A and ω_B , separated by the ion cyclotron frequency. Thus, $\omega_c = \omega_A - \omega_B$. When an alternating field, B_1 , is then applied in parallel with B_s , the resulting frequency modulation of levels ω_A and ω_B will change the probability of ion transition, P , from an excited level to some ground state of frequency ω_0 . Applying earlier work (Podgoretskii & Khrustalev, 1963), Lednev then predicted that the time average of P will be

$$\tilde{P} = K_1 + (-1)^n K_2 J_n(x) \cos \delta \quad \text{Eq. 4.26}$$

where K_1 and K_2 depend on the amplitudes of infrared radiation corresponding to transitions from ω_A and ω_B to ω_0 , δ is the difference in phase of the radiation from two sublevels, and the argument of the Bessel function $J_n(x)$ is

$$x = \frac{nB_1}{B_S} \quad \text{Eq. 4.27}$$

The Bessel function $J_n(x)$ in equation 4.26 leads to maxima and minima when the frequency of the applied sinusoidal magnetic field is

$$f = \frac{\omega_c}{2\pi n} = \frac{f_c}{n} \quad \text{Eq. 4.28}$$

where n is an integer. Lednev's model thus not only predicts 'resonances' at the cyclotron frequency and its subharmonics but also prescribes the relative amplitudes of B_1 and B_S for which the 'resonance' effects should be maximized. These are given by the values of the argument x that corresponds to extreme values of $J_n(x)$. For example, $J_1(x)$ has its first maximum at $x = 1.84$. The model furthermore predicts, at a fixed B_S and resonance frequency f_c , a variation of system response as the amplitude of B_1 is varied, changing the magnitude of $J_n(x)$.

One apparent advantage of this particular theoretical model was that it could be tested by applying appropriate fields B_S and B_1 to proteins in chemical reactions without the presence of complicated cells or tissue. Experiments to study the effect of parallel directed B_S and B_1 fields on the phosphorylation of myosin in the presence of calmodulin and troponin—performed, however, over only a very narrow frequency range—seemed at first to confirm the theoretical predictions (Shuvalova *et al.*, 1991). A similar experiment also showed that phosphorylation of myosin can respond to purely static magnetic fields between 0 and 200 μT in the absence of an alternating field (Markov *et al.*, 1993). An investigation of calcium binding to metallochromic dyes involving an indirect measurement of Ca^{++} binding to calmodulin in the presence of combined AC (50 and 120 Hz) and DC (0 to 299 μT) magnetic fields, however, failed to show any effect of the magnetic field (Bruckner-Lea *et al.*, 1992).

The principal difficulty of the theory is that the width of the infrared spectral lines, due to vibration of Ca^{++} in the calmodulin molecule, must be extremely narrow ($< f_c$) if splitting into two frequencies, separated by f_c , is to be significant. Lednev suggested that shielding of the Ca^{++} ion within the structure of the calmodulin molecule would prevent at least Doppler broadening. Furthermore, an ion inside a molecule is largely protected from collision with atoms or molecules in the external environment.

Calmodulin is ubiquitous in living organisms and is essential to normal cell function (Cheung, 1982). It interacts with many Ca^{++} -dependent enzymes and regulates their

activity (Stryer, 1989). Since the location of Ca^{++} ions at four possible binding sites within calmodulin and the strength of binding at each site (Rainteau *et al.*, 1989) profoundly influence the interaction of calmodulin with various enzymes, any effect of magnetic fields on Ca^{++} binding with calmodulin would affect a wide range of physiological processes.

(b) *Ion parametric resonance*

Blackman *et al.* (Blackman *et al.*, 1994; Blackman *et al.*, 1995) subjected PC-12 cells stimulated by nerve growth factor to combinations of AC/DC magnetic fields and found that the number of cultured cells with neurite outgrowths decreased in comparison with unexposed cells as a function of AC/DC amplitude. That behavior was, however, restricted to narrow frequency bands determined by the amplitude of the applied DC magnetic field, suggesting a ‘resonance’ behavior. They were able to fit their data to a Bessel function by assuming a dependence

$$\tilde{P} = K_1 + K_2(-1)^n J_n(2nB_1 / B_0) \quad \text{Eq. 4.29}$$

in which the factor of (2) in the argument of the Bessel function accounts for a dependence on the B_1/B_0 ratio that differs substantially from that predicted by Lednev’s equations 4.26 and 4.27. Using fairly elaborate curve fitting, they suggested that the data for PC-12 cells indicate ‘resonances’ corresponding to ions of vanadium, magnesium, manganese, and hydrogen. The original experiments were later replicated under double-blind conditions in the same laboratory [Blackman, In Press #1788]. Blackman *et al.* (Blackman *et al.*, 1996) also demonstrated that their experimental results are not related to the amplitude of the magnetically induced electric field (Blackman *et al.*, 1993a) and that mutually perpendicular, rather than parallel oriented, AC and DC magnetic fields evoke different biological responses.

The results obtained by Blackman *et al.* (Blackman *et al.*, 1994; Blackman *et al.*, 1995; Blackman *et al.*, 1998; Trillo *et al.*, 1996) for neurite outgrowth of PC-12 cells appear to confirm the Blanchard and Blackman (Blanchard & Blackman, 1994; Blanchard *et al.*, 1995) version of the ion parametric resonance theory (equation 4.29). The results of experiments with living land snails (Prato *et al.*, 1996), however, agree better with Lednev’s original proposal (equations 4.26–4.28).

Despite these experimental results, questions remain about the validity of the ion parametric resonance theory. Adair (Adair, 1992) pointed out that it requires the radiating ion to be shielded from collision-like interactions with the surrounding material. Even if the de-excitation time of the above-ground state oscillation were as long as 0.1 s, the width of that state would be only 10 Hz, and a 16 Hz cyclotron resonance would be ill defined. Furthermore, presumably any substantial transient change in the ion-excited state would interrupt the mechanism, which depends on a specific energy difference between

the split states (at frequencies ω_A and ω_B). Adair (Adair, 1992) suggested that large transient electric fields from far-off collisions would destroy the fine tuning required by the mechanism; however, such transients would most likely shift the vibrational sublevels at frequencies ω_A and ω_B equally, so that the important difference ω_C would be preserved. He pointed out that an ion as heavy as Ca^{++} would not radiate strongly and noted that the mechanism also requires perfect three-dimensional symmetry of the vibration before the perturbing alternating field is applied, e.g. equal 'spring constants' in different directions. In addition, a large set of ions would have to be excited and modulated coherently by the external field for a noticeable effect to occur.

Lednev (Lednev, 1994) responded that the model applies primarily to the effects of external fields on vibration of Ca^{++} or Mg^{++} in calcium-binding proteins and that the atomic structure of Ca^{++} binding sites is known from X-ray diffraction studies in a number of calcium-binding proteins, including calmodulin (Babu *et al.*, 1988). These results indicate that the symmetry condition is satisfied. As an example, Lednev referred to the radial distribution of protein oxygens around the Ca^{++} at two calcium-binding sites in parvalbumin, which show sharp peaks at the identical ultraviolet wavelength (Ahlstrom *et al.*, 1987).

Concerning the requirement that the excited vibrational mode have a 'long' lifetime (i.e. long de-excitation time) in order for the ELF field (periods, 10–50 ms) to be effective, Lednev cited Ritov (Ritov, 1976), Martin *et al.* (Martin *et al.*, 1985), and Cox (Cox, 1988) to confirm that the lifetime of Ca^{++} and Mg^{++} chelated in the calmodulin–kinase complex is about 1 s.

In a detailed analysis of the ion parametric resonance mechanism, applying quantum mechanics, Engstrom (Engstrom, 1996) concluded that the model makes many predictions for biological systems that are sensitive to differences in excited states of biochemicals, and that these predictions can be tested experimentally. Another interesting direction of research is investigation of the effects of fields at angles other than parallel and perpendicular orientations. In the context of a search for mechanisms that can explain the biological effects of weak magnetic fields, a particularly important feature of the ion parametric resonance model is that it assumes no energy input from the applied magnetic field into the affected biological system. It postulates only that the energy already in the system will be redistributed. Lednev (Lednev, 1994) suggested that, for this reason, it is not applicable to a system in equilibrium such as the solution containing calmodulin and CaCl_2 that was used in the experiments of Bruckner-Lea *et al.* (Bruckner-Lea *et al.*, 1992) mentioned earlier in this section.

4.8.3.3 Biological electron transfer

Long-range intermolecular and intramolecular electron transfer plays an important role in conferring the specificity and directionality of numerous biological processes (Gray & Winkler, 1996). These include the classical enzyme reactions that have been suggested as

a medium for field interactions (Grundler *et al.*, 1992). Specific examples may be cytochrome C oxidation by the enzyme cytochrome oxidase and effects of EMF on Na/K ATPase function (Blank, 1992; Blank & Soo, 1992a; Blank *et al.*, 1995). It has also been shown that a non-equilibrium chemical reaction catalyzed by a membrane enzyme can act as an active element in an external electric circuit and provide the energy for driving electrical oscillations (Derenyi & Astumian, 1998).

One difficulty in accepting biological electron transfer as a likely initial site for detection of weak externally applied electric or magnetic fields is that the endogenous energies involved in electron binding are many orders of magnitude larger than those contained in the weak fields of interest here. Electron affinity values for organic molecules generally fall within the range 0.5–2.0 eV (19–75 $k_B\tau$) (Pethig, 1979). Free or diffusing electrons might, however, be affected by even weak electric or magnetic fields. As mentioned earlier, the electric mobility μ_e of ions in biological fluids is of the order of 10^{-7} m^2/V s. The interaction of a magnetic field with any charged particle by Lorentz' force depends on the velocity of that particle [equation (a) on Figure 4.3]. Since that velocity v is related to the electric mobility by $v = \mu_e E_0$, the magnitude of effects on charged particle motion by a magnetic field B can be estimated by considering the ratio of the transverse electric field E_T (transverse force/charge q) to the electric field E_0 (probably of endogenous origin) that was responsible for the original linear motion at velocity v . That ratio is $\mu_e B$. While the mobility of electrons over long distances along protein strands is probably also small, it could be sufficiently large in some locations for electron motion to be affected by a relatively weak magnetic field.

It has been shown that electron mobility along the π bonds in the central core of DNA strands can be surprisingly large (Arkin *et al.*, 1996; Meade & Kayyem, 1995; Murphy *et al.*, 1993; Stemp *et al.*, 1995); however, it is not known whether it is large enough to make transverse deflection of electron currents due to applied magnetic fields plausible. Direct effects on DNA of externally applied EMF have been suggested (Blank & Goodman, 1997).

Another important site for consideration of possible effects on electron transfer by applied magnetic fields is the mitochondrial membrane (Nicholls, 1982), where proton and electron transfer are involved in energy conversion mediated by ATPases (Polk, 1997).

4.8.3.4 Effects on biogenic magnetite

Magnetite biomineralization occurs in the human brain (Kirschvink *et al.*, 1992), and one line of human leukemic leukocytes was nearly 100 times more magnetic than brain tissues, giving cellular magnetic moments of $\sim 10_{-12}$ A m^2 (Kirschvink & Kobayashi-Kirschvink, 1993). Kirschvink (Kirschvink, 1992a) suggested that the interaction energy of even weak ELF magnetic fields with magnetic particles of magnetic domain size would be larger than the thermal energy of $(1/2) k_B\tau$ per degree of freedom within a system in thermal equilibrium. Using a model of magnetic particles floating in a fluid medium, Adair (Adair,

1993) proposed that a 60 Hz magnetic field weaker than 5 μT could not generate significant biological effects in the cell by acting on magnetic elements. That conclusion appears to be premature, however, because not enough is known about the relationship of the magnetite particles to other components of the cell interior or of the cell membrane to formulate a mathematical model that is adequate for precise numerical predictions.

A description of the dynamics of any kind of anchoring of the ‘magnetosomes’ to the cell structure would require a non-linear differential equation; even a linearized equation would have no constant coefficients unless the applied alternating magnetic field is exactly perpendicular to the geomagnetic field and the magnetosome deflection is very small. In addition, the effective viscosity of the fluid within the cell in the vicinity of the magnetosomes, which is a critical parameter in the Adair model, cannot be well specified. Even if this clearly oversimplified model is used but combined action by multiple magnetosomes within the cell is allowed, a signal-to-noise ratio well above 1 might be possible with a 60 Hz magnetic field of 2 μT (Polk, 1994). Neither estimate can be considered adequate at the present time; however, it is likely that any effect of multiple magnetosomes within a cell would make use of their coherent motion, and thus there would be no significant thermal noise limitation if the energy supplied by an applied field to a single magnetosome were much smaller than $k_B\tau$. For single domain particles of Fe_3O_4 , the magnetic moment is given by (Frankel, 1986):

$$\mu = \text{volume} \times 4.8 \times 10^5 \text{ A m}^2 \quad \text{Eq. 4.30}$$

and the energy supplying torque to a spherical particle of 60-nm diameter in a 2 μT field would already be 0.1 $k_B\tau$ at 37 °C. Therefore, it is important to perform further experimental work on the behavior of such particles within cells or of similar particles that might be present in cell culture media (Dobson & Grassi, 1996; Kobayashi *et al.*, 1995). Vaughan and Weaver (Vaughan & Weaver, 1996; Vaughan & Weaver, 1998) suggested that endogenous or contaminating magnetic particles could create pores in cell membranes when magnetic field pulses are applied; however, they indicated that for simple biologically synthesized magnetosomes (radius = 10^{-7} m; magnetic moment = 2×10^{-17} A m²) and typical cell membranes, the estimated pulse magnitude must exceed $B_0 \approx 1\text{--}7 \times 10^{-2}$ T, and the optimal pulse duration is in the range 10^{-5} s < $t_{\text{pulse}} < 10^{-1}$ s. For larger contaminating particles with larger net magnetic moments, the pulse magnitudes could only be somewhat smaller, and the optimal durations are about the same.

4.8.3.5 Magnetochemistry: Effects of magnetic fields on free-radical reactions

Free radicals are important in many biological processes (Freifelder, 1985). For example, they are formed as intermediate products when light is incident upon the visual pigment rhodopsin. It has been known for some time that chemical reactions that involve free radicals are strongly influenced by static magnetic fields (Blankenship *et al.*, 1977; Hoff *et al.*, 1977; Werner *et al.*, 1978), but more recent work (Cozens & Scaiano, 1993; Hamilton *et al.*, 1988; McLauchlan, 1989) suggested that DC fields as low as 1–10 Gauss may

affect such chemical processes. By implication, as is shown below, alternating fields of the same order of magnitude, acting in concert with steady fields should also affect reaction yields. The effects of even smaller alternating fields have been predicted by analytical work (Adair, 1997; Brocklehurst & McLauchlan, 1996; Canfield *et al.*, 1994) and are discussed further on.

Observations in this area are based on Pauli's exclusion principle, which states that the electronic states of an atom can only be occupied in such a way that no two electrons have exactly the same set of quantum numbers. Thus, if there are, for example, two valence electrons in the same orbital, characterized by the same set of orbital quantum numbers, their individual spin quantum numbers must be $+1/2$ and $-1/2$; i.e. their spins must be in opposite directions. If two electrons in a chemical bond are paired in this manner and if this bond is broken, for example by incident light, resulting in two free radicals, subsequent recombination is possible only if the two electrons preserve this oppositely directed spin. Interaction with the local magnetic field—due to nuclear magnetic moments or other nearby spinning and orbiting electrons—can, depending on the particular molecular structure, either favor or destroy opposite spins. In the latter case, of now equally orientated spins, recombination of the radicals becomes impossible. Conversely, if the radical pair was formed from excited atomic states with the unpaired electrons coming from different atomic shells, they may already have equal spin, preventing chemical combination of intermediate products.

As long as the electrons have opposite spin, the products have a 'singlet' character, i.e. the total quantum number J , which characterizes the electron states, is equal to the orbital quantum number L , since the spin quantum number $S = (1/2) - (1/2) = 0$ and $J = S + L$. As the products diffuse, however, some fraction will acquire a 'triplet' character; i.e. the electron spins may become parallel, and $S = \pm (1/2 + 1/2) = \pm 1$ and J can have three values, $L + 1$, $L - 1$, and L , in view of the quantum rules for combination of angular momenta. If the products were initially in the triplet state, diffusion will have the opposite effect, i.e. partial conversion from a triplet to a singlet character.

The singlet and triplet states have, in general, different energies, as indicated at $B = 0$ on Figure 4.5. Any magnetic field, including that of nearby magnetic nuclei, will cause triplet states $T + 1$ and $T - 1$, which have electron spin in the direction of the field, to gain or lose energy. Therefore, the energy levels of these states will separate with increasing B , as indicated on Figure 4.5. Interconversion between the singlet and triplet states can occur either by external energy input or between T_0 and S through a distance-dependent 'electron exchange interaction' at any level of B . At some critical level of $B = B_c$, interconversion between $T - 1$ and S is also possible without external energy input. It has been shown experimentally that this level is approximately 1 mT in a pyrene–dimethylaniline system (Hamilton *et al.*, 1988).

Since interconversion between singlet and triplet states in the direction of greater singlet product will make chemical combination possible, application of the correct value of B_c will obviously affect the rate of chemical reaction. It is also possible that an ambient flux

density (from external and internal sources) may have a value B_1 , which is either slightly larger or smaller than the required B_c . In that case, addition of an alternating field $B_A \cos \omega t$ will periodically establish optimum conditions for conversion (the period $2\pi/\omega$ of ELF fields is much longer than the nanoseconds required for the $T-1 \rightarrow S$ transition). It appears therefore to be at least possible that small AC magnetic fields in the presence of the geomagnetic field could affect chemical reactions in biological systems that involve free radicals as intermediate products. Many authors, e.g. Walleczek (Walleczek, 1995), have pointed out that the spin of valence electrons in free radicals is not coupled strongly to the thermal environment and is therefore not subject to a $k_B\tau$ thermal noise limit.

With regard to the basic free-radical effect of magnetic fields, the frequency of an ELF field would not be recognized, since the diffusion time of the free radical is much shorter than the period of an applied ELF field. The latter would therefore be indistinguishable from a static field. It has been shown (Eichwald & Walleczek, 1997), however, that sensitivity to ELF fields results if the radical pair process is integrated into a scheme involving dynamicsignaling.

Time-dependent perturbation theory with iterative solution of Schroedinger's equation has been applied to the problem of singlet-to-triplet yields in radical-pair reactions subjected to oscillating magnetic fields (Canfield *et al.*, 1994). Considering frequencies of the alternating magnetic field between 0.5 and 3.0 MHz, which include the precession frequency of an electron (1.4 MHz) in the Earth's magnetic field (50 μ T), they showed effects on triplet yield at a surprisingly low amplitude of 0.7 μ T when the static field was 50 μ T. They emphasized that the radical-pair mechanism is inherently non-linear and that the effects on the singlet-to-triplet yields did not always increase as the oscillating field strength was increased. Thus, if this mechanism does indeed account for some of the biological effects of magnetic fields, simple dose-response should not be expected. They also pointed out that the singlet-to-triplet yield versus frequency spectrum could be altered dramatically by simply changing the orientation of the oscillating field and that the effects of two simultaneously applied oscillating fields are not simply additive but interact in a nonlinear fashion. They concluded that such nonlinear interactions (due to second-order and higher perturbation expansion terms) of experimentally applied fields, which become more apparent at higher oscillating field strengths, with uncontrolled environmental fields may account for some of the conflicts in the literature on the biological effects of magnetic fields.

In another theoretical treatment of radical-pair re-formation by very weak magnetic fields, thus far reported only in an abstract (Adair, 1997), the author reported that, using exact calculations on an appropriately general model system, small but significant modifications of the recombination rate by a 50 μ T field could be expected only under a narrow range of circumstances. The radical-pair containment time must be exceptionally long, 50 ns or longer; the hyperfine field of neither radical must be appreciably greater than that which generates a precession period greater than the cage containment time; and the characteristic recombination time of the radical pair in the singlet state must be about

equal to the containment time. Fields as small as 5 μT produced no significant change in the recombination rate. He concluded that environmental magnetic fields much weaker than the Earth's field have no significant biological effect by modifying the recombination probabilities of radical pairs. The figure included in the abstract, however, shows an approximately two-to-one change of the difference in the escape probability of the radical when a 5 μT field was added to a 50 μT (\approx geomagnetic) field, see Figure 4.6. For a 'cage' confinement of the radical lasting 100 ns, this is a change from 0.01 to 0.02. One might question whether such a small change in escape probability could ultimately have a large effect under some circumstances. One possibility might be the existence of magnetic field-dependent radical-pair chain reactions. Analysis of such reactions (Grissom, 1995) indicated that even a small field-induced change in the concentration of radical propagators would have a large effect on the reaction rate of the process, because each radical can cause multiple chain events. A numerical simulation (Eichwald & Walleczek, 1996b) showed that an amplification factor can be derived in some enzyme reactions from the specific relationships between rate constants. As a consequence, although the magnetic field-induced change in radical-pair recombination probability is very small, the effect on the enzyme reaction rate is much larger, for example by a factor of 1–100.

The effects of magnetic fields on radical-pair chemical reactions are firmly established, both theoretically and experimentally. Some experiments have shown that effects can occur at applied static field levels as low as 100 μT (Batova *et al.*, 1993; Nossol *et al.*, 1993). The effects of low-intensity ELF fields on free-radical reactions in biological systems have been studied experimentally in very few systems (Harkins & Grissom, 1994). Since studies in this area may explain many presently poorly understood experimental results (Sciano *et al.*, 1994), it deserves substantial effort in the future.

4.8.3.6 Non-linear dynamics and application of stochastic resonance

It has been recognized for about 30 years that non-linear, non-equilibrium phenomena play a very important role in biological systems (Adey, 1975; Adey, 1981; Adey, 1983; Frohlich, 1968). Such systems are characterized by sensitivity to initial conditions, such that slight changes in one or more parameters can significantly alter the state of the system after some time. Some non-linear, non-equilibrium processes were considered in preceding sections (e.g. magnetochemistry).

The effects of electric fields on chemical oscillations have been established experimentally (Barnes, 1996; Eichwald & Kaiser, 1993; Eichwald & Kaiser, 1995; Eichwald & Walleczek, 1996a; Eichwald & Walleczek, 1996b; Kaiser, 1994; Sevcikova *et al.*, 1992; Wachtel, 1979). Such studies have shown that biological and functional status is of fundamental importance for an effective interaction. For example, in studies of the regulation of calcium uptake by cells of the immune system, particularly T lymphocytes, either stimulatory, inhibitory, or no effects are observed for identical field parameters, depending on the degree of cellular activation. Eichwald and Walleczek (Eichwald & Walleczek, 1996a) presented a theoretical approach to account qualitatively for effects of

exposure to EMF that depend on the degree of cellular activation and that show a biphasic response (stimulation and inhibition). In this model, biochemical stimulation of the cell resulted in activation of specific signaling pathways that regulate calcium dynamics in the cell (release from intracellular stores and capacitative entry). They assumed that a specific EMF-sensitive enzyme system which is controlled by these pathways becomes activated. The activated enzyme, in turn, would exert feedback control on the signal processes, thus leading to modulation of calcium entry which may affect other cellular processes that are calcium-dependent such as DNA synthesis.

One phenomenon, that is characteristic of some non-linear systems is the possible occurrence of stochastic resonance (McNamara & Wiesenfeld, 1989; Moss & Wiesenfeld, 1995), in which the output signal-to-noise ratio improves, at first with increasing input noise before it decreases as the noise increases further. The importance of this phenomenon for the detection of weak biological signals has been suggested by several authors (Grundler *et al.*, 1992; Kaiser, 1994) and is confirmed by some experimental results (Collins *et al.*, 1996; Douglass *et al.*, 1993; Gluckman *et al.*, 1996). Most applications of this theory have been based on threshold triggered systems in which a weak, below-threshold signal is raised above the threshold by the presence of noise (Moss & Wiesenfeld, 1995; Wiesenfeld *et al.*, 1994). A mathematical model developed by Bezrukov and Vodyanoy (Bezrukov, 1996; Bezrukov & Vodyanoy, 1997b) shows that stochastic resonance can also occur in ‘threshold-free systems’, i.e. systems that can respond to signals of arbitrarily small amplitude. They considered time-dependent Poisson processes, such as the opening and closing of voltage-dependent ion channels, where the system output can be described as a random train of identical pulses with the probability of pulse generation exponentially dependent on the input signal. In particular, they assume that the pulse generation rate is given by

$$r[V(t)] = r(0) \exp[V(t)] \quad \text{Eq. 4.31}$$

where $r(0)$ is the equilibrium rate of pulse generation and $V(t)$ is a dimensionless voltage. After publication of the paper by Bezrukov and Vodyanoy (Bezrukov & Vodyanoy, 1997b), Astumian *et al.* (Astumian *et al.*, 1997) described computations made with the model that showed that the mechanism could not explain the reported finding that fields of < 0.1 V/m caused effects on cells. In their response, Bezrukov and Vodyanoy (Bezrukov & Vodyanoy, 1997a) stated that selection of more realistic cell parameters and particularly long biological integration times would give effects at lower strengths.

Galvanovskis and Sandblom (Galvanovskis & Sandblom, 1997) considered the effect of a weak sinusoidal signal on opening and closing rates of ion channels and consequent modulation of ion currents. They applied the original theory of McNamara and Wiesenfeld (McNamara & Wiesenfeld, 1989) but extended it from a single device to N ion channels subjected simultaneously to the same sinusoidal signal. A very interesting result was obtained when the underlying transition rate was assumed to be asymmetrical with the channel open time, at 10 times the closed time (but still in the order of microseconds). In that case the ‘output’ (i.e. the periodic component of the ion current across the

membrane) contained not only the applied frequency but also several harmonics (Figure 4 in their paper). For $N = 1000$, a signal frequency of 50 Hz, and a ‘cylindrical’ human of only 10 cm in radius, the authors concluded that, under optimum conditions, even very weak low-frequency electromagnetic signals (< 100 Hz and $100 \mu\text{T}$) could be detected in a cellular system with a large number of ion channels. They also noted that the capacity of a cell to detect periodic changes in ionic influx is essential for the effect of an external sinusoidal signal to be biologically important. The cytosolic Ca^{++} oscillator, a complex system of biochemical reactions that allows a cell to create sophisticated spatiotemporal patterns of Ca^{++} intracellular concentrations, may function as a detector of the small component of Ca influx.

4.8.4 Summary

Examination of the forces and energies involved in biochemical processes indicates that they are far stronger than those corresponding to power-frequency electric fields inside cultured tissues or cells ($\leq 10^{-3}$ V/m) or, equivalently, induced in humans by 60 Hz magnetic fields ($< 3 \times 10^{-5}$ T). Biological tissues and cells are, however, extremely inhomogeneous, and when the average electric field is $\leq 10^{-3}$ V/m the actual field at selected locations (e.g. cell membranes) may be orders of magnitude larger. Since the magnetic permeability of tissue is usually very close to that of free space, no enhancement of the internal over the external magnetic field is to be expected, except for biogenic magnetite.

Living systems contain many structures that can sum inputs over both time and space. Thus, several thousand receptors of a particular type on a single cell may send the same message to the cell interior, where they may be added; likewise, repetitions of the same message sent over a finite period may be cumulative. In contrast, the ‘noise’ or random fluctuations may differ at different receptors and partially cancel. The averaging of noise over time or number of receptors can substantially improve a system’s ability to detect small signals.

Most life processes, although in steady state, are far from thermal equilibrium and depend on continuous energy input. Therefore, analyses based on equilibrium thermodynamics can lead to erroneous results. Furthermore, while the ‘quantity of molecular change’ is certainly important, the rate at which change is accomplished is equally important: life as we know it would be impossible without the acceleration of biochemical reactions accomplished by the presence of enzymes. Furthermore, biological signal processing may not depend only—and possibly in some cases not at all—on the amplitude of a signal but also on the rate at which it is repeated (e.g. the frequency and duration of Ca^{++} oscillations).

Many biochemical and biomechanical processes (e.g. Ca^{++} oscillations and the motion of magnetizable particles attached to tissue) can be accurately described only by nonlinear

differential equations. The solutions of such equations are subject to very small changes in boundary conditions and also give rise to the phenomenon of ‘stochastic resonance’, i.e. enhancement of the output signal-to-noise ratio by the presence (up to a certain level) of noise rather than its absence. The application of non-linear dynamics to biology is still in its infancy.

The stochastic nature and ultimate discreteness (‘graininess’) of electrochemical life processes is likely to enhance rather than obviate the sensing of weak electric and magnetic fields. It has been suggested that time-varying pericellular electric fields of 10^{-4} to 10^{-3} V/m can affect biological signals and that the electrical inhomogeneity of living tissue can raise field intensities to this level at some points, although the field averages, calculated over a large volume, may be much lower. At 60 Hz, a 3 μ T magnetic field can generate a 10^{-4} V/m electric field in the human body. While ion channels cannot be excluded as locations for initial detection of fields at this level, receptors and enzymes are possibly more likely sites.

The necessary non-linearity in the mathematical description of biochemical processes at the molecular level leads to time and amplitude ‘windows’ and guarantees that ‘more’ (i.e. a larger signal) is not necessarily ‘better’, or (depending on the point of view) ‘worse’. Direct effects of time-varying magnetic fields, e.g. effects that do not occur primarily as a consequence of magnetically induced electric fields, are very likely at amplitudes above 100 μ T, and there is experimental evidence to support these predictions, but their existence at lower intensities cannot be excluded. The spatial and temporal coherence of externally applied EMF and their application for extended times must play an important role in the biological detection of low-intensity fields. The entire area of biological signal transmission by frequency and/or pulse code modulation needs much further research.

All of the theories of the biological effects of small-amplitude EMF—both those that deny the possibility and those that address experimental observations—are speculative and unproved. They suffer from a lack of detailed, quantitative knowledge about the processes to be modeled, such as the ‘second messenger’ signal cascade, the *modus operandi* of many receptors, the precise origin of Ca^{++} oscillations and their biological function, the timing of the making and breaking of chemical bonds, chemical transition states, the dependence of magnetic fields on specific free-radical processes, and even the effective viscosity inside particular cells. Nevertheless, theoretical models are useful, even in the absence of critical data, because they can indicate which data are needed, suggest previously un contemplated experiments, or elicit modifications to routinely performed investigations and thus generate ‘solid’ new information.

In the area of low-intensity, low-frequency bioelectromagnetics, experiments that would contribute to the construction and verification of theoretical models might address:

- the duration of exposure to fields that is necessary to produce effects over several different exposure periods;

- different frequencies of exposure, even when the ultimate interest is in the effects of 60 Hz fields;
- different field intensities (preferably those suggested by theoretical models), not necessarily to establish ‘thresholds’ but to determine how results depend on field intensity;
- changes in observed biological effects in response to deliberate addition of different types of electric and/or magnetic ‘noise’;
- the physical basis for the sensory perception of electric and magnetic fields by animals;
- temperature variations during exposure to fields and, when an effect can be mimicked by chemical exposure, the temperature-dependence of the effects due to exposure to fields and chemicals;
- whether an effect is produced by a magnetically induced electric field, by the magnetic field alone, or by a combination of the two;
- measurement of static magnetic fields and their orientation relative to the alternating magnetic field;
- the possibility of ‘contaminating’ magnetic particles in all experiments *in vitro*; and
- the presence of high-intensity EMF transients in epidemiological studies in the workplace and their characterization with regard to amplitude, rate of rise, duration, and frequency of occurrence for use in *in-vitro* studies.

The fundamental laws of electricity and magnetism are well understood, but they clearly allow a great variety of possible interactions with extremely complex, inhomogeneous, often anisotropic, and continuously varying living organisms. In the inanimate world, EMF have very different effects in electric motors, Xerox machines, radios, and computers. Only 50 years ago, understanding of the interaction of EMF with semiconductors was in its infancy, and new devices incorporating field effects are still being invented. There is no reason to believe that only one type of field coupling exists in the vastly complex, still poorly understood living systems. Different types of interaction are likely to be important at various field intensities in different organisms. Thus, several theoretical models may be appropriate for different intensities and in different biological environments. Valid quantitative models for the action of fields at the molecular level require quantitative understanding of biological processes, such as enzyme catalysis and biological signal processing.

Figure 4.1 Equivalent circuit for an array of N membrane channels with conductive media on each side of the membrane (A discrete resistance value is associated with each channel (R_G) and with each of the access resistances (R_A and R_B) near the channel mouths. All resistors in the circuit produce voltage noise, and these sources (V_{Gi} , V_{Ai} , and V_{Bi}) are completely independent and uncorrelated. When circuit analysis techniques with the proper methods are used for summing incoherent signals, the net noise voltage across an arbitrary channel (V_1 in this figure) can be calculated. Note that the noise voltage of interest (V_1) is that occurring across the channel, and not across the series combination of the channel and access resistances. The model assumes that any voltage gating mechanism is inside the channel or at the channel mouth. From Gailey (Gailey, 1996).

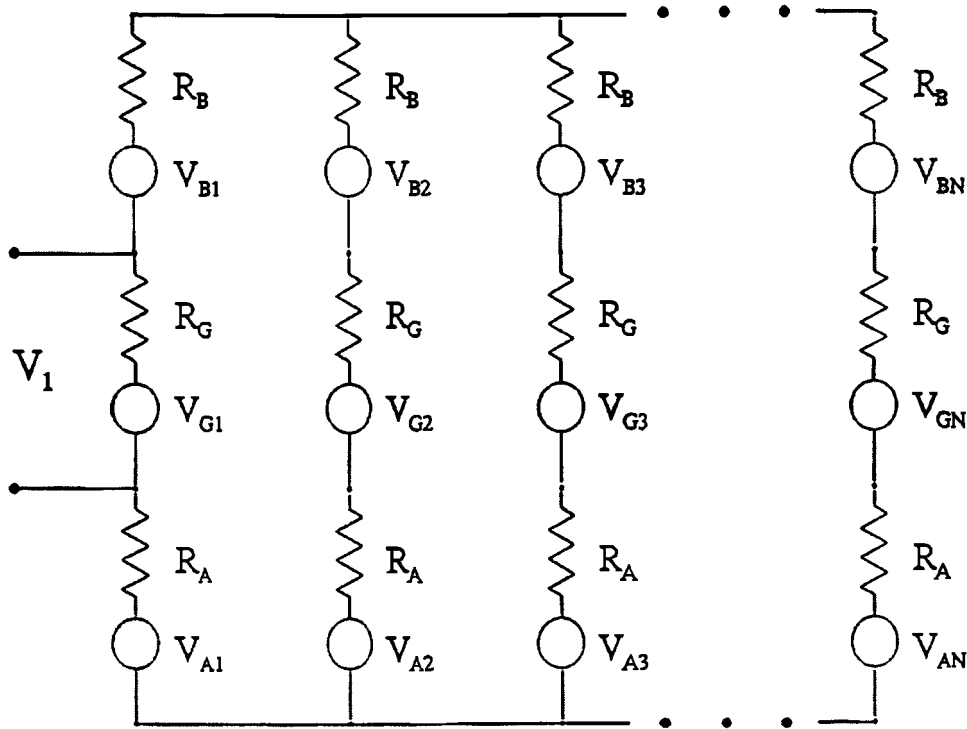


Figure 4.2 Normalized correlation coefficients for thermal electrical noise occurring across an ion channel as a function of the number of channels in the membrane (Electrical parameters used in this calculation apply to gap-junction channels with a channel resistance of $6.5 \text{ G}\Omega$ and an access resistance of $0.33 \text{ G}\Omega$). The coherence or correlation between noise signals occurring in different channels decreases by a factor of 10 per decade with increasing number of channels. From Gailey (Gailey, 1996).

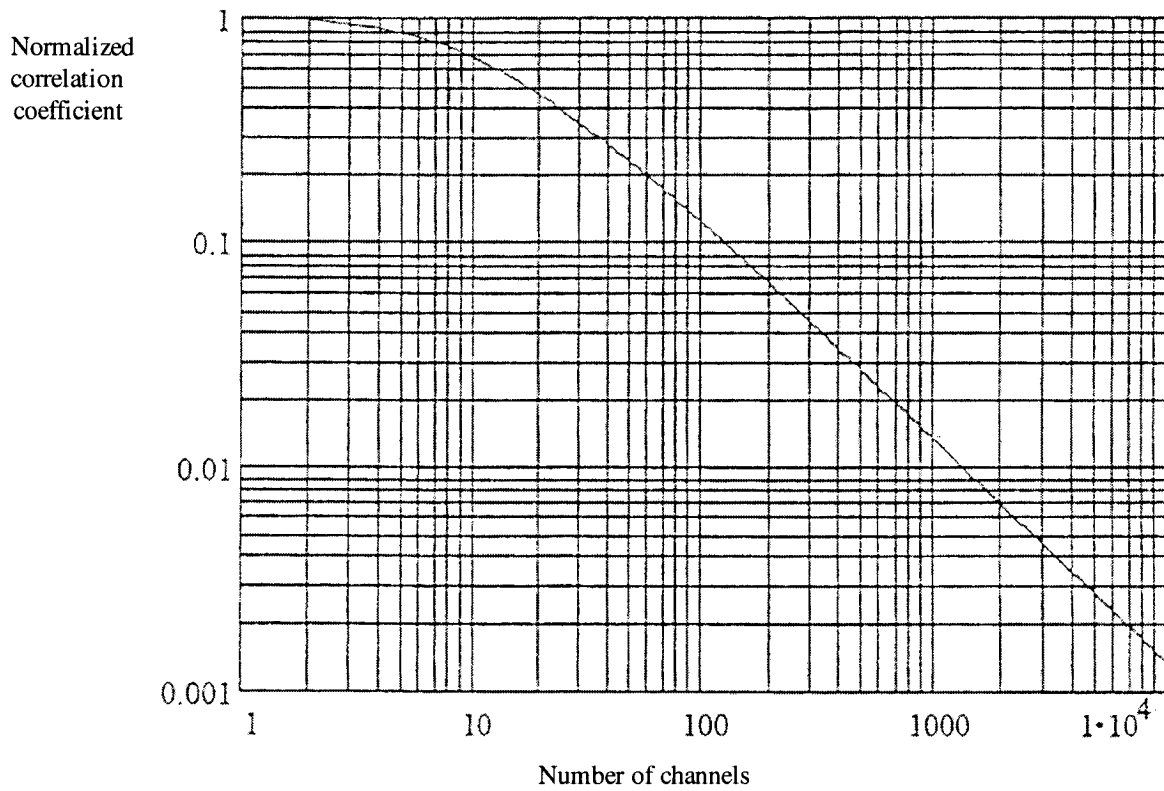


Figure 4.3. Improvement in signal-to-(thermal) voltage noise ratio due to lack of correlation between noise signals occurring in different open channels in the membrane (The x axis is the absolute value of the slope of the closing rate constant divided by the slope of the opening rate constant. The solid line was generated from equation 4.15 with equal opening and closing rate constants and assuming no effect of thermal voltage noise on the closing rate constants ($\gamma = 0$, $N_o \rightarrow \infty$)). When the slight correlation between voltage noise in the open channels and the effect of the uncorrelated noise in these channels is included, the dashed line is obtained for a membrane with 50,000 open channels. From Gailey (Gailey, 1996).

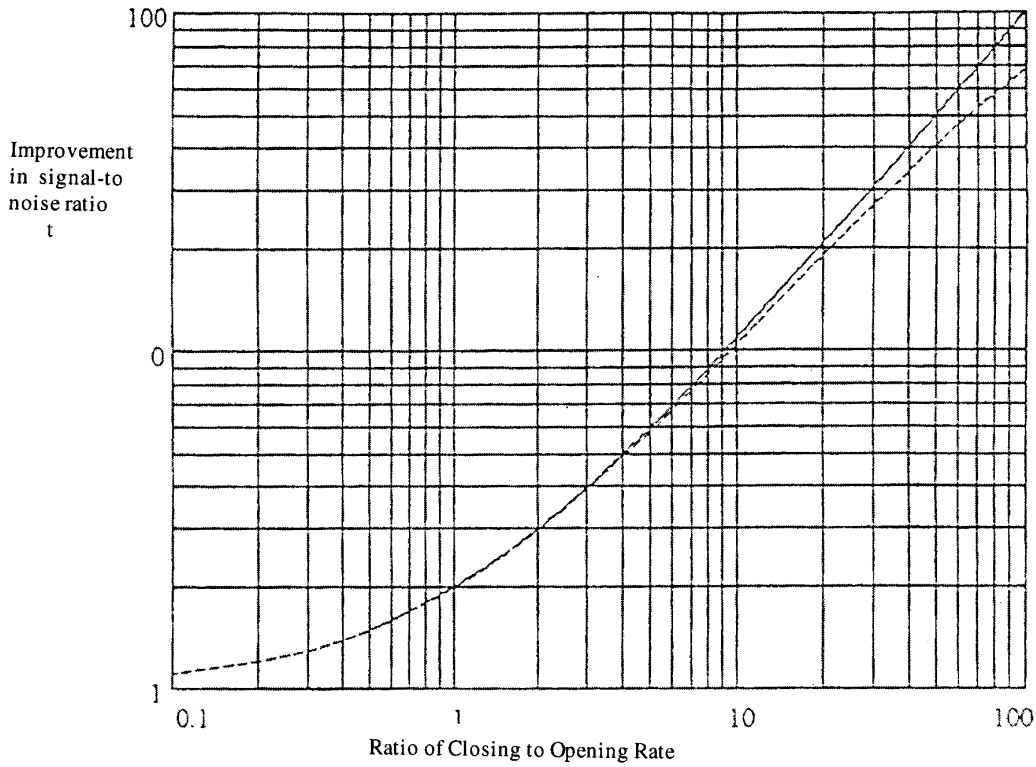


Figure 4.4. Voltage noise spectra of a frog node of Ranvier at various membrane potentials. From Verveen and DeFelice (Verveen & DeFelice, 1974); reproduced by Barnes (Barnes, 1986).

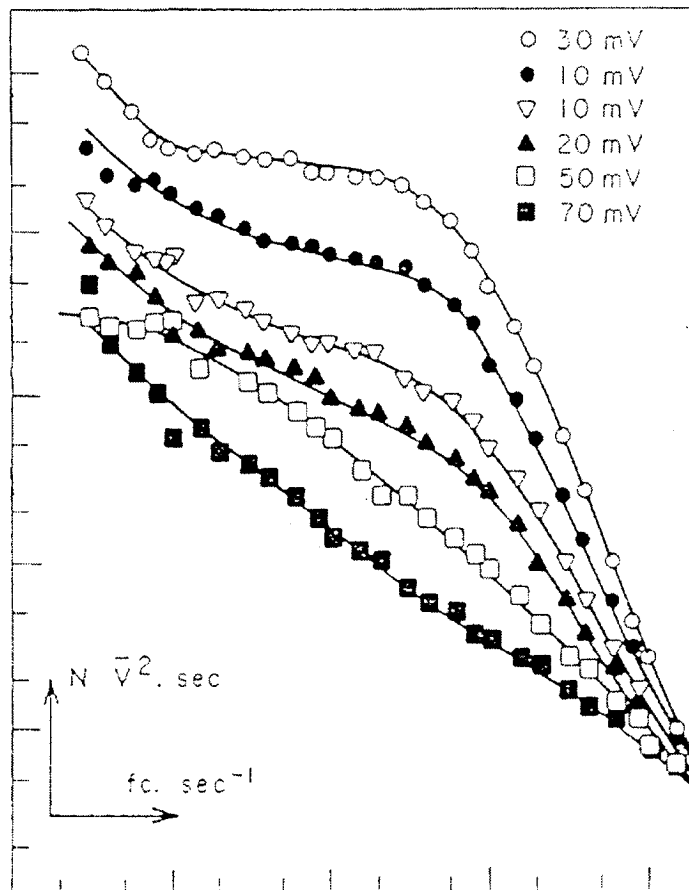


Figure 4.5. Effect of magnetic fields on radical-pair energy levels (Electron spins in the three sub-levels of the triplet state: T_{+1} spins parallel in the direction of the magnetic field, T_{-1} spins parallel in the direction opposite to the magnetic field, T_0 spins antiparallel but in phase in the field direction.). S, singlet state From Polk (Polk, 1992a).

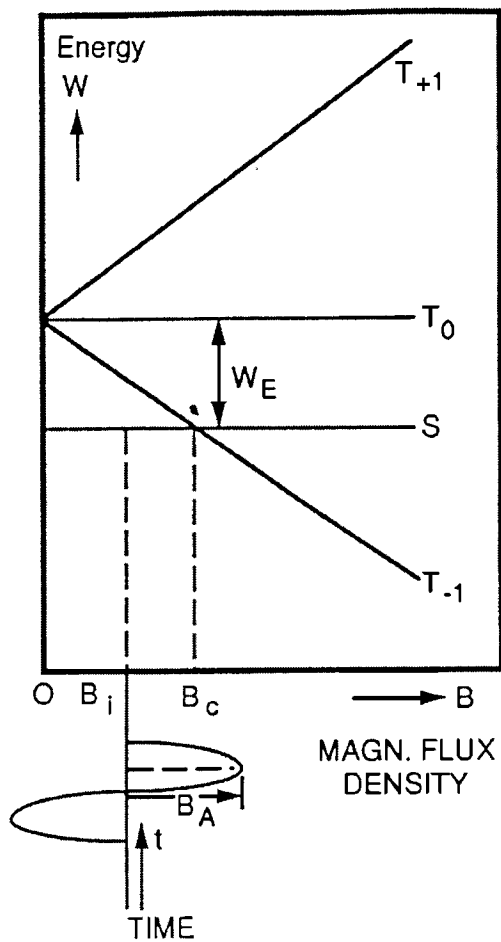


Figure 4.6. Maximum change in escape probability and maximum relative change are shown as a function of cage retention time for an increment of $5 \mu\text{T}$ to an external field of $50 \mu\text{T}$ (The recombination probability for electrons in a relative singlet state is taken as twice the escape probability and the internal field magnitudes and directions are selected from Monte Carlo procedures, as is the direction of the external field. The variation of escape probability with cage time of radicals with fields chosen so as to maximize the escape at a cage time of 10 ns, is also shown.) From Adair (Adair, 1997).

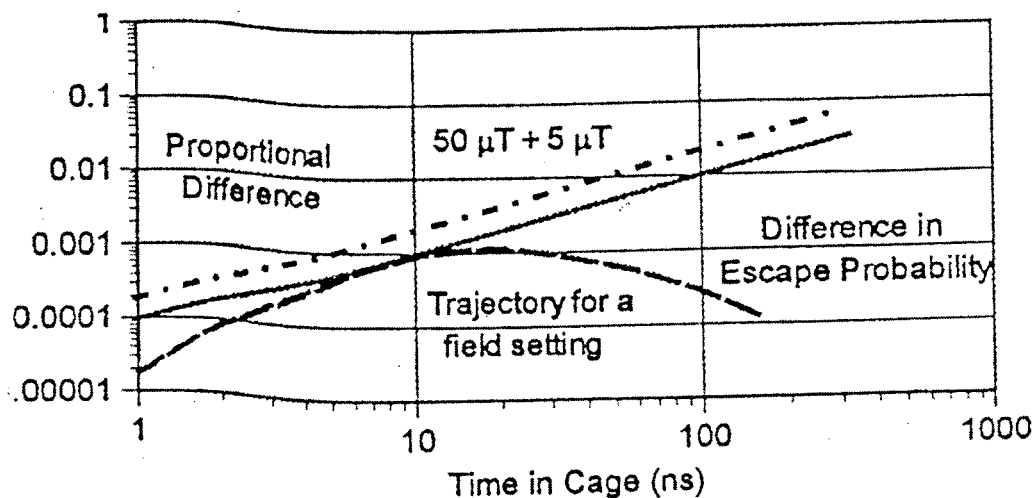


Table 4.46 Maximum numbers of turnovers of some enzymes

Enzyme	Turnover number (per second)
Carbonic anhydrase	600,000
3-Ketosteroid isomerase	280,000
Acetylcholinesterase	25,000
Penicillinase	2,000
Lactate dehydrogenase	1,000
Chymotrypsin	100
DNA polymerase I	15
Tryptophan synthetase	2
Lysozyme	0.5

From Stryer (Stryer, 1989)

Table 4.47 Cells showing Ca⁺⁺ oscillations

Cell	Stimulus	Period (s)
Rat myocyte	Caffeine	0.3-3
Rat hepatocyte	Vasopressin	18-240
Macrophage	Cell spreading	19-69
Smooth muscle	Phenylephrine or histamine	30-48
REF52 fibroblasts	Gramicidin + vasopressin	35-100
Endothelial cells	Histamine	40-125
B lymphocytes	Antigen	50-75
Mouse oocyte	Fertilization	600-1800

From Lauffenberger and Linderman (Lauffenberger & Linderman, 1993)

Table 4.48 Average endogenous fields due to heart activity induced field (Hz)

Tissue	Induced field (Hz)		
	0 - 40	40 - 70	70 - 100
Brain	0.30	0.04	0.01
Cerebrospinal fluid	0.26	0.03	0.009
Pineal gland	0.18	0.02	0.006
Pituitary gland	0.46	0.06	0.02
Eye humor	0.16	0.02	0.005
Lung	38.1	5.73	2.39
Heart	160	25.4	12.4
Liver	18.5	2.15	0.78
Stomach	33.8	3.75	2.06
Pancreas	15.1	1.64	0.61
Intestine	4.85	0.52	0.19
Kidney	4.42	0.54	0.18
Bladder	1.19	0.13	0.05
Prostate	0.91	0.10	0.04
Testis	0.35	0.04	0.01

From Hart and Gandhi (Hart & Gandhi, 1997)

Table 4.49 Experimental papers reporting resonance depending on the static magnetic fields (B_{DC})

Reference	Frequency of exposure (Hz)	B_{AC} (μT)	B_{DC} (μT)	f_R (μT)	Ion	Cells organism	Exposure duration	Effect	Notes
(Prato <i>et al.</i> , 1996)	60	299 peak	78 ± 1	60	$^{40}Ca^{2+}$	Snails	15 min	Attenuation of oploid- Included analgesia by approximately 20%	B_{AC} /and B_{DC} variable
(Yost & Liburdy, 1992)	16	42.1	23.4	16	$^{45}Ca^{2+}$	Mitogen-activated lymphocyte	60 min	Inhibits Ca Influx triggered by ConA	No effect: DC only A only
(Tofani <i>et al.</i> , 1995)	32	150 rms 75 rms	42	ND	$^{40}Ca^{2+}$	Human Lymphocytes	72 h	Micronuclei formation frequency increased 97 to 100% 6 subjects (marker of chromosomal damage) No effect	Genotoxic effect Off resonance (no DC)
	50 32	150 rms. 75, 150 rms	0	ND					
(Blackman <i>et al.</i> , 1994)	45	7.7-46.8	36.6	45	Mg, V, Mn Li, H	PC-12 Neuite Outgrowth	23 h	Reduction of % cells with neuite outgrowth No effect	Subharmonics, B_{AC}/B_{DC} dependence Off resonance (effect depends on NGF concentration)
	25	7.8-18.1	20.3	25					
	45	0.79-2.1	2.0						
(Trillo <i>et al.</i> , 1996)	45	0.29-4.11 rms	2.96	45	H^+	PC-12	23 h	Reduction of % cells with neurite outgrowth according to IPR, except near (B_{AC}/B_{DC}) =0.85 No effect	Effect at main resonan (n=1) Off resonance
	30	0.79-2.05 rms	1.97	30					
	45	0.79-2.05	1.97						
(Jenrow <i>et al.</i> , 1995)	60	10 peak	78.4	60	$^{40}Ca^{2+}$	Planaria	300 h	Delay of cephalic regeneraton by 48 h No effect	Controls: B_{DC} =18.2 μT , or B_{AC} =0
	60	10 peak	51.13	60	K^+				
(Smith <i>et al.</i> , 1987)	60	20 peak	78.4, 39.2, 26.1, 153.3 76.6, 51.1, 47.5, 9.5	60	$^{40}Ca^{2+}$ K^+ Mg^{2+}	Radish seeds	21 d	Ca tuning slowed germination, stimulates growth K tuning speeded germination, inhibits growth. Mg tuning did not affect germination, stimulates growth.	Also AC unexposed controls

Table 4.49 (continued)

Reference	Frequency of exposure (Hz)	B _{AC} (μT)	B _{DC} (μT)	f _R (μT)	Ion?	Cells organism	Exposure duration	Effect	Notes
(Bowman <i>et al.</i> , 1995)	60	>0.3	38 ± 4.5 50.6 ± 4.5	29 39.5	⁴⁰ Ca ²⁺	Children	1-11 years	Increase in childhood leukemia risk.	Resonant DC fields B=fR / n for n = 2 & 3/ are derivd from Ca-efflux studies
(Fitzsimmons <i>et al.</i> , 1994)	13.5-18	20 peak	20	16.3	⁴⁵ Ca ²⁺	TE-85 Sa OS-2	10 min. 40 min.	Increase of ⁴⁵ Ca uptake into bone cells	2 Hz, 50% band width
(Fitzsimmons <i>et al.</i> , 1995)	15.3	20 peak	20 ± 2	15.3	⁴⁰ Ca ²⁺	TE-85	10 min optimum	Increase of IGF-II release (human osteosarcoma)	DNA synt. incr. durin 24 h post exposure Maximum e = 1.6x10 ⁻⁵ V/m
(Davies, 1996)	60	14.4	78.3		Ca ²⁺	Seeds (Replication of Smith <i>et al.</i>)			
(Liboff <i>et al.</i> , 1995)	45, 25	7.7-46.8 7.8-18.1	36.6 20.3		Mg ²⁺	PC-12 (Discussion of Blackman <i>et al.</i>)			
(Blanchard <i>et al.</i> , 1995)	45, 25				Several	(Response to above)			
(Blackman <i>et al.</i> , 1996)	45	12-35 perp.	36.6 16.6		Several	PC-12			
(Blackman <i>et al.</i> , 1993a)	50	< 10	44.7			PC-12			
(Blackman <i>et al.</i> , 1995)	45	23.3- 141.6	36.6		Mg ²⁺ , Mn	PC-12			

Table 4.49 (continued)

Reference	Frequency of exposure (Hz)	B _{AC} (μT)	B _{DC} (μT)	f _R (μT)	Ion?	Cells organism	Exposure duration	Effect	Notes
(Blackman <i>et al.</i> , 1998)	45	23.8	36.6		ND	PC-12			
(Liboff <i>et al.</i> , 1987)	10-30	50-150	21		Ca ²⁺	Human lymphocytes			
(McLeod <i>et al.</i> , 1987b)	5-32	0-14.6	20.9		Ca ²⁺	Diatoms			
(Smith <i>et al.</i> , 1987)	16, 32, 48, 64	20.9	20.9		Ca ²⁺	Diatoms			
(Reese <i>et al.</i> , 1991)	16	20.9	20.9		Ca ²⁺	Diatoms			
(Prasad <i>et al.</i> , 1991)	10-30	50-150	21		No Ca ²⁺	Human lymphocytes			
(McLeod <i>et al.</i> , 1987a)	8-64	15	110.4 5, 20.9		Ca ²⁺ , K ⁺	Diatoms			
(Smith <i>et al.</i> , 1991b)	16, 80	14.14	12.7- 40.9		Ca ²⁺ , Mg ²⁺	Chick femurs			

ND, not determined

5 Final Summary and Evaluation

As mentioned in the Introduction, the final evaluation of the carcinogenicity of extremely low frequency electric and magnetic fields (ELF EMF) was made following the working procedures and evaluation method of the International Agency for Research on Cancer (IARC), as modified in Appendix A. The final evaluations for non-cancer end-points were made by a similar procedure, with consideration of other data relevant to the evaluation of carcinogenicity and its mechanisms (Section 12 (b) in Appendix A). A brief discussion of the levels of evidence as defined by the IARC is warranted.

The predominant evaluations of the various health end-points covered in this report are ‘limited’ and ‘inadequate’ evidence. ‘Limited evidence’ is not an unusual finding for epidemiological data in the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. This degree of evidence is generally provided by studies for which there is credible evidence of an association and for which a causal linkage cannot be established with a high degree of certainty. This does not mean the effect is weak, nor does it mean there is clearly an effect, although these issues enter into the evaluation. In most cases, this degree of evidence is associated with one or more of the following problems: questionable identification of the exposure factor(s) associated with the disease outcome (either a dose surrogate was used or individuals were missclassified as to their exposure category), bias may have played a small role in the finding, confounders were not ruled out to the satisfaction of the original investigator and/or the Working Group, the observed effect was small, making clear detection of an effect difficult, and/or there is little information on dose–response in the available report. The careful reader is directed to the sections on human epidemiological findings for a clear description of each study. For experimental animal bioassays, ‘limited evidence’ for an effect is generally driven by clear findings in only a single study for a single end-point or minor problems with a set of data which otherwise would have been positive; confounding, bias, and exposure missclassification generally should not exist in laboratory studies.

‘Inadequate evidence’ can imply one of four possibilities: (1) there are insufficient data for making a judgment of any kind (e.g. poor study design, making interpretation impossible); (2) the data suggest a positive effect but, due to limitations in design or very weak findings, cannot be interpreted as suggesting a causal linkage; (3) the data suggest a negative effect but, due to limitations in design or very few findings, cannot be interpreted as suggesting no effect; and (4) the data are contradictory and no clear pattern is discernible. For case (1), given a solid hypothesis, it may be beneficial to continue to study an inadequate finding using a better design in the same experimental system. For case (2), if the effect seen is of public health consequence, it should be studied further but with a clear hypothesis and perhaps in conjunction with other studies such as those providing mechanistic interpretation. In case (3), unless there is a clear scientific reason for further study, again involving a defined hypothesis, there is little need to continue to study the observed effect. Finally, for case (4), the effect might be further studied if the scientific issues are compelling or if health concerns are raised, but it is unlikely that

another study of similar design would be performed. Additional studies might not be needed. Again, a careful reader searching for scientific hypotheses for further study should read the more detailed descriptions of the findings presented in the three preceding chapters.

The final evaluations and a brief description of the evidence supporting these evaluations are given below.

5.1 Carcinogenicity in humans

The Working Group concluded that ELF EMF are **possibly carcinogenic to humans** (Group 2B, Appendix B). This evaluation was supported by 19 members of the Working Group; 8 members considered that the evidence fell into Group 3 ('ELF EMF are not classifiable as to their carcinogenicity to humans'), 1 member considered that the evidence fell into Group 4 ('ELF EMF are probably not carcinogenic to humans'), 1 member abstained from the vote, and 0 members were absent and did not vote. 2 members of the Working Group who were absent for the final vote left clear instructions as to what their vote would be, and these are recorded in the counts given above.

5.1.1 Evidence from epidemiological studies to support the evaluation

The majority (20 out of 26) of the Working Group members who voted concluded there is limited evidence that residential exposure to ELF magnetic fields is carcinogenic to children on the basis of the results of studies of childhood leukemia; the remaining 6 voting members concluded that there was inadequate evidence. Three lines of evidence supported the overall finding: the association between exposure to calculated magnetic fields and risk for childhood leukemia, the association between exposure to measured 24-h magnetic fields and risk for childhood leukemia, and continued concern about the association between wire codes and risk for childhood leukemia. There was inadequate evidence from spot measurements of magnetic fields in homes to support this finding.

The majority (14 out of 25) of the Working Group members who voted considered that there is limited evidence that occupational exposure to ELF magnetic fields is carcinogenic to humans on the basis of results of studies of chronic lymphocytic leukemia (CLL); the remaining 11 voting members concluded that there is inadequate evidence. The association between exposure to magnetic fields and risk for CLL was considered in three studies of its incidence (two in Sweden and one in Canada and France) and in one study of mortality from this disease (in the USA). No association was found in the US study, which was based on diagnoses derived from death certificates. In the Canada–France study, a nonsignificantly increased risk was seen overall and in two of the three cohorts. Differences in definition and in follow-up of the three cohorts, however, limit the interpretation of these results. A significant increase in risk was seen in both of the

Swedish studies (Feychting *et al.*, 1997; Floderus *et al.*, 1993). Although the study of Feychting *et al.* provides unique information on the potential importance of combined occupational and residential exposure in adults, it suffers from small numbers and weakness in exposure assessment, particularly for women. In the study of Floderus *et al.*, the risk increased with increasing exposure; it was particularly strong for the highest exposure category and increased somewhat when adjusted for exposure to potential confounders. The refusal rate in that study, however, could have introduced a bias in the results.

The majority (22 out of 25) of the Working Group members who voted concluded that there is inadequate evidence for an association between occupational exposure to ELF EMF and the risk for other cancers; 2 voting members concluded that there is limited evidence and one that there is evidence for lack of an effect. The cancers considered were acute myelogenous leukemia (4 studies), brain cancer (5 studies), male breast cancer (10 studies), and female breast cancer (4 studies). Overall, the inadequacy of the findings is due to limitations in study design, inconsistency in findings across studies, and/or a lack of association.

The majority (24 out of 25) of the Working Group members who voted concluded that there is inadequate evidence that residential exposure to ELF magnetic fields is carcinogenic to adults; the other voting member concluded there is evidence suggesting lack of effect. The cancers considered in this evaluation included leukemias (2 studies of use of appliances, 3 studies of distance from power lines, 2 studies of measured fields, and one study of calculated fields), breast cancer (4 studies), and cancers of the nervous system (3 studies). Overall, the inadequacy of the findings is due to limitations in study design, inconsistency in findings across studies, and/or a lack of association. In general, none of the associations between residential exposure to magnetic fields and the risk for cancer was by itself convincingly positive; however, the quality of the exposure assessment is a serious limitation in all of these studies.

There is inadequate evidence with respect to childhood nervous system tumors. This conclusion was supported by 25 Working Group members; there were 2 abstentions and 2 absent.

There is inadequate evidence with respect to childhood lymphoma. This conclusion was supported by 25 Working Group members; there were 2 abstentions and 2 absent.

5.1.2 Evidence from studies of carcinogenicity in experimental animals *in vivo* to support the evaluation

The majority (19 out of 27) of the Working Group members who voted concluded that there is inadequate evidence in experimental animals for the carcinogenicity of exposure to ELF EMF; the other 8 members concluded that there was evidence for a lack of effect.

The overall conclusion of the Working Group was that most of the studies suggest a lack of carcinogenicity, and the few that gave results of borderline positivity are inadequate to conclude that exposure to magnetic fields at the magnitude and configurations at which they were investigated increases the incidence of cancer in rodents. Two long-term bioassays showed no carcinogenic response, but one showed an equivocal response at one tumor site in animals of one sex of one species. Within the limits of the experimental model of multistage mammary carcinogenesis, the results of the ensemble of experiments did not provide convincing evidence for a promoting effect of EMF on chemically induced mammary cancer. In another commonly investigated model, skin carcinogenesis, exposure to magnetic fields had no effect. EMF did not induce leukemia or lymphoma in mice or rats in several studies.

5.1.3 Mechanistic and *in vitro* evidence to support the evaluation

When mechanistic data are available to support reported toxicological results, the IARC guidelines allow that support to be categorized as ‘weak’, ‘moderate’, or ‘strong’. All (27) of the Working Group members who voted concluded that a limited number of well-performed studies provide moderate evidence for mechanistically plausible effects of ELF EMF *in vitro* at intensities greater than 100 μT on end-points generally regarded as reflecting the action of toxic agents. All (26) of the Working Group members who voted concluded that the *in-vitro* evidence and information on physical mechanisms provide weak support for an effect of fields of intensities below approximately 100 μT .

A series of recent (1996–98) studies has shown that field exposure induces gene mutations. ELF fields at flux densities below 100 μT have consistently been shown to have no effect on mutation rates, but fields of 200–400 000 μT reproducibly and significantly enhance mutation rates after initiation with either X-rays or gamma-rays. Moreover, exposure to 400 000 μT has been shown to increase the number of mutations in the absence of ionizing radiation in two human cell lines. Thus, multiple, self-consistent reports demonstrate a dose-dependent effect on a process or end-point commonly considered to be associated with carcinogenesis. Importantly, the flux densities used in all of these studies ($\geq 100 \mu\text{T}$) are within the range of a single physical transduction mechanism, specifically magneto-chemical transduction. The potential for magneto-chemical effects at flux densities above 100 μT has been firmly established in both theoretical analyses and biochemical investigations.

Numerous well-performed studies have also shown strong effects on other end-points commonly associated with carcinogenesis, including significantly increased cell proliferation, disruption of signal transduction pathways, and inhibition of differentiation, all of these effects occurring at field intensities greater than 100 μT . Like the studies of gene mutations, these investigations were performed at sufficiently high intensities that magneto-chemical transduction is a plausible mechanism of field–cell transduction, although this does not preclude other mechanisms of interaction.

5.1.4 Discussion

There is little doubt that the evidence in support of the decision to classify ELF EMF into Group 2B is driven by the results of studies on childhood leukemia in residential environments and on CLL in adults in occupational settings. The fact that limited evidence was seen for CLL in adults should not be construed as providing support for the finding with regard to leukemia in children, however: childhood leukemia and adult CLL are very different diseases with different etiologies. Also, the inadequacy of the evidence for an effect on the risk for CLL in adults in the studies of residential exposure neither supports nor refutes the findings in the studies of occupational exposure. The in-vitro and mechanistic data provide, at best, marginal support for the conclusion that ELF EMF are possibly carcinogenic to humans. While ELF magnetic fields at intensities greater than 100 μ T provide moderate support for effects *in vitro*, there was little evidence of effects at intensities below this limit, which cover most of the range of exposure in the studies of residential childhood exposure and adult occupational exposure. Relatively few of the studies of occupational exposure addressed exposure to electric fields. Finally, the inadequate evidence from long-term bioassays for carcinogenicity in rodents is driven more by lingering concerns about single findings in two separate studies than by an overall concern that something has been missed in these studies or that there is a trend toward a positive effect in poorly conducted studies.

5.2 Non-cancer health effects

5.2.1 Non-cancer adverse health effects

None of the evidence for adverse health effects seen after exposure to ELF EMF achieved a degree of evidence exceeding 'inadequate' (for humans) or 'weak' (for experimental animals). The end-points evaluated in humans were adverse birth outcomes after maternal exposure, adverse reproductive effects after paternal exposure, Alzheimer disease, amyotrophic lateral sclerosis and other motor neuron diseases, suicide and depression, and cardiovascular disease.

There is inadequate evidence that maternal occupational exposure to ELF EMF causes adverse birth outcomes. This conclusion was supported by 22 Working Group members; there were 2 votes for 'lack' of evidence, 1 abstention, and 4 absent.

There is inadequate evidence that paternal occupational exposure to ELF EMF causes reproductive effects. This conclusion was supported by 20 Working Group members; there were 3 votes for 'lack' of evidence, 2 abstentions, and 4 absent.

There is inadequate evidence that occupational exposure to ELF EMF causes Alzheimer disease. This conclusion was supported by 23 Working Group members; there was 1 vote for 'lack' of evidence, 1 abstention, and 4 absent.

There is inadequate evidence that occupational exposure to ELF EMF causes amyotrophic lateral sclerosis. This conclusion was supported by 24 Working Group members; there was 1 abstention and 4 absent.

There is inadequate evidence that occupational exposure to ELF EMF causes suicide or depression. This conclusion was supported by 17 Working Group members; there were 6 votes for 'lack' of evidence, 2 abstentions, and 4 absent.

There is inadequate evidence that occupational exposure to ELF EMF causes cardiovascular disease. This conclusion was supported by 24 Working Group members; there was 1 abstention and 4 absent.

There is inadequate evidence that environmental exposure to ELF EMF has adverse effects on pregnancy outcome or is associated with depression. This conclusion was supported by 23 Working Group members; there was one vote for 'no' evidence, 1 abstention, and 4 absent.

There is no evidence in experimental animals for effects of ELF EMF on the immune system. This conclusion was supported by 13 members of the Working Group; there were six votes for 'weak' evidence, one abstention, and nine absent.

There is no evidence that exposure to power-line frequency EMF affects the hemotological parameters of rodents. This conclusion was supported by 17 members of the Working Group; there was 1 abstention and 11 absent.

There is weak evidence for the neurobehavioral, neuropharmacological, neurophysiological, and neurochemical effects of electromagnetic fields in experimental animals. This conclusion was supported by 9 members of the Working Group; there were 8 votes for 'moderate' evidence, 3 abstentions, and 9 absent.

There is no evidence for the reproductive or developmental effects of exposure to sinusoidal magnetic fields in experimental animals. This conclusion was supported by 17 Working Group members; there were 3 votes for 'weak' evidence, 8 abstentions, 1 absent.

Because of the complexity of the electromagnetic environment, the review of epidemiological and other biological studies did not allow precise determination of the specific, critical conditions of exposure to ELF EMF associated with the disease end-points studied.

5.2.2 Other biological effects

There was one biological effect which the majority (14 out of 19) of the Working Group found to have strong evidence; exposure to electric and magnetic fields affects bone repair and adaptation. The remaining 5 votes were for moderate evidence. There appears to be substantial, accumulating evidence that complex clinical exposures to PEMF have a significant effect on the primary bone healing processes. The studies of both osteotomy and spinal fusion show a robust effect. While quantification and analysis were weak in these two studies, they are prospective, randomized, double-blind trials, a rarity in the field of orthopedics. Perhaps the most convincing trial is that of the response of bone tissue during limb lengthening. While no effect on secondary bone healing was observed, there was significant inhibition of bone resorption and evidence of new bone formation. Studies in animals *in vivo* indicate only limited efficacy. Magnetic therapy appears incapable of enhancing the healing of osteotomies, ingrowth of bone into a defect, bone elongation, or graft healing and, in at least one case (ingrowth), may inhibit the normal process. The results obtained in a model of endochondral ossification after exposure of whole animals suggest, however, that magnetic field therapy can be effective. Conversely, magnetic fields in animals appear to have a strong, reproducible effect on the process of appositional (surface) bone growth and on inhibition of bone resorption.

The Working Group could not reach a conclusion about whether exposure to electric and magnetic fields affect nervous and non-bone connective tissue repair and adaptation in vertebrates. This conclusion was supported 12 Working Group members abstaining; there were 10 votes for ‘moderate’ evidence, 6 votes for ‘weak’ evidence, and 1 absent.

There is weak evidence that short term human exposure to ELF EMF causes changes in heart-rate variability. This conclusion was supported by 13 Working Group members; there was 1 vote for ‘moderate’ evidence, 2 votes for ‘no’ evidence, 8 abstentions, and 5 absent.

There is weak evidence that short term human exposure to ELF EMF causes changes in sleep disturbance. This conclusion was supported by 15 Working Group members; there were 9 abstentions and 5 absent.

There is weak evidence that short term human exposure to ELF EMF causes suppression of melatonin. The conclusion for effects on melatonin was supported by 16 Working Group members; there was 1 vote for ‘moderate’ evidence, 2 votes for ‘no’ evidence, 5 abstentions, and 5 absent.

There is no evidence that such exposure has other effects on the biological end-points studied in the laboratory. This conclusion was supported by 12 Working Group members; there were 2 votes for ‘weak’ evidence, 11 abstentions, and 5 absent. The tie vote was broken by the Chair.

There is weak evidence that exposure to electric and magnetic fields alters the levels of melatonin in rodents. This conclusion is supported by 14 members of the Working Group; there were 9 votes for moderate support; 4 abstentions; 2 absent.

There is *no* evidence that exposure to electric and magnetic fields alters the levels of melatonin in sheep or baboons. This conclusion is supported by 14 members of the Working Group; there were 13 abstentions; 2 absent.

There is no evidence in experimental animals for effects of ELF EMF on hematological system from exposure to ELF electromagnetic fields. This conclusion was supported by 17 members of the Working Group; there was 17 abstention and 11 absent.

There is strong evidence that electric fields can be perceived. This conclusion was supported by 18 members of the Working Group; 2 abstentions; 9 absent.

5.3 Overall evaluation

A majority of the Working Group concluded that classification of ELF EMF as possibly carcinogenic (Group 2B) is a conservative, public-health decision based on limited evidence of an increased risk for childhood leukemias with residential exposure and an increased occurrence of CLL associated with occupational exposure. For these particular cancers, the results of *in vivo*, *in vitro*, and mechanistic studies do not confirm or refute the findings of the epidemiological studies. The overall body of evidence has, however, laid a foundation for furthering our understanding of the biological effects, mechanisms, and exposure circumstances that may be related to the possible carcinogenicity and other adverse human health effects of exposure to ELF EMF.

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7 Abbreviations

Å	angstrom
AC	alternating current
ALL	acute lymphocytic leukemia
ALS	amyotrophic lateral sclerosis
AML	acute myelogenous leukemia
ANLL	acute nonlymphocytic leukemia
ANOVA	analysis of variance
B	flux density
bw	body weight
CI	confidence interval
CLL	chronic lymphocytic leukemia
CML	chronic myelogenous leukemia
CNS	central nervous system
DC	direct current
DG	days gestation
DMBA	7,12-dimethylbenz[<i>a</i>]anthracene
DOE	Department of Energy
EDF	Électricité de France
EEG	electroencephalogram
ELF	extremely low frequency
EMF	electric and magnetic fields
EMFRAPID	Electric and Magnetic Fields Research and Public Information Dissemination
ENU	ethyl- <i>N</i> -nitrosourea
EPRI	Electric Power Research Institute
ERP	event-related potential
FSH	follicle - stimulating hormone
G	gauss
GH	growth hormone
GLP	good laboratory practice

GM	geometric mean
GSD	geometric standard deviation
H	magnetic field strength
HCC	high current configuration
HF	high frequency
HRV	heart-rate variability
IARC	International Agency for Research on Cancer
IRR	incidence rate ratio
JEM	job–exposure matrix
LCC	low current configuration
LH	luteinizing hormone
MNU	methyl- <i>N</i> -nitrosourea
MT	melatonin
NA	not applicable
ND	not determined
NIEHS	National Institute of Environmental Health Sciences
NINCDS-ADRDA	National Institute of Neurologic and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association
NIOSH	National Institute of Occupational Safety and Health
NS	not significant
NTP	National Toxicology Program
ODC	ornithine decarboxylase
OHCC	ordinary hi current configuration
6-OHMS	6-hydroxymelatonin sulfate
OLCC	ordinary low current configuration
OR	odds ratio
PEMF	pulsed electromagnetic fields
PKC	protein kinase C
PIR	proportional incidence ratio
RCMS	standardized rate of change metric
REM	rapid eye movement
rms	root mean square
RR	relative risk

RT	relative time
SD	standard deviation
SIR	standardized incidence ratio
SMR	standardized mortality ratio
TPA	12- <i>O</i> -tetradecanoylphorbol 13-acetate
TWA	time-weighted average
UG	underground wiring
VDT	video display terminal
VHCC	very high current configuration
VLCC	very low current configuration
VLF	very low frequency

8 glossary

AC magnetic field	A magnetic field originating from AC electricity. Commonly used as an antonym for <i>DC magnetic field</i> , regardless of the source.
Average-sensing rms response	Time response of a meter that gives the average of the rectified signal, calibrated to give the <i>root-mean-square (RMS)</i> of a sinusoidal <i>power frequency</i> input. If the field has <i>harmonics</i> , an average-sensing rms meter will have some errors
Axial ratio	The ratio of the rms magnitudes of the semi-minor and semi-major axes for a single frequency. Ranges from zero for linear <i>polarization</i> to one for circular polarization.
Characteristics	Detailed physical properties of electric or magnetic fields, such as the magnitude, frequency spectrum, polarization, etc.
DC magnetic field	Magnetic fields originating from DC electricity. Commonly-used term for all <i>static magnetic fields</i> , including <i>geomagnetic fields</i> and those originating from permanent magnets.
Data processing	A summary table heading which describes the calculation of an <i>exposure metric</i> from an instrument's digital <i>output</i> , whether performed on a calculator, a personal computer, or a programmed microprocessor within the instrument.
Data-logger	An digital memory device which automatically records one or more measurements along with the measurement time.
Dose	A toxicological term for the amount of a chemical or physical agent delivered to a target organ. Since neither the target organ nor the mechanism of delivery are well understood for most biological effects of ELF fields, an EMF dose can seldom be defined, and the concept of <i>exposure metric</i> is used instead.
Dosimeter	An instrument that can be worn on a person for measuring exposures over time. Since the <i>dose</i> cannot usually be determined for ELF fields, "dosimeter" is a misnomer, and a term like <i>personal monitor</i> or "exposure meter" is preferred.

Duration	The total time over which an instrument is regularly taking samples. (See <i>Sample</i> and <i>Sampling time</i> .)
Dynamic range	The range between an instrument's overload input and its minimum acceptable input (as determined by noise, resolution, distortion, etc.).
Electric field	A vector field E measured in volts / meter.
Electromagnetic fields	The combination of electric and magnetic fields in the environment. This term is easily confused with “electromagnetic radiation”, and can therefore be misleading when used with extremely low frequencies whose radiation is barely detectable. Therefore “electric and magnetic fields” is the preferred term.
ELF (extremely low frequency)	The frequency range from 3 - 3000 Hz.
EMF	Electric and magnetic fields.
Exposure	The amount of a chemical or physical agent in the environment that a person comes in contact with over a some period of time.
Exposure assessment	The evaluation of a person's exposure by measurements, modeling, information about sources, or other means.
Exposure metric	A single number which summarizes an electric and/or magnetic field exposure. An exposure metric is usually determined by a combination of the instrument's signal processing and the data analysis performed after the measurement. Also called an “effects function” and an "exposure summary."
Filter	Electronic components of an instrument which modify its <i>frequency response</i> to an analog or digital signal. ELF magnetic field meters generally have <i>bandpass filters</i> whose response is set equal to one at the <i>power frequency</i> . These ELF bandpass filters have been classified in various ways: <i>flat, linear, broadband, narrowband, fundamental, and harmonic</i>
Free-body sensor	An electric field sensor that is supported in space without conductive contact to any object.

Frequency response	An instrument's output as a function of frequency relative to the magnitude of the input signal. Specification of an instrument's frequency response includes the type of <i>filter</i> and its <i>bandwidth</i> .
Frequency spectrum	An EMF <i>characteristic</i> as a function of frequency, which can be plotted as a bar graph. Usually means the frequency components of the <i>rms vector magnitude</i> calculated by a <i>fast Fourier transform (FFT)</i> . However, the <i>rms component</i> magnitudes, the component's <i>phases</i> , and <i>axial ratios</i> also have frequency spectra.
Fundamental (filter)	A narrowband <i>filter</i> that responds to the <i>power frequency</i> (50 or 60 Hz) but not to any <i>harmonics</i> .
Fundamental (frequency)	The lowest frequency component of the Fourier series of a periodic <i>waveform</i> .
Geomagnetic fields	Magnetic fields originating from the earth (including the atmosphere). Predominantly a <i>static magnetic field</i> , but includes some oscillating components and <i>transients</i> .
Ground reference sensor	An electric field sensor that measures the induced current or charge oscillating between an isolated electrode and a grounded conductor.
Harmonic (filter)	A broadband <i>filter</i> in the EMDEX-II meter that responds to the magnetic field's <i>harmonics</i> but not the 60 Hz <i>power frequency</i> .
Harmonic (frequency)	Frequencies that are integral multiples of the <i>power frequency</i> or some other reference frequency.
Hazard surveillance	Assessing exposures to chemical or physical agents in a large sample of workplaces for purposes of evaluating the extent of a health hazards and planning efforts for its evaluation and control.
Health hazard evaluation	A short-term study for the assessment of a potential health hazard in a workplace.
Intermittent fields	Fields whose <i>rms vector magnitude</i> changes rapidly. In contrast to <i>transients</i> , intermittent fields may have high levels for longer times and are generally in the <i>ELF</i> frequency range.

LF (low frequencies)	The frequency range from 30-300 kHz.
Magnetic field strength	A vector field H with units of ampere/meter.
Magnetic field	Both the H and B fields. In health studies, these two fields are essentially interchangeable since their vectors are parallel in air, the human body, and other non-ferromagnetic materials. In studies at <i>extremely low frequencies</i> , “magnetic field” is generally used for the <i>magnetic flux density</i> (B field). When the topic is radio frequencies and microwaves, the term usually means the <i>magnetic field strength</i> (H field).
Magnetic flux density	A vector field B with units of tesla (SI) or gauss (CGS).
Magnitude	See <i>Vector magnitude</i> .
Maximum field	The greatest rms magnitude of an electric or magnetic field measured by rotating a single-axis sensor in all directions
Method	A complete set of instructions for the measurement of EMF exposures in an environment.
Metric	See <i>Exposure metric</i> .
Monitor	An instrument for measuring exposures over time. As a verb, to measure over time.
Output	The final numbers which an instrument routinely produces from measurements, either as its read-out or a digital <i>data-logger</i> file which can be transferred to a computer.
Personal monitor	An instrument that can be worn on a person for measuring exposure over time.
Polarization	The shape traced by the tip of an EMF vector over a single cycle. For fields with a single frequency, the polarization is either linear, elliptical or circular. For fields with multiple frequencies, the polarization can be a complex shape, and is better expressed as a spectrum of the <i>axial ratio</i> at different frequencies.

Power frequency	The frequency at which AC electricity is generated. For electric utilities, the power frequency is 60 Hz in North America, Brazil, and parts of Japan. Electric power is 50 Hz in much of the rest of the world. Isolated AC electrical systems may have other power frequencies, <i>e.g.</i> 440 Hz in commercial airliners.
Principal harmonic	See <i>Power frequency</i> and <i>Fundamental</i> .
Resultant	The mathematical function used to calculate the <i>vector magnitude</i> B from the <i>vector components</i> B _x , B _y , B _z with the Pythagorean theorem: If B _x , B _y , and B _z are the rms components of a field, the resultant equals the rms vector magnitude. (See <i>Root-mean-square</i> .) In ELF measurements, "resultant" is commonly used to mean "rms vector magnitude" of the magnetic or electric field. However, the resultant function can also be used to obtain the instantaneous vector magnitude B(t) and the magnitude B _o of the <i>static (DC) field</i> .
Root-mean-square (rms)	The most versatile mathematical function for averaging the magnitude of time-varying electric and magnetic fields.. Meters that measure the rms of a signal can have <i>true rms</i> or <i>average-sensing rms</i> circuitry.
Sample	A continuous measurement covering a fraction of the <i>duration</i> over which the exposure is monitored.
Samplingrate	The frequency with which samples are taken, expressed as the time between the beginning of each sample.
Sampling strategy	A strategy for determining the sites, subjects, timing, duration, and methods for measuring exposures.
Sample time	The length of a sample, <i>i.e.</i> the time over which an instrument is continuously taking measurements, (as opposed to the <i>duration</i> which is the total time the monitor is taking samples)
Semi-majoraxis	The longest axis of the trace of an elliptically polarized field.
Semi-minoraxis	The shortest axis of the trace of an elliptically polarized field.
Spot measurement	An instantaneous measurements at a designated location.

Static field	A field vector that does not vary with time. In most environments, electric and magnetic fields change with time, but their <i>frequency spectra</i> has a component at 0 Hz.. This “quasi-static” component of the field is measured by an instrument with a low-pass <i>filter</i> set at a small frequency (<i>e.g.</i> 3 Hz) or by averaging the oscillating signal over the <i>sample time</i> .
Sub-harmonics	Frequencies in the spectrum that are lower than the <i>power frequency</i> .
Three-axis (3D) sensor	A sensor with three axial probes aligned orthogonally in order to measure the field's three spatial <i>components</i> simultaneously.
Time response	The methods by which an instrument responds to the signal's variations over time, such as <i>A/D conversion</i> , the capture of digitized <i>waveforms</i> , and a true <i>rms</i> response.
Time-weighted average (TWA)	A weighted average of exposure measurements taken over a period of time with the weighting factor equal to the time interval between measurements. When the measurements are taken with a <i>monitor</i> with a fixed <i>sampling rate</i> , the TWA equals the arithmetic mean of the measurements.
Trace	The three-dimensional pattern made by the tip of an electric or magnetic field vector over one or more periods of oscillation.
Transients	Brief bursts of high frequency fields, usually resulting from mechanical switching of AC electricity. (Not to be confused with <i>Intermittent fields</i> .)
True rms response	The time response of a meter that gives the <i>root-mean-square (RMS)</i> of the input signal accurately.
ULF (ultra low frequency)	The frequency range below 3 Hz.
Vector components	The length of a vector when it is projected onto three orthogonal axes.
Vectormagnitude	The length of an EMF vector.
VLF (very low frequency)	The frequency range from 3 - 30 kHz.

Walkthrough survey	An exposure assessment conducted by walking through a workplace or other environment while carrying a <i>monitor</i> . Exposures in the workplace are summarized from different <i>exposure metrics</i> calculated from the measurements made during the walkthrough.
Waveform	A single <i>component</i> of the field measured as a function of time by an instrument with a <i>response time</i> much faster than the field's frequency of oscillation. The term also means the shape of the wave as displayed on a graph or oscilloscope trace.
Waveform capture	Measuring <i>waveforms</i> with an oscilloscope or other instrument which can display the waveform and/or digitize the data for further calculations.

Table 8.1 Units

Quantity	Symbol	Units	
		International System (SI)	CGS
Electric field	E	Volts / meter (V/m)	Volts / cm
Magnetic flux density	B	Tesla (T) 1 mT = 10 G	Gauss (G)
Magnetic field strength	H	Ampere / meter (A/m)	Gauss or Oersted
Magnetic field conversion in vacuum and non-ferromagnetic media.		$B = \omega_0 H$ where $\omega_0 = 4\pi \times 10^{-7} \text{ T}\cdot\text{m} / \text{A}$	$B = H$

Appendix A

IARC MONOGRAPHS PROGRAMME ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMAN

PREAMBLE

1. BACKGROUND

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme to evaluate the carcinogenic risk of chemicals to humans and to produce monographs on individual chemicals. The *Monographs* programme has since been expanded to include consideration of exposures to complex mixtures of chemicals (which occur, for example, in some occupations and as a result of human habits) and of exposures to other agents, such as radiation and viruses. With Supplement 6 (IARC, 1987a), the title of the series was modified *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans* to *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, in order to reflect the widened scope of the programme.

The criteria established in 1971 to evaluate carcinogenic risk to humans were adopted by the working groups whose deliberations resulted in the first 16 volumes of the *IARC Monographs series*. Those criteria were subsequently updated by further ad-hoc working groups (IARC, 1977, 1978, 1979, 1982, 1983, 1987b, 1988, 1991a; Vainio *et al.*, 1992).

2. OBJECTIVE AND SCOPE

The objective of the programme is to prepare, with the help of international working groups of experts, and to publish in the form of monographs, critical reviews and evaluations of evidence on the carcinogenicity of a wide range of human exposures. The *Monographs* may also indicate where additional research efforts are needed.

The *Monographs* represent the first step in carcinogenic risk assessment, which involves examination of all relevant information in order to assess the strength of the available evidence that certain exposures could alter the incidence of cancer in humans. The second step is quantitative risk estimation. Detailed, quantitative evaluations of epidemiological data may be made in the *Monographs*, but without extrapolation beyond the range of the

data available. Quantitative extrapolation from experimental data to the human situation is not undertaken.

The term ‘carcinogen’ is used in these monographs to denote an exposure that is capable of increasing the incidence of malignant neoplasms; the induction of benign neoplasms may in some circumstances contribute to the judgment that the exposure is carcinogenic. The terms ‘neoplasm’ and ‘tumour’ are used interchangeably.

Some epidemiological and experimental studies indicate that different agents may act at different stages in the carcinogenic process, and several different mechanisms may be involved. The aim of the *Monographs* has been, from their inception, to evaluate evidence of carcinogenicity at any stage in the carcinogenesis process, independently of the underlying mechanisms. Information on mechanisms may, however, be used in making the overall evaluation (IARC, 1991a; Vainio *et al.*, 1992).

The *Monographs* may assist national and international authorities in making risk assessments and in formulating decisions concerning any necessary preventive measures. The evaluations of IARC working groups are scientific, qualitative judgments about the evidence for or against carcinogenicity provided by the available data. These evaluations represent only one part of the body of information on which regulatory measures may be based. Other components of regulatory decisions may vary from one situation to another and from country to country, responding to different socioeconomic and national priorities. **Therefore, no recommendation is given with regard to regulation or legislation, which are the responsibility of individual governments and/or other international organizations.**

The *IARC Monographs* are recognized as an authoritative source of information on the carcinogenicity of a wide range of human exposures. A survey of users, made in 1988 indicated that the *Monographs* are consulted by various agencies in 57 countries. About 4000 copies of each volume are printed, for distribution to governments, regulatory bodies and interested scientists. The *Monographs* are also available from the International Agency for Research on Cancer in London and via the Distribution and Sales Service of the World Health Organization.

3. SELECTION OF TOPICS FOR MONOGRAPHS

Topics are selected on the basis of two main criteria: (a) there is evidence of human exposure, and (b) there is some evidence or suspicion of carcinogenicity. The term ‘agent’ is used to include individual chemical compounds, groups of related chemical compounds physical agents (such as radiation) and biological factors (such as viruses). Exposures to mixtures of agents may occur in occupational exposures and as a result of personal and cultural habits (like smoking and dietary practices). Chemical analogues and compounds with biological or physical characteristics similar to those of suspected carcinogens may

also be considered, even in the absence of data on a possible carcinogenic effect in humans or experimental animals.

The scientific literature is surveyed for published data relevant to an assessment of carcinogenicity. The IARC surveys of chemicals being tested for carcinogenicity (IARC, 1973-1992) and directories of ongoing research in cancer epidemiology (IARC, 1976-1994) often indicate those exposures that may be scheduled for future meetings. Ad-hoc working groups convened by IARC in 1984, 1989, 1991 and 1993 gave recommendations as to which agents should be evaluated in the IARC Monographs series (IARC, 1984, 1989, 1991b, 1993).

As significant new data on subjects on which monographs have already been prepared become available, re-evaluations are made at subsequent meetings, and revised monographs are published.

4. DATAFORMONOGRAPHS

The *Monographs* do not necessarily cite all the literature concerning the subject of an evaluation. Only those data considered by the Working Group to be relevant to making the evaluation are included.

With regard to biological and epidemiological data, only reports that have been published or accepted for publication in the openly available scientific literature are reviewed by the working groups¹. In certain instances, government agency reports that have undergone peer review and are widely available are considered. Exceptions may be made on an ad-hoc basis to include unpublished reports that are in their final form and publicly available, if their inclusion is considered pertinent to making a final evaluation (see pp. A.17 *et seq.*). In the sections on chemical and physical properties, on analysis, on production and use and on occurrence, unpublished sources of information may be used.

5. THEWORKINGGROUP

Reviews and evaluations are formulated by a working group of experts. The tasks of the group are: (i) to ascertain that all appropriate data have been collected; (ii) to select the data relevant for the evaluation on the basis of scientific merit; (iii) to prepare accurate summaries of the data to enable the reader to follow the reasoning of the Working Group; (iv) to evaluate the results of epidemiological and experimental studies on cancer; (v) to

¹ The EMF-RAPID Working Group elected to include non-published literature under the conditions that a) it passed peer review of the Working Group members, b) the author(s) of the document agreed to allow inclusion and release of the document following completion of the monograph and c) the manuscript made a substantive contribution to the overall document.

evaluate data relevant to the understanding of mechanism of action; and (vi) to make an overall evaluation of the carcinogenicity of the exposure to humans.

Working Group participantsⁱⁱ who contributed to the considerations and evaluations within a particular volume are listed, with their addresses, at the beginning of each publication. Each participant who is a member of a working group serves as an individual scientist and not as a representative of any organization, government or industry. In addition, nominees of national and international agencies and industrial associations may be invited as observers.

6. WORKING PROCEDURESⁱⁱⁱ

Approximately one year in advance of a meeting of a working group, the topics of the monographs are announced and participants are selected by IARC staff in consultation with other experts. Subsequently, relevant biological and epidemiological data are collected by IARC from recognized sources of information on carcinogenesis, including data storage and retrieval systems such as BIOSIS, Chemical Abstracts, CANCERLIT, MEDLINE and TOXLINE—including EMIC and ETIC for data on genetic and related effects and reproductive and developmental effects, respectively.

For chemicals and some complex mixtures, the major collection of data and the preparation of first drafts of the sections on chemical and physical properties, on analysis, on production and use and on occurrence are carried out under a separate contract funded by the US National Cancer Institute^{iv}. Representatives from industrial associations may assist in the preparation of sections on production and use. Information on production and trade is obtained from governmental and trade publications and, in some cases, by direct contact with industries. Separate production data on some agents may not be available because their publication could disclose confidential information. Information on uses may be obtained from published sources but is often complemented by direct contact with manufacturers. Efforts are made to supplement this information with data from other national and international sources.

Six months before the meeting, the material obtained is sent to meeting participants, or is used by IARC staff to prepare sections for the first drafts of monographs. The first

ⁱⁱ Virtually all members of the NIEHS Working Group were chosen through a process of nomination and review involving NIEHS senior staff and two external advisory committees (the National EMF Advisory Committee and the EMF-*RAPID* Interagency Committee). Last minute substitutes replacing cancellations (3 scientists) were appointed by the NIEHS without external review. Every attempt was made to include these advisory groups in decisions concerning the format, structure and voting procedures of the Working Group.

ⁱⁱⁱ The selection of areas for review and associated literature were done by NIEHS staff, two permanent advisory groups and three ad-hoc advisory groups formed for three symposia held prior to the Working Group meeting (see Introduction).

^{iv} separate contracts with scientists knowledgeable about ELF-EMF health effects were funded by the NIEHS to provide first drafts. These individuals are listed at the beginning of this publication.

drafts are compiled by IARC staff and sent, prior to the meeting, to all participants of the Working Group for review^v.

The Working Group meets in Lyon for seven to eight days^{vi} to discuss and finalize the texts of the monographs and to formulate the evaluations. After the meeting, the master copy of each monograph is verified by consulting the original literature, edited and prepared for publication. The aim is to publish monographs within six months of the Working Group meeting.

The available studies are summarized by the Working Group, with particular regard to the qualitative aspects discussed below. In general, numerical findings are indicated as they appear in the original report; units are converted when necessary for easier comparison^{vii}. The Working Group may conduct additional analyses of the published data and use them in their assessment of the evidence; the results of such supplementary analyses are given in square brackets. When an important aspect of a study, directly impinging on its interpretation, should be brought to the attention of the reader, a comment is given in square brackets.

7. EXPOSURE DATA

Sections that indicate the extent of past and present human exposure, the sources of exposure, the people most likely to be exposed and the factors that contribute to the exposure are included at the beginning of each monograph.

Most monographs on individual chemicals, groups of chemicals or complex mixtures include sections on chemical and physical data, on analysis, on production and use and on occurrence. In monographs on, for example, physical agents, occupational exposures and cultural habits, other sections may be included, such as: historical perspectives, description of an industry or habit, chemistry of the complex mixture or taxonomy. Monographs on biological agents have sections on structure and biology, methods of detection, epidemiology of infection and clinical disease other than cancer.

For chemical exposures, the Chemical Abstracts Services Registry Number, the latest Chemical Abstracts Primary Name and the IUPAC Systematic Name are recorded- other synonyms are given, but the list is not necessarily comprehensive. For biological agents, taxonomy and structure are described, and the degree of variability is given, when applicable.

^v Most drafts were circulated two months prior to the Working Group meeting.

^{vi} The NIEHS Working Group met in Brooklyn Park, Minnesota for nine days.

^{vii} In general, SI units were used in this publication and conversions are discussed in Chapter 2.

Information on chemical and physical properties and, in particular, data relevant to identification, occurrence and biological activity are included. For biological agents, mode of replication, life cycle, target cells, persistence and latency and host response are given. A description of technical products of chemicals includes trade names, relevant specifications and available information on composition and impurities. Some of the trade names given may be those of mixtures in which the agent being evaluated is only one of the ingredients.

The purpose of the section on analysis or detection is to give the reader an overview of current methods, with emphasis on those widely used for regulatory purposes. Methods for monitoring human exposure are also given, when available. No critical evaluation or recommendation of any of the methods is meant or implied. The IARC publishes a series of volumes, *Environmental Carcinogens: Methods of Analysis and Exposure Measurement* (IARC, 1978-93), that describe validated methods for analyzing a wide variety of chemicals and mixtures. For biological agents, methods of detection and exposure assessment are described, including their sensitivity, specificity and reproducibility.

The dates of first synthesis and of first commercial production of a chemical or mixture are provided: for agents which do not occur naturally, this information may allow a reasonable estimate to be made of the date before which no human exposure to the agent could have occurred. The dates of first reported occurrence of an exposure are also provided. In addition, methods of synthesis used in past and present commercial production and different methods of production which may give rise to different impurities are described.

Data on production, international trade and uses are obtained for representative regions, which usually include Europe, Japan and the United States of America. It should not, however, be inferred that those areas or nations are necessarily the sole or major sources or users of the agent. Some identified uses may not be current or major applications, and the coverage is not necessarily comprehensive. In the case of drugs, mention of their therapeutic uses does not necessarily represent current practice nor does it imply judgment as to their therapeutic efficacy.

Information on the occurrence of an agent or mixture in the environment is obtained from data derived from the monitoring and surveillance of levels in occupational environments, air, water, soil, foods and animal and human tissues. When available, data on the generation, persistence and bioaccumulation of the agent are also included. In the case of mixtures, industries, occupations or processes, information is given about all agents present. For processes, industries and occupations, a historical description is also given, noting variations in chemical composition, physical properties and levels of occupational exposure with time and place. For biological agents, the epidemiology of infection is described.

Statements concerning regulations and guidelines (e.g., pesticide registrations, maximal levels permitted in foods, occupational exposure limits) are included for some countries as indications of potential exposures, but they may not reflect the most recent situation, since such limits are continuously reviewed and modified. The absence of information on regulatory status for a country should not be taken to imply that country does not have regulations with regard to the exposure. For biological agents, legislation and control, including vaccines and therapy, are described.

8. STUDIES OF CANCER IN HUMANS

(a) Types of studies considered

Three types of epidemiological studies of cancer contribute to the assessment of carcinogenicity in humans—cohort studies, case-control studies and correlation (or ecological) studies. Rarely, results from randomized trials may be available. Case series and case reports of cancer in humans may also be reviewed.

Cohort and case-control studies relate individual exposures under study to the occurrence of cancer in individuals and provide an estimate of relative risk (ratio of incidence or mortality in those exposed to incidence or mortality in those not exposed) as the main measure of association.

In correlation studies, the units of investigation are usually whole populations (e.g., in particular geographical areas or at particular times), and cancer frequency is related to a summary measure of the exposure of the population to the agent, mixture or exposure circumstance under study. Because individual exposure is not documented, however, a causal relationship is less easy to infer from correlation studies than from cohort and case-control studies. Case reports generally arise from a suspicion, based on clinical experience, that the concurrence of two events—that is, a particular exposure and occurrence of a cancer—has happened rather more frequently than would be expected by chance. Case reports usually lack complete ascertainment of cases in any population, definition or enumeration of the population at risk and estimation of the expected number of cases in the absence of exposure. The uncertainties surrounding interpretation of case reports and correlation studies make them inadequate, except in rare instances, to form the sole basis for inferring a causal relationship. When taken together with case-control and cohort studies, however, relevant case reports or correlation studies may add materially to the judgment that a causal relationship is present.

Epidemiological studies of benign neoplasm, presumed preneoplastic lesions and other end-points thought to be relevant to cancer are also reviewed by working groups. They may, in some instances, strengthen inferences drawn from studies of cancer itself.

(b) Quality of studies considered

The Monographs are not intended to summarize all published studies. Those that are judged to be inadequate or irrelevant to the evaluation are generally omitted. They may be mentioned briefly, particularly when the information is considered to be a useful supplement to that in other reports or when they provide the only data available. Their inclusion does not imply acceptance of the adequacy of the study design or of the analysis and interpretation of the results, and limitations are clearly outlined in square brackets at the end of the study description.

It is necessary to take into account the possible roles of bias, confounding and chance in the interpretation of epidemiological studies. By 'bias' is meant the operation of factors in study design or execution that lead erroneously to a stronger or weaker association than in fact exists between disease and an agent, mixture or exposure circumstance. By 'confounding' is meant a situation in which the relationship with disease is made to appear stronger or to appear weaker than it truly is as a result of an association between the apparent causal factor and another factor that is associated with either an increase or decrease in the incidence of the disease. In evaluating the extent to which these factors have been minimized in an individual study, working groups consider a number of aspects of design and analysis as described in the report of the study. Most of these considerations apply equally to case-control, cohort and correlation studies. Lack of clarity of any of these aspects in the reporting of a study can decrease its credibility and the weight given to it in the final evaluation of the exposure.

Firstly, the study population, disease (or diseases) and exposure should have been well defined by the authors. Cases of disease in the study population should have been identified in a way that was independent of the exposure of interest, and exposure should have been assessed in a way that was not related to disease status.

Secondly, the authors should have taken account in the study design and analysis of other variables that can influence the risk of disease and may have been related to the exposure of interest. Potential confounding by such variables should have been dealt with either in the design of the study, such as by matching, or in the analysis, by statistical adjustment. In cohort studies, comparisons with local rates of disease may be more appropriate than those with national rates. Internal comparisons of disease frequency among individuals at different levels of exposure should also have been made in the study

Thirdly, the authors should have reported the basic data on which the conclusions are founded, even if sophisticated statistical analyses were employed. At the very least, they should have given the numbers of exposed and unexposed cases and controls in a case-control study and the numbers of cases observed and expected in a cohort study. Further tabulations by time since exposure began and other temporal factors are also important. In a cohort study, data on all cancer sites and all causes of death should have been given, to

reveal the possibility of reporting bias. In a case-control study, the effects of investigated factors other than the exposure of interest should have been reported.

Finally, the statistical methods used to obtain estimates of relative risk, absolute rates of cancer, confidence intervals and significance tests, and to adjust for confounding should have been clearly stated by the authors. The methods used should preferably have been the generally accepted techniques that have been refined since the mid-1970s. These methods have been reviewed for case-control studies (Breslow & Day, 1980) and for cohort studies (Breslow & Day, 1987).

(c) Inferences about mechanism of action

Detailed analyses of both relative and absolute risks in relation to temporal variables, such as age at first exposure, time since first exposure, duration of exposure, cumulative exposure and time since exposure ceased, are reviewed and summarized when available. The analysis of temporal relationships can be useful in formulating models of carcinogenesis. In particular, such analyses may suggest whether a carcinogen acts early or late in the process of carcinogenesis, although at best they allow only indirect inferences about the mechanism of action. Special attention is given to measurements of biological markers of carcinogen exposure or action, such as DNA or protein adducts, as well as markers of early steps in the carcinogenic process, such as proto-oncogene mutation, when these are incorporated into epidemiological studies focused on cancer incidence or mortality. Such measurements may allow inferences to be made about putative mechanisms of action (IARC, 1991a; Vainio *et al.*, 1992).

(d) Criteria for causality

After the quality of individual epidemiological studies of cancer has been summarized and assessed, a judgement is made concerning the strength of the evidence that the agent, mixture or exposure circumstance in question is carcinogenic for humans. In making their judgment, the Working Group considers several criteria for causality. A strong association (a large relative risk) is more likely to indicate causality than a weak association although it is recognized that relative risks of small magnitude do not imply lack of causality and may be important if the disease is common. Associations that are replicated in several studies of the same design or using different epidemiological approaches or under different circumstances of exposure are more likely to represent a causal relationship than isolated observations from single studies. If there are inconsistent results among investigations, possible reasons are sought (such as differences in amount of exposure), and results of studies judged to be of high quality are given more weight than those from studies judged to be methodologically less sound. When suspicion of carcinogenicity arises largely from a single study, these data are not combined with those from later studies in any subsequent reassessment of the strength of the evidence.

If the risk of the disease in question increases with the amount of exposure, this is considered to be a strong indication of causality, although absence of a graded response is not necessarily evidence against a causal relationship. Demonstration of a decline in risk after cessation of or reduction in exposure in individuals or in whole populations also supports a causal interpretation of the findings.

Although a carcinogen may act upon more than one target, the specificity of an association (an increased occurrence of cancer at one anatomical site or of one morphological type) adds plausibility to a causal relationship, particularly when excess cancer occurrence is limited to one morphological type within the same organ.

Although rarely available, results from randomized trials showing different rates among exposed and unexposed individuals provide particularly strong evidence for causality.

When several epidemiological studies show little or no indication of an association between an exposure and cancer, the judgment may be made that, in the aggregate, they show evidence of lack of carcinogenicity. Such a judgment requires first of all that the studies giving rise to it meet, to a sufficient degree, the standards of design and analysis described above. Specifically, the possibility that bias, confounding or misclassification of exposure or outcome could explain the observed results should be considered and excluded with reasonable certainty. In addition, all studies that are judged to be methodologically sound should be consistent with a relative risk of unity for any observed level of exposure and, when considered together, should provide a pooled estimate of relative risk which is at or near unity and has a narrow confidence interval, due to sufficient population size. Moreover no individual study nor the pooled results of all the studies should show any consistent tendency for relative risk of cancer to increase with increasing level of exposure. It is important to note that evidence of lack of carcinogenicity obtained in this way from several epidemiological studies can apply only to the type(s) of cancer studied and to dose levels and intervals between first exposure and observation of disease that are the same as or less than those observed in all the studies. Experience with human cancer indicates that, in some cases, the period from first exposure to the development of clinical cancer is seldom less than 20 years; latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity.

9. STUDIES OF CANCER IN EXPERIMENTAL ANIMALS

All known human carcinogens that have been studied adequately in experimental animals have produced positive results in one or more animal species (Wilbourn *et al.*, 1986 Tomatis *et al.*, 1989). For several agents (aflatoxins, 4-aminobiphenyl, azathioprine, betel quid with tobacco, BCME and CMME (technical grade), chlorambucil, chlornaphazine, ciclosporin, coal-tar pitches, coal-tars, combined oral contraceptives, cyclophosphamide, diethylstilboestrols melphalan, 8-methoxypsoralen plus UVA, mustard gas, myleran, 2-naphthylamines nonsteroidal oestrogens, oestrogen replacement therapy/steroidal

oestrogens, solar radiation, thiotepa and vinyl chloride), carcinogenicity in experimental animals was established or highly suspected before epidemiological studies confirmed the carcinogenicity in humans (Vainio *et al*, 1995). Although this association cannot establish that all agents and mixtures that cause cancer in experimental animals also cause cancer in humans. nevertheless, **in the absence of adequate data on humans, it is biologically plausible and prudent to regard agents and mixtures for which there is sufficient evidence of carcinogenicity in experimental animals as if they presented a carcinogenic risk to humans.** The possibility that a given agent may cause cancer through a species-specific mechanism which does not operate in humans should also be taken into consideration.

The nature and extent of impurities or contaminants present in the chemical or mixture being evaluated are given when available. Animal strain, sex, numbers per group, age at start of treatment and survival are reported.

Other types of studies summarized include: experiments in which the agent or mixture was administered in conjunction with known carcinogens or factors that modify carcinogenic effects; studies in which the end-point was not cancer but a defined precancerous lesion; and experiments on the carcinogenicity of known metabolites and derivatives.

For experimental studies of mixtures, consideration is given to the possibility of changes in the physicochemical properties of the test substance during collection, storage, extraction, concentration and delivery. Chemical and toxicological interactions of the components of mixtures may result in nonlinear dose-response relationships.

An assessment is made as to the relevance to human exposure of samples tested in experimental animals, which may involve consideration of: (i) physical and chemical characteristics, (ii) constituent substances that indicate the presence of a class of substances, (iii) the results of tests for genetic and related effects, including genetic activity profiles, DNA adduct profiles, proto-oncogene mutation and expression and suppressor gene inactivation. The relevance of results obtained, for example, with animal viruses analogous to the virus being evaluated in the monograph must also be considered. They may provide biological and mechanistic information relevant to the understanding of the process of carcinogenesis in humans and may strengthen the plausibility of a conclusion that the biological agent that being evaluated is carcinogenic in humans.

(a) Qualitative aspects

An assessment of carcinogenicity involves several considerations of qualitative importance, including (i) the experimental conditions under which the test was performed, including route and schedule of exposure, species, strain, sex, age, duration of follow-up; (ii) the consistency of the results, for example, across species and target organ(s); (iii) the

spectrum of neoplastic response, from preneoplastic lesions and benign tumours to malignant neoplasma; and (iv) the possible role of modifying factors.

As mentioned earlier the *Monographs* are not intended to summarize all published studies. Those studies in experimental animals that are inadequate (e.g., too short a duration, too few animals, poor survival; see below) or are judged irrelevant to the evaluation are generally omitted. Guidelines for conducting adequate long-term carcinogenicity experiments have been outlined (e.g., Montesano *et al.*, 1986).

Considerations of importance to the Working Group in the interpretation and evaluation of a particular study include: (i) how clearly the agent was defined and, in the case of mixtures, how adequately the sample characterization was reported; (ii) whether the dose was adequately monitored, particularly in inhalation experiments; (iii) whether the doses and duration of treatment were appropriate and whether the survival of treated animals was similar to that of controls; (iv) whether there were adequate numbers of animals per group; (v) whether animals of both sexes were used; (vi) whether animals were allocated randomly to groups; (vii) whether the duration of observation was adequate; and (viii) whether the data were adequately reported. If available, recent data on the incidence of specific tumours in historical controls, as well as in concurrent controls, should be taken into account in the evaluation of tumour response.

When benign tumours occur together with an originate from the same cell type in an organ or tissue as malignant tumours in a particular study appear to represent a stage in the progression to malignancy, it may be valid to combine them in assessing tumour incidence (Huff *et al.*, 1989). The occurrence of lesions presumed to be preneoplastic may in certain instances aid in assessing the biological plausibility of any neoplastic response observed. If an agent or mixture induces only benign neoplasms that appear to be end-points that do not readily undergo transition to malignancy, it should nevertheless be suspected of being a carcinogen and requires further investigation.

(b) Quantitative aspects

The probability that tumours will occur may depend on the species, sex, strain, and age of the animal, the dose of the carcinogen, and the route and length of exposure. Evidence of an increased incidence of neoplasms with increased level of exposure strengthens the inference of a causal association between the exposure and the development of neoplasms.

The form of the dose-response relationship can vary widely, depending on the particular agent under study and the target organ. Both DNA damage and increased cell division are important aspects of carcinogenesis, and cell proliferation is a strong determinant of dose-response relationships for some carcinogens (Cohen & Ellwein, 1990). Since many chemicals require metabolic activation before being converted into their reactive intermediates, both metabolic and pharmacokinetic aspects are important in determining the dose-response pattern. Saturation of steps such as absorption, activation,

inactivation, and elimination may produce nonlinearity in the dose-response relationship, as could saturation of processes such as DNA repair (Hoel *et al.*, 1983; Gart *et al.*, 1986).

(c) Statistical analysis of long-term experiments in animals

Factors considered by the Working Group include the adequacy of the information given for each treatment group: (i) the number of animals studied and the number examined histologically, (ii) the number of animals with a given tumour type and (iii) length of survival. The statistical methods used should be clearly stated and should be the generally accepted techniques refined for this purpose (Peto *et al.*, 1980; Gart *et al.*, 1986). When there is no difference in survival between control and treatment groups, the Working Group usually compares the proportions of animals developing each tumour type in each of the groups. Otherwise, consideration is given as to whether or not appropriate adjustments have been made for differences in survival. These adjustments can include: comparisons of the proportions of tumour-bearing animals among the effective number of animals (alive at the time the first tumour is discovered), in the case where most differences in survival occur before tumours appear; life-table methods, when tumours are visible or when they may be considered 'fatal' because mortality rapidly follows tumour development; and the Mantel-Haenszel test or logistic regression, when occult tumours do not affect the animals' risk of dying but are 'incidental' findings at autopsy.

In practice, classifying tumours as fatal or incidental may be difficult. Several survival-adjusted methods have been developed that do not require this distinction (Gart *et al.*, 1986), although they have not been fully evaluated.

10. OTHER DATA RELEVANT TO AN EVALUATION OF CARCINOGENICITY AND ITS MECHANISMS

In coming to an overall evaluation of carcinogenicity in humans, the Working Group also considers related data. The nature of the information selected for the summary depends on the agent being considered.

For chemicals and complex mixtures of chemicals such as those in some occupational situations and involving cultural habits (e.g., tobacco smoking), the other data considered to be relevant are divided into those on absorption, distribution, metabolism and excretion; those on toxic effects; reproductive and developmental effects; and genetic and related effects.

Concise information is given on absorption, distribution (including placental transfer) and excretion in both humans and experimental animals. Kinetic factors that may affect the dose-response relationship, such as saturation of uptake, protein binding, metabolic activation, detoxification and DNA repair processes, are mentioned. Studies that indicate

the metabolic fate of the agent in humans and in experimental animals are summarized briefly, and comparisons of data from humans and animals are made when possible. Comparative information on the relationship between exposure and the dose that reaches the target site may be of particular importance for extrapolation between species. Data are given on acute and chronic toxic effects (other than cancer), such as organ toxicity, increased cell proliferation, immunotoxicity and endocrine effects. The presence and toxicological significance of cellular receptors is described. Effects on reproduction, teratogenicity, fetotoxicity and embryotoxicity are also summarized briefly.

Tests of genetic and related effects are described in view of the relevance of gene mutation and chromosomal damage to carcinogenesis (Vainio *et al.*, 1992). The adequacy of the reporting of sample characterization is considered and, where necessary, commented upon with regard to complex mixtures, such comments are similar to those described for animal carcinogenicity tests. The available data are interpreted critically by phylogenetic group according to the end-points detected, which may include DNA damage, gene mutation, sister chromatid exchange, micronucleus formation, chromosomal aberrations, aneuploidy and cell transformation. The concentrations employed are given, and mention is made of whether use of an exogenous metabolic system *in vitro* affected the test result. These data are given as listings of test systems, data and references; bar graphs (activity profiles) and corresponding summary tables with detailed information on the preparation of the profiles (Waters *et al.*, 1987) are given in appendices.

Positive results in tests using prokaryotes, lower eukaryotes, plants, insects and cultured mammalian cells suggest that genetic and related effects could occur in mammals. Results from such tests may also give information about the types of genetic effect produced and about the involvement of metabolic activation. Some end-points described are clearly genetic in nature (e.g., gene mutations and chromosomal aberrations), while others are to greater or lesser degree associated with genetic effects (e.g., unscheduled DNA synthesis). In-vitro tests for tumour-promoting activity and for cell transformation may be sensitive to changes that are not necessarily the result of genetic alterations but that may have specific relevance to the process of carcinogenesis. A critical appraisal of these tests has been published (Montesano *et al.*, 1986).

Genetic or other activity manifest in experimental mammals and humans is regarded as being of greater relevance than that in other organisms. The demonstration that an agent or mixture can induce gene and chromosomal mutations in whole mammals indicates that it may have carcinogenic activity, although this activity may not be detectably expressed in any or all species. Relative potency in tests for mutagenicity and related effects is not a reliable indicator of carcinogenic potency. Negative results in tests for mutagenicity in selected tissues from animals treated *in vivo* provide less weight, partly because they do not exclude the possibility of an effect in tissues other than those examined. Moreover, negative results in short-term tests with genetic end-points cannot be considered to provide evidence to rule out carcinogenicity of agents or mixtures that act through other mechanisms (e.g., receptor-mediated effects, cellular toxicity with regenerative proliferation, peroxisome proliferation) (Vainio *et al.*, 1992). Factors that may lead to

misleading results in short-term tests have been discussed in detail elsewhere (Montesano *et al.*, 1986).

When available, data relevant to mechanisms of carcinogenesis that do not involve structural changes at the level of the gene are also described.

The adequacy of epidemiological studies of reproductive outcome and genetic and related effects in humans is evaluated by the same criteria as are applied to epidemiological studies of cancer.

Structure-activity relationships that may be relevant to an evaluation of the carcinogenicity of an agent are also described.

For biological agents—viruses, bacteria and parasites—other data relevant to carcinogenicity include descriptions of the pathology of infection, molecular biology (integration and expression of viruses, and any genetic alterations seen in human tumours) and other observations, which might include cellular and tissue responses to infection, immune response and the presence of tumour markers.

11. SUMMARY OF DATA REPORTED

In this section, the relevant epidemiological and experimental data are summarized. Only reports other than in abstract form, that meet the criteria outlined are considered for evaluating carcinogenicity. Inadequate studies are generally not summarized: such studies are usually identified by a square-bracketed comment in the preceding text.

(a) Exposures

Human exposure to chemicals and complex mixtures is summarized on the basis of elements such as production, use, occurrence in the environment and determinations in human tissues and body fluids. Quantitative data are given when available. Exposure to biological agents is described in terms of transmission, and prevalence of infection.

(b) Carcinogenicity in humans

Results of epidemiological studies that are considered to be pertinent to an assessment of human carcinogenicity are summarized. When relevant, case reports and correlation studies are also summarized.

(c) Carcinogenicity in experimental animals

Data relevant to an evaluation of carcinogenicity in animals are summarized. For each animal species and route of administration, it is stated whether an increased incidence of preneoplastic lesions was observed, and the tumour sites are indicated. If the agent or mixture produced tumours after prenatal exposure or in single-dose experiments, that is also indicated. Negative findings are also summarized. Dose-response and other quantitative data may be given when available.

(d) Other data relevant to an evaluation of carcinogenicity and its mechanisms

Data on biological effects in humans that are of particular relevance are summarized. These may include toxicological, kinetic and metabolic considerations and evidence of DNA binding, persistence of DNA lesions or genetic damage in exposed humans. Toxicological information, such as that on cytotoxicity and regeneration, receptor binding and hormonal and immunological effects, and data on kinetics and metabolism in experimental animals are given when considered relevant to the possible mechanism of the carcinogenic action of the agent. The results of tests for genetic and related effects are summarized for whole mammals, cultured mammalian cells and nonmammalian systems.

When available, comparisons of such data for humans and for animals, and particularly animals that have developed cancer, are described.

Structure-activity relationships are mentioned when relevant.

For the agent, mixture or exposure circumstance being evaluated, the available data on end-points or other phenomena relevant to mechanisms of carcinogenesis from studies in humans, experimental animals and tissue and cell test systems are summarized within one or more of the following descriptive dimensions:

- (i) Evidence of genotoxicity (structural changes at the level of the gene): for example, structure-activity considerations, adduct formation, mutagenicity (effect on specific genes), chromosomal mutation/aneuploidy
- (ii) Evidence of effects on the expression of relevant genes (functional changes at the intracellular level): for example, alterations to the structure or quantity of the product of a proto-oncogene or tumour suppressor gene, alterations to metabolic activation/inactivation/DNA repair
- (iii) Evidence of relevant effects on cell behaviour (morphological or behavioural changes at the cellular or tissue level): for example, induction of mitogenesis, compensatory cell proliferation, preneoplasia and hyperplasia, survival of premalignant or malignant cells (immortalization, immunosuppression), effects on metastatic potential

(iv) Evidence from dose and time relationships of carcinogenic effects and interactions between agents: for example, early/late stage, as inferred from epidemiological studies; initiation/promotion/progression/malignant conversion, as defined in animal carcinogenicity experiments; toxicokinetics

These dimensions are not mutually exclusive, and an agent may fall within more than one of them. Thus, for example, the action of an agent on the expression of relevant genes could be summarized under both the first and second dimension, even if it were known with reasonable certainty that those effects resulted from genotoxicity.

12. EVALUATION

Evaluations of the strength of the evidence for carcinogenicity arising from human and experimental animal data are made, using standard terms.

It is recognized that the criteria for these evaluations, described below, cannot encompass all of the factors that may be relevant to an evaluation of carcinogenicity. In considering all of the relevant data, the Working Group may assign the agent, mixture or exposure circumstance to a higher or lower category than a strict interpretation of these criteria would indicate.

(a) Degrees of evidence for carcinogenicity in humans and in experimental animals and supporting evidence

These categories refer only to the strength of the evidence that an exposure is carcinogenic and not to the extent of its carcinogenic activity (potency) nor to the mechanisms involved. A classification may change as new information becomes available.

An evaluation of degree of evidence, whether for a single agent or a mixture, is limited to the materials tested, as defined physically, chemically or biologically. When the agents evaluated are considered by the Working Group to be sufficiently closely related, they may be grouped together for the purpose of a single evaluation of degree of evidence.

(i) Carcinogenicity in humans

The applicability of an evaluation of the carcinogenicity of a mixture, process, occupation or industry on the basis of evidence from epidemiological studies depends on the variability over time and place of the mixtures, processes, occupations and industries. The Working Group seeks to identify the specific exposure, process or activity which is considered most likely to be responsible for any excess risk. The evaluation is focused as narrowly as the available data on exposure and other aspects permit.

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between exposure to the agent, mixture or exposure circumstance and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence.

Limited evidence of carcinogenicity: A positive association has been observed between exposure to the agent, mixture or exposure circumstance and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

Inadequate evidence of carcinogenicity: The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association, or no data on cancer in humans are available.

Evidence suggesting lack of carcinogenicity: There are several adequate studies covering the full range of levels of exposure that human beings are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent, mixture or exposure circumstance and any studied cancer at any observed level of exposure. A conclusion of 'evidence suggesting lack of carcinogenicity' is inevitably limited to the cancer sites, conditions and levels of exposure and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues

(ii) Carcinogenicity in experimental animals

The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between the agent or mixture and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) in two or more independent studies in one species carried out at different times or in different laboratories or under different protocols.

Exceptionally, a single study in one species might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset.

Limited evidence of carcinogenicity: The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g., (a) the evidence of carcinogenicity is restricted to a single experiment; or (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the study; or (c) the agent or mixture increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential, or of certain neoplasms which may occur spontaneously in high incidences in certain strains.

Inadequate evidence of carcinogenicity: The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available.

Evidence suggesting lack of carcinogenicity: Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent or mixture is not carcinogenic. A conclusion of evidence suggesting lack of carcinogenicity is inevitably limited to the species, tumour sites and levels of exposure studied.

(b) Other data relevant to the evaluation of carcinogenicity and its mechanisms

Other evidence judged to be relevant to an evaluation of carcinogenicity and of sufficient importance to affect the overall evaluation is then described. This may include data on preneoplastic lesions, tumour pathology, genetic and related effects, structure-activity relationships, metabolism and pharmacokinetics, physicochemical parameters and analogous biological agents.

Data relevant to mechanisms of the carcinogenic action are also evaluated. The strength of the evidence that any carcinogenic effect observed is due to a particular mechanism is assessed, using terms such as weak, moderate or strong. Then, the Working Group assesses if that particular mechanism is likely to be operative in humans. The strongest indications that a particular mechanism operates in humans come from data on humans or biological specimens obtained from exposed humans. The data may be considered to be especially relevant if they show that the agent in question has caused changes in exposed humans that are on the causal pathway to carcinogenesis. Such data may, however, never become available, because it is at least conceivable that certain compounds may be kept from human use solely on the basis of evidence of their toxicity and/or carcinogenicity in experimental systems.

For complex exposures, including occupational and industrial exposures, chemical composition and the potential contribution of carcinogens known to be present are considered by the Working Group in its overall evaluation of human carcinogenicity. The

Working Group also determines the extent to which the materials tested in experimental systems are related to those to which humans are exposed.

(c) Overall evaluation

Finally, the body of evidence is considered as a whole, in order to reach an overall evaluation of the carcinogenicity to humans of an agent, mixture or circumstance of exposure.

An evaluation may be made for a group of chemical compounds that have been evaluated by the Working Group. In addition, when supporting data indicate that other, related compounds for which there is no direct evidence of capacity to induce cancer in humans or in animals may also be carcinogenic, a statement describing the rationale for this conclusion is added to the evaluation narrative; an additional evaluation may be made for this broader group of compounds if the strength of the evidence warrants it.

The agent, mixture or exposure circumstance is described according to the wording of one of the following categories, and the designated group is given. The categorization of an agent, mixture or exposure circumstance is a matter of scientific judgment, reflecting the strength of the evidence derived from studies in humans and in experimental animals and relative or from other relevant data.

Group 1—The agent (mixture) is carcinogenic to humans

This exposure circumstance entails exposures that are carcinogenic to humans.

This category is used when there is *sufficient evidence* of carcinogenicity in humans. Exceptionally an agent (mixture) may be placed in this category when evidence in humans is less than sufficient but there is *sufficient evidence* of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent (mixture) acts through a relevant mechanism of carcinogenicity.

*Group 2—*This category includes agents, mixtures and exposure circumstances for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost sufficient, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents, mixtures and exposure circumstances are assigned to either group 2A (probably carcinogenic to humans) or group 2B (possibly carcinogenic to humans) on the basis of epidemiological and experimental evidence of carcinogenicity and other relevant data.

Group 2A—The agent (mixture) is probably carcinogenic to humans.

The exposure circumstance entails exposures that are probably carcinogenic to humans.

This category is used when there is *limited evidence* of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals. In some cases, an agent (mixture) may be classified in this category when there is inadequate evidence of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent, mixture or exposure circumstance may be classified in this category solely on the basis of limited evidence of carcinogenicity in humans.

*Group 2B—The agent (mixture) is possibly carcinogenic to humans.
The exposure circumstance entails exposures that are possibly carcinogenic to humans.*

This category is used for agents, mixtures and exposure circumstances for which there is *limited evidence* of carcinogenicity in humans and less than *sufficient evidence* of carcinogenicity in experimental animals. It may also be used when there is *inadequate evidence* of carcinogenicity in humans but there is *sufficient evidence* of carcinogenicity in experimental animals. In some instances, an agent, mixture or exposure circumstance for which there is *inadequate evidence* of carcinogenicity in humans but *limited evidence* of carcinogenicity in experimental animals together with supporting evidence from other relevant data may be placed in this group.

Group 3—The agent (mixture or exposure circumstance) is not classifiable as to its carcinogenicity to humans.

This category is used most commonly for agents, mixtures and exposure circumstances for which the evidence of carcinogenicity is inadequate in humans and inadequate or limited in experimental animals.

Exceptionally, agents (mixtures) for which the evidence of carcinogenicity is inadequate in humans but sufficient in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents, mixtures and exposure circumstances that do not fall into any other group are also placed in this category.

Group 4—The agent (mixture) is probably not carcinogenic to humans.

This category is used for agents or mixtures for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents or mixtures for which there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of other relevant data, may be classified in this group.

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APPENDIX B

Minority Statement on Animal Carcinogenicity

1. Introduction

The vote on the animal carcinogenicity data on EMF, which suggests that they provide evidence for an effect on cancer is not consistent with the recommendation of the subgroup on studies of animals *in vivo* and is not justified by the data in the report.

This disagreement seems to focus on four points:

- (1) the weight given to data from the Löscher laboratory on the interaction between DMBA and EMF in inducing mammary cancer in the Sprague-Dawley rat;
- (2) the interpretation of induction of C-cell tumors in the thyroid in animals of one strain, one exposure group and one sex in a single long-term bioassay;
- (3) the focus on only adverse effects of EMF exposure and the lack of acknowledgment of the observations of the effect of EMF to decrease several tumor types for single-dose points in the long-term bioassay; and
- (4) weight given to the negative results of high-quality long-term bioassays.

2. Mammary carcinogenicity in the Sprague-Dawley rat

The Sprague-Dawley rat is hypersensitive to chemicals that induce mammary cancer. This hypersensitivity proceeds from an oversecretion of prolactin, which acts to “promote initiating events.” For instance, Welsh *et al.* (Welsh *et al.*, 1997) showed that tamoxifen, which prevents prolactin-induced proliferation of mammary epithelial cells, dramatically inhibits radiation-induced cancer. Tamoxifen also reduced mammary cancer incidence in women at increased risk for this cancer.

This hypersensitivity to initiating events was exploited in order to distinguish between the carcinogenic effects of neutrons and photons in the classical study of Shellabarger *et al.* (1980) which demonstrated unequivocally that histopathological examination is essential to discriminate between fibroadenomas and adenocarcinomas, the former benign tumor being a confounder that can obscure the induction of overt cancer. Further, this and

other studies, showed the importance of measuring the number of tumors per animal. The hypersensitivity of Sprague-Dawley rats to initiating events limits their use as a model for initiation-promotion studies. The dose of the initiating agent sets the dynamic range of possible response to the promoter; if it is too potent, it obscures interpretation of the “promoting” agent.

Löscher’s data fail on all three points. They do not observe increases in the number of tumors per animal; the study does not consistently report an increase in tumor size or demonstrate an association between tumors palpated early and histological verification in early stages (i.e. determination of tumor latency conducted by population only); and the initiating doses are too high.

3. C-Cell thyroid tumors

The relevance of induction of this cancer, is compromised in four ways:

- (1) It is not induced by any known animal or human carcinogen.
- (2) It is a microscopic tumor susceptible to sampling artifacts.
- (3) The historical rates (4-36%), are highly variable.
- (4) It is not found in females.
- (5) Pre-neoplastic hyperplasia is most prevalent in controls and least prevalent in exposed animals.

4. Protective effects of EMF against cancer:

NTP study:

- (1) mononuclear-cell leukemia in male mice (B6C3F1) exposed to 1000 μ T ($p = 0.045$);
- (2) alveolar/bronchial adenoma in male mice exposed to 2 or 200 μ T ($p < 0.001$) and in female mice exposed to 200 μ T ($p = 0.002$);
- (3) combined adenoma and carcinoma in male and female mice exposed to 200 μ T ($p = 0.041$ and 0.015);

- (4) malignant lymphoma in female mice exposed to 1000 μT ($p = 0.045$). (Mandeville, 1997);
- (5) incidence of pituitary adenoma was reduced at 2 μT ($p = 0.01$) and at 2000 μT ($p = 0.02$).

5. Long-term bioassays are the most predictive of all laboratory models for human response.

The strong predictive power of the long-term bioassay in rodents has been demonstrated in hundreds of such studies with known human carcinogens. While studies with a single species of rodents may have limited predictive value, the use of one mouse and one rat strain increases the predictive power. Most of the inconsistencies between the responses of different animal species to chemical carcinogens have been shown to result from the different pharmacokinetics and metabolism of the species, a confounder that is not likely to affect EMF.

The four long-term bioassays performed with exposure to EMF include studies in species demonstrated to be sensitive to mammary carcinogens and to leukemogenesis. Indeed, the Fischer 344 rat is particularly susceptible to leukemia, as the Sprague-Dawley rat is hypersensitive to mammary cancer. The results of all of the studies are completely negative. Furthermore, as described above, significant decreases in the incidences of specific tumors were seen in animals of one sex and one species at some doses. These findings are probably the result of random variation in the large number of response categories.

6. In summary:

- (1) The study of Löscher is fundamentally flawed by its lack of consistency in effect and absence of critical histological data.
- (2) Although the incidence of thyroid C-cell tumor was elevated in a single study, this tumor has never been considered relevant in assessing the carcinogenic potential of any agent. The natural history of the tumor makes it difficult to measure with precision.
- (3) In five cases, reduced induction of specific types of cancer was seen after exposure to EMF in well-executed bioassays.

- (4) In well-executed long-term bioassays conducted in animal models known to be susceptible to the induction of lymphoma/leukemia and mammary cancer as well as other forms of cancer, there is no suggestion of an increased incidence of cancer. The single exception is C-cell thyroid tumor, the incidence of which was elevated in only one bioassay, however, this observation has no predictive value for human or animal carcinogens, as noted above.

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