Exhibit No.: _____
Issues: Potential Health Effects
Witness: Dennis Smith, DO
Type of Exhibit: Rebuttal
Sponsoring Party: MO Landowners Alliance
Case No.: EA-2014-0207
Date Testimony Prepared: August, 2014

MISSOURI PUBLIC SERVICE COMMISSION

CASE NO. EA-2014-0207

REBUTTAL TESTIMONY OF

DENNIS SMITH, DO

ON BEHALF OF

MISSOURI LANDOWNERS ALLIANCE

September 15, 2014

Q. Please state your name, and where you reside.

A. Dennis Smith, and I live in Moberly, Missouri.

Q. By whom are you employed, and in what capacity?

A. I am employed as the Medical Director of the Emergency Department, at the Moberly Regional Medical Center, Moberly, Missouri.

Q. What is your educational background?

A. I received the degree of Doctor of Osteopathic Medicine from Des Moines University in 1994, and I am a Board Certified Emergency Physician by the American Board of Emergency Medicine. A copy of my CV is attached as Schedule DS-1 to my testimony.

Q. What is the purpose of your testimony?

A. I am addressing the potential health effects of Grain Belt's proposed transmission line from electromagnetic fields, or EMFs, static magnetic fields, and static electric fields. In doing so, I will be commenting on the testimony on this subject submitted by Grain Belt's witness Dr. Anthony Galli.

Q. What are your overall conclusions regarding the potential health effects of the EMFs, static magnetic fields, and static electric fields from Grain Belt's proposed line?

A. Dr. Galli says "There is no conclusive evidence to support the contention that EMFs from transmission lines are linked to health related risks to humans, plants, or animals." (Galli Direct Testimony, p. 27, 1. 4-5) I can state with just as much certainty that there is no conclusive evidence that EMFs do not pose health related risks to humans, plants, or animals. To the contrary there is evidence that fields produced by HVDC lines

like the proposed Grain Belt line do cause human health effects as well as effects on animals. World-wide, one of the principal precepts of bioethics taught to all healthcare students is "First, Do No Harm."

Q. Are you familiar with the material cited by Dr. Galli to support his position that there are no adverse effects on humans, animals, or plant life due to exposure to static or slowly varying fields produced by the proposed HVDC line?

A. Yes, I have reviewed the references mentioned by Dr. Galli and I am aware of his interpretation of those documents. Some of these documents set levels of exposure to EMFs which the agency in question considers acceptable, while others comment on health. While Dr. Galli interprets the documents to support his stand on the impact of EMFs from transmission lines, one of those documents makes a statement of grave concern to me as a physician.

Q. Which publication are you referring to?

A. The monograph published by the International Agency for Research on Cancer, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 80: Static and Extremely Low-Frequency (ELF) Electric and Magnetic Fields (Lyon, France, IARC Press, 2002). In the last paragraph of the document, under the heading "Overall evaluation", is the following conclusion: "Extremely low-frequency magnetic fields are possibly carcinogenic to humans. (Group 2B)"

Q. What is the significance of a Group 2B classification for carcinogenic risk?

A. This is the same Group classification held by the HIV virus and the Human Papilloma virus which are both known to cause cancer in humans. Schedule DS-2 of my

testimony is an excerpt from the Agents Classified By the IARC Monographs, which indicates at page 14 of the document (page 2 of my Schedule DS-2) that the HIV virus and the Human Papilloma virus are both listed in group 2B: "Possibly carcinogenic to humans." Clearly, there is considerable risk which cannot be taken lightly by physicians or the general public.

Q. What are the elements produced by a HVDC line which you believe could produce adverse health effects?

A. Clean Line's fact sheet, available in their folder at their public meetings, quotes the Electric Field at 20-30 kV/m and the Magnetic Field at 300-600 mG for a ± 500 kV DC transmission line. (Schedule DS-3)

One paper published by a non-biased source reports that a ±450kV HVDC line will produce about 25 microTelsa of Electromagnetic Field. (Schedule DS-4, p. 842) This level of EMF is above safe exposure levels recommended in scientific sources and papers since the latest reference quoted by Clean Line.

Q. Why are you convinced that the emissions of HVDC lines like the one proposed by Clean Line are very possibly harmful to human health?

A. As a practicing Emergency Physician, I strive to practice evidence-based medicine. Human beings do not always respond to toxins or environmental agents in a manner that allows us to evaluate the response using linear statistical models. Due to the sometimes illogical response of the human organism it may take many years to make the connection between a harmful stimulus or toxin and the adverse health event. An example is asbestos which was used for years to protect our most vulnerable from fire only to discover that we had introduced a very harmful toxin into their lives.

Q. Is there any particular report which leads you to believe that the level of EMF at issue here might be harmful?

A. A review of the BioInitiative Report in 2012 was the first document to raise my concern over the health risks of a HVDC line. That document consists of nearly 1,500 pages, and so I am including only portions of it here, at Schedule DS-5. Dr. Galli says he is aware of this document, but dismisses it as not being independent and conducted by "a group of activists". (Dr. Galli answer to data request no. 36 in MLA's first set of data requests to him). Actually this study quotes multiple sources and was produced by ten medical doctors, 21 PHD's, and 3 MsC, MA, or MPHs. Three are former presidents of the Bioelectromagnetics Society and five are full members of the Bioelectromagnetics Society. Two of the physicians in this group have testified multiple times as experts regarding power lines such as this one. The Bioelectromagnetics Society promotes the exchange of ideas to advance the science of natural and applied electromagnetic fields in biology and medicine. Its members are scientists from approximately 40 countries.

The BioInitiative 2012 was written as a meta-analysis. Many of the references specifically relating to the type of fields released by HVDC lines were read by me and the articles referenced were peer reviewed.

Q. Are you relying for your conclusions here only on the BioInitiative report?

A. No, I also focused on the literature since 2009 in addition to that quoted by the BioInitiative 2012 and have found additional studies that indicate adverse health effects of exposure to the fields produced by a HVDC line.

Q. Please list these additional studies.

A. Haleez, K. et al. (2013). To Investigate Environmental Effects of HVDC versus HVAC Systems. J. Basic. Appl. Sci. Res., 3(8)840-843.

Fragopoulou, A. et al. (2010). Scientific Panel on Electromagnetic Field Health Risks: Consensus Points, Recommendations and Rationales. Reviews on Environmental Health Vol. 25, No. 4, 2010.

Blank, M. and Goodman, R. (2009). Electromagnetic Fields Stress Living Cells. Pathophysiology 16, 71-78.

Sermage-Faure, C. et al. (2013). Childhood Leukemia Close to High-Voltage Power Lines – the Geocap study, 2002-2007. British Journal of Cancer 1-8 (2013).

Pall, M. (2013). Electromagnetic Fields Act Via Activation of Voltage-gated Calcium Channels to Produce Beneficial or Adverse Effects. J. Cell. Mol. Med. Vol. XX, No. X, p. 1-9 (2013).

Cieslar, G. et al. (2007). The Influence of Static Electric Field Generated Nearby High Voltage Direct Current Transmission Lines on Hormonal Activity of Experimental Animals. EHE '07 2nd International Conference on Electromagnetic Fields, Health and Environment.

Huss, A. et al. (2008). Residence Near Power Lines and Mortality From Neurodegenerative Diseases: Longitudinal Study of the Swiss Population. Am. J. Epidemiol 2009; 169: 167-175.

Carrubba, S. and Marino, A. (2008). The Effects of Low-Frequency Environmental-Strength Electromagnetic Fields on Brain Electrical Activity: A Critical Review of the Literature. Electromagnetic Biology and Medicine 27: 83-101 (2008).

Q. Why do you question the validity of the exposure limits set by the various agencies cited by Clean Line Energy?

A. Industry experts and engineers would have a potential for bias in recommendations for exposure. The BioInitiative Report, Schedule DS-5, page 5, raises a concern that the industry view of allowable risk and proof of harm is more influential than those of public health experts.

In November 2009 a scientific panel on Electromagnetic health risks in Seletun, Norway concluded. "Present guidelines, such as IEE, FCC, and ICNIRP, are not adequate to protect humans from harmful effects of chronic EMF exposure." (Schedule DS-6)

A study by M. Blank found that EMF exposure caused release of the same stress chemicals at a cellular level as toxins such as alcohol, toxic metals, pH changes, and osmotic pressure changes. He concluded that the low threshold of exposure required to produce these stress chemicals shows that the current standards are set much too high to be considered safe. (Schedule DS-7)

Q. Is there any new evidence connecting childhood leukemia to exposure to the fields produced by power lines?

A. Yes, there is. A 2013 report published in the British Journal of cancer was done in a manner to reduce the chance of bias and supports the finding that Acute Childhood Leukemia results more often when exposed to 0.4 microTelsa of Electromagnetic field. (Schedule DS-8). An independent paper indicated the EMF output by a ±450 kV HVDC line is 25 microTelsa, sixty-two times the level associated with childhood acute leukemia reported in this paper. (Schedule DS-4)

Q. Is there any evidence that static electric fields or static magnetic fields are harmful?

A. I am aware that Clean Line maintains that the fields produced by a HVDC line are static and therefore are not the fields associated with health risks. In a discussion with Dr. David O Carpenter, one of the experts on the BioInitiative panel, it was pointed out to me that by simply moving in and out of these static fields there becomes an AC component and therefore an Electromagnetic field.

Wind velocities do not remain constant and the current demands on the receiving end of such a DC line will not remain constant. The fluctuations in the variables of wind speed and current demand will result in changes within the line that will produce EMFs.

In addition, a 2013 article in the Journal of Cellular and Molecular medicine shows both therapeutic bone growth stimulation and DNA breaks through stimulation of Voltage Gated Calcium Channels (VGCCs). This VGCC stimulation is caused by EMF, static electric fields, static magnetic fields, and nanosecond pulses. (Schedule DS-9) Therefore, this report clearly disputes Dr. Galli's position that strong static magnetic fields do not cause long-term health effects. (Dr. Galli direct testimony, p. 23, l. 1-2) Stimulation of bone growth and DNA breaks are classified as long-term health effects.

Q. Is there any evidence of health related risks to animals?

A. Animals are often used to first identify risk to humans; however, there is no animal equivalent to Acute Childhood Leukemia. Clean Line maintains there are no health related risks to humans, plants, or animals, but a study presented at the 2nd International Conference on Electromagnetic Fields, Health and Environment indicates otherwise.

This study found that exposure to an Electric Field at an intensity above 16 kV/m influenced hormonal activity of the adrenal gland, thyroid gland and testicles in experimental animals. (Schedule DS-10) Significantly, Dr. Galli stated that the right of way electrical field would be expected to be approximately 40 kV/m. (Galli direct testimony page 21 lines 8-9).

Q. What other health effects are related to exposure to fields produced by high voltage power lines?

A. A longitudinal study of the Swiss population reported in the American Journal of Epidemiology in 2009 found an increased risk of Alzheimer's disease in persons living near 220-380 kV power lines. (Schedule DS-11) The proposed transmission line is +500 kV. In addition, the BioInitiative Report discussed above lists studies which link EMF exposure to adult leukemia, malignant melanoma, and breast cancer.

Q. The WHO study relied on by Dr. Galli cites the lack of reproducibility in studies dealing with the effects of electric fields, magnetic fields and electromagnetic fields. What is your response?

A. Earlier in my testimony I commented on the illogical response of the human organism to various stimuli. A paper published in Electromagnetic Biology and Medicine addressed the lack of consistent responses and found that nonlinear statistical methods found biologic responses in "essentially every subject examined ...." (Schedule DS-12, p. 98)

Q. Based on your review of the literature, are you able to state with certainty that EMFs, Static Electric Fields and Static Magnetic Fields do or do not have serious harmful effects on humans?

A. The practice of medicine is based on evidence. I can say with certainty that there is enough evidence of harmful effects from EMFs, Static Electric Fields and Static Magnetic fields that the universal premise of medicine, "First Do No Harm", forces me to oppose this line. Human experimentation is prohibited in medicine without complete disclosure and acceptance of the risk by the subjects of the study. This is an experiment that I do not consent to participate in, and granting eminent domain would be condemning people to participate without consent.

Q. Does that conclude your testimony?

A. Yes, it does.

BEFORE THE PUBLIC SERVICE COMMISSION

OF THE STATE OF MISSOURI

In the Matter of the Application of Grain Belt Express Clean Line LLC for a Certificate of Convenience and Necessity Authorizing it to Construct, Own, Operate, Control, Manage, and Maintain a High Voltage, Direct Current Transmission Line and an Associated Converter Station Providing an interconnection on the Maywood-Montgomery 345 kV Transmission Line	)	EA-2014-0207

AFFIDAVIT OF DENNIS SMITH

STATE OF MISSOURI)
) SS
COUNTY OF Randolph)

Dennis Smith, being first duly sworn on his oath states:

1. My name is Dennis Smith.

2. Attached hereto and made a part hereof for all purposes is my Rebuttal Testimony, submitted on behalf of the Missouri Landowners Alliance.

3. I hereby swear and affirm that my answers contained in the attached testimony to the questions therein asked, including any attachments thereto, are true and accurate to the best of my knowledge, information and belief.

Dennis Smith

Subscribed and sworn before me this 28th day of August, 2014.

Notary Public

PAMELA KAY DOLLICH
Notary Public, Notary Seal
State of Missouri
Randolph County
Commission # 11285926
My Commission Expires December 28, 2015

Dennis Smith, DO
Medical Director, Emergency Department
Moberly Regional Medical Center
Moberly, MO

Board Certified Emergency Medicine Physician by the American Board of Emergency Medicine and a Fellow in the American College of Emergency Physicians. Fellow in the American Academy of Emergency Physicians.

Experience and training includes dealing routinely with toxicologic emergencies such as overdoses of prescription and recreational drugs, toxic chemical exposures and decontamination, thermal injury, electrical injury, and community disasters. Military deployments provided training and exposure to chemical warfare, microwave, radiofrequency, and electromagnetic field beaming as a form of warfare.

Job Title: Medical Director, Emergency Department, Moberly Regional Medical Center, Moberly, Missouri

EDUCATION AND TRAINING

American College of Emergency Medicine Fellow
Darnall Army Hospital, Fort Hood, Texas, June 1997-October 1999
Requisites for this title were completed while practicing, teaching residents as an Associate Professor in Emergency Medicine, and doing research within the residency program.
Recognized as Mentor of the Year 1999 by residents in training.

***Internship and Residency in Emergency Medicine*: June 1994-June 1997**
Darnall Army Hospital, Fort Hood, Texas

***Doctor of Osteopathic Medicine:* June 1990-June 1994**
Des Moines University, Des Moines, Iowa
Graduated with honors.

***Physician Assistant*: August 1978-June 1980**
Albany-Hudson Valley Physician Assistant Program, Troy, New York

MILITARY EXPERIENCE

United States Navy, Hospital Corpsman 1972-1976
Service as a Line Corpsman, 3rd Marine Division 11/74-11/75
Operations Eagle Pull and Frequent Wind, Viet Nam
Support for USS Mayaquez Recovery, Cambodia
Specialty Training - Hospital Corps School, San Diego,CA
- Field Medical School, Camp Pendleton, CA

United States Army 1994-2000
Training; Emergency Medicine
Tri-Services Combat Casualty Care Course
Desert Warfare Training Ft Irwin, California
Chemical Warfare Training, Ft Irwin CA and Ft. Hood, Tx
Multinational NATO Force Training, Ft. Polk, LA
Emergency Department and Trauma Director 21st Combat Support Hospital, Tuzla, Bosnia 1999
Awards: Humanitarian Service Award X 3
Armed Forces Expeditionary Medal X3
Army Meritorious Service Award

International Agency for Research on Cancer
World Health Organization

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

AGENTS CLASSIFIED BY THE *IARC MONOGRAPHS*, VOLUMES 1–109

Group 1	*Carcinogenic to humans*	113 agents
Group 2A	*Probably carcinogenic to humans*	66
Group 2B	*Possibly carcinogenic to humans*	285
Group 3	*Not classifiable as to its carcinogenicity to humans*	505
Group 4	*Probably not carcinogenic to humans*	1

For definitions of these groups, please see the Preamble.

It is strongly recommended to consult the complete *Monographs* on these agents, the publication date, and the list of studies considered. Significant new information might support a different classification.

For agents that have not been classified, no determination of non-carcinogenicity or overall safety should be inferred.

- List of classifications by alphabetical order
- List of classifications by CAS® Registry Number order
- List of classifications by Group
- List of classifications by cancer site

See Preventable Exposures Associated With Human Cancers (Cogliano *et al.*, 2011)

Although care was taken in preparing these lists, mistakes may be present.
If you find an error, please notify us at imo@iarc.fr.

Last update: 31 March 2014

Schedule DS-2
Page 1 of 2

IARC, 150 Cours Albert Thomas, 69372 Lyon CEDEX 08, France - Tel: +33 (0)4 72 73 84 85 - Fax: +33 (0)4 72 73 85 75

Agents Classified by the *IARC Monographs*, Volumes 1–110

CAS No	Agent	Group	Volume	Year
	Hexachlorocyclohexanes	2B	20, Sup 7	1987
000067-72-1	Hexachloroethane	2B	73	1999
000142-83-6	2,4-Hexadienal	2B	101	2013
000680-31-9	Hexamethylphosphoramide	2B	15, Sup 7, 71	1999
	Human immunodeficiency virus type 2 (infection with)	2B	67	1996
	Human papillomavirus types 5 and 8 (in patients with epidermodysplasia verruciformis)	2B	100B	2012
	Human papillomavirus types 26, 53, 66, 67, 70, 73, 82	2B	100B	2012
	Human papillomavirus types 30, 34, 69, 85, 97 (NB: Classified by phylogenetic analogy to the HPV genus alpha types classified in Group 1)	2B	100B	2012
000302-01-2	Hydrazine	2B	4, Sup 7, 71	1999
000058-93-5	Hydrochlorothiazide	2B	50, 108	in prep
000129-43-1	1-Hydroxyanthraquinone	2B	82	2002
000193-39-5	Indeno[1,2,3-*cd*]pyrene	2B	92	2010
009004-66-4	Iron-dextran complex	2B	2, Sup 7	1987
000078-79-5	Isoprene	2B	60, 71	1999
	JC polyomavirus (JCV)	2B	104	2013
009000-38-8	Kava extract	2B	108	in prep
000303-34-4	Lasiocarpine	2B	10, Sup 7	1987
007439-92-1	Lead	2B	23, Sup 7	1987
000632-99-5	Magenta	2B	57, 99, 100F	2012
	Magnetic fields, extremely low-frequency	2B	80	2002
068006-83-7	MeA-alpha-C (2-Amino-3-methyl-9*H*-pyrido[2,3-*b*]indole)	2B	40, Sup 7	1987
000071-58-9	Medroxyprogesterone acetate	2B	21, Sup 7	1987
077094-11-2	MeIQ (2-Amino-3,4-dimethylimidazo[4,5-*f*]quinoline)	2B	56	1993
077500-04-0	MeIQx (2-Amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline)	2B	56	1993
000531-76-0	Merphalan	2B	9, Sup 7	1987
000124-58-3	Methylarsonic acid	2B	100C	2012
000075-55-8	2-Methylaziridine (Propyleneimine)	2B	9, Sup 7, 71	1999
000592-62-1	Methylazoxymethanol acetate	2B	10, Sup 7	1987
003697-24-3	5-Methylchrysene	2B	92	2010
000838-88-0	4,4'-Methylene bis(2-methylaniline)	2B	4, Sup 7	1987
000101-77-9	4,4'-Methylenedianiline	2B	39, Sup 7	1987
000093-15-2	Methyleugenol	2B	101	2013
000693-98-1	2-Methylimidazole	2B	101	2013
000822-36-6	4-Methylimidazole	2B	101	2013
000108-10-1	Methyl isobutyl ketone	2B	101	2013

CLEAN LINE ENERGY PARTNERS FACT SHEET

UNDERSTANDING ELECTRIC AND MAGNETIC FIELDS OF HVDC LINES

High voltage direct current (HVDC) transmission lines offer significant electrical, economic, and environmental advantages for the transport of electricity over long distances. HVDC is a well-established technology with decades of safe and reliable operation across the world. HVDC is particularly well-suited to transport large amounts of renewable power generated in remote areas over long distances to demand centers. Currently, there are more than 20 HVDC transmission facilities in the United States and more than 35 across the North American electric grid.

STATIC ELECTRIC AND MAGNETIC FIELDS

The electric and magnetic fields produced by direct current (DC) lines are referred to as static fields because their sources, voltage and current, do not alternate over time. Thus, DC fields are qualitatively different in nature than the alternating current (AC) electric and magnetic fields (often called EMF) produced by AC transmission lines. While AC EMF can cause the induction of currents or voltages in nearby objects, this does not occur with DC fields. DC electric and magnetic fields are identical to those found in the natural environment.[1,4]

Static Electric Fields

Static electric fields occur as a result of voltage. Natural sources of static electric fields include the electric fields produced by the charge on a body after shuffling across a carpet or the "static cling" found on clothing.[1]

Static Magnetic Fields

Static magnetic fields result from the flow of DC electricity. The steady flow of currents in the Earth's core produces the static "geomagnetic" field that causes a compass to point north. Common sources of static magnetic fields much stronger than those associated with DC transmission lines include permanent magnets, battery-powered appliances (e.g., telephones, electric tooth brushes, hearing aids, laptops, etc.) and some electrified railway systems.[1]

Static electric and magnetic field levels close to common sources.

ELECTRIC FIELDS	
Source	**Electric Field Level**
Friction from walking across carpet (at body surface)	Up to 500 kV/m
Computer screen (at 30 centimeters)	10-20 kV/m
± 500 kV DC transmission line (standing beneath conductors)	20-30 kV/m
MAGNETIC FIELDS	
Source	**Magnetic Field Level**
MRI machines	15,000,000–40,000,000 mG
Refrigerator magnets	10,000-50,000 mG
Battery-operated appliances	3,000–10,000 mG
Electrified railways	<10,000 mG
The Earth	300-700 mG
± 500 kV DC transmission line (standing beneath conductors)	300-600 mG

mG = milligauss
kV/m = kilovolts per meter (1 kV/m = 1,000 volts/m)

RESEARCH ON THE IMPACT OF STATIC FIELDS

Much of the research on static fields has focused on the strong magnetic fields associated with certain occupational exposures and the operation of MRI machines. The International Agency for Research on Cancer (IARC)[3], the World Health Organization (WHO)[2], and others[1,4,5] have all concluded that the current body of research does not indicate that strong static electric or magnetic fields cause long-term health effects.

Research has also been conducted to assess the impact of DC transmission lines on farm and ranching operations. Noteworthy findings from this research include:

- A ±400 kV DC line did not affect crops, vegetation, or nearby wildlife; nor were the fields perceived by persons walking on the right-of-way[5]
- No differences were found between cattle and crops raised under ±500 kV DC transmission lines and those raised away from the lines[7]
- Multiple indicators of herd health did not differ between periods before and after a nearby ±400 kV DC line was energized or with distance from the line in a study of over 500 herds of dairy cattle[8]

[a] DC transmission lines are not connected to AC distribution systems. Therefore they are not sources of AC voltages on farm or building equipment that can cause disturbances to livestock (i.e., stray voltage).

CLEAN LINE ENERGY PARTNERS

Schedule DS-3
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I I " ' ANDING ELECTRI AND MAGNETIC FIELDS OF HVD LINE A

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MRI mnchmes

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CLEAN LINE

ENERGY PARTNERS

CORONA PHENOMENA

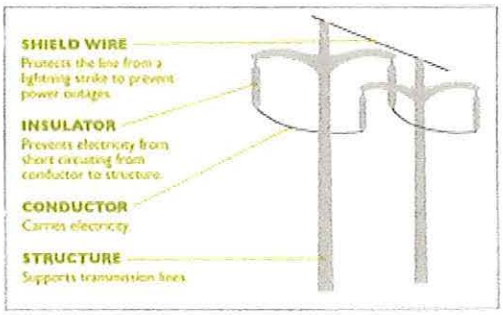
Corona refers to the partial electrical breakdown of the air surrounding points on the transmission line conductor surface by the electric field. This breakdown results in the release of small amounts of energy that may be detected near the line as audible noise and "static" on radio and analog television receivers. The US Environmental Protection Agency (EPA) and the Institute of Electrical and Electronic Engineers (IEEE) have established guidelines for the production of such noise and static, which are met in the design and construction of a HVDC transmission line.

Corona also creates air ions, which are molecules that have temporarily gained or lost electrons. Air ions also occur as a result of geologic, atmospheric, weather-related and combustion phenomena. Some air ions from DC transmission lines remain in the air for seconds before contacting an opposite charge or transferring charge to aerosol particles. Air ions and charges on aerosols collectively are called "space charge," and their presence adds to the static electric field of a DC transmission line. Space charge has been studied for over one hundred years.

No health agencies have proposed exposure limits for space charge or confirmed any health risks from this natural phenomenon.

ELECTRONIC DEVICES

The static fields of DC transmission lines are too weak to affect the operation of implanted medical devices such as cardiac pacemakers. As already noted, the corona from DC transmission lines can produce AM radio and analog TV picture signal interference. This interference is typically limited to within approximately 100 feet of the transmission line. Due to right-of-way requirements, such noise interference has not been a significant issue for most landowners. Cellular telephones, GPS receivers and other electronic equipment are used near existing DC transmission lines without issue. Thus, the possibility of interference with the operation of such devices is unlikely.



A DC transmission line has two conductor bundles called "poles." Conductors are the wires that hang from the towers and are often bundled in groups of two or three. Like a car battery, the two bundles of DC conductors have opposite polarity, one positive and one negative. The voltage of a DC transmission line, therefore, is usually referred to as ± (plus or minus) voltage. For example, a 500 kilovolt (kV) DC transmission line is referred to as a ±500 kV DC transmission line.

REFERENCES

1. Bailey WH, Weil DE, Stewart JR. HVDC Power Transmission Environmental Issues Review. Oak Ridge: Oak Ridge National Laboratory; 1996.
2. World Health Organization (WHO). 2006. Environmental Health Criteria Monograph No. 232. Static Fields.
3. International Agency for Research on Cancer (IARC). 2002. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 80. Static and Extremely Low-Frequency (ELF) Electric and Magnetic Fields. IARC Press, Lyon, France.
4. National Radiological Protection Board (NRPB). 2004. Advice on Limiting Exposure to Electromagnetic Fields (0–300 GHz). Volume 15, No. 2.
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May 2011
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CORONA PHENOMENA

Corona refers to the partial electrical breakdown of the air

SHIELD WIRE

Protects the line from a lightmng sinks to prevent

by the electric This breakdown results in the release of

the electric fleld. This breakdown results in the release of y . leuLm-on / small amounts of energy that may be detected near the Ime esecmciry from

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as audible noise and "static" on radio and analog television l receivers. The US Environmental Protection Agency (EPA) l CONDUCTOR " and the Institute of Electrical and Electronic Engineers (IEEE) | Carnes eiecmciry.

have established guidelines for the production of such noise | "Rum-URE

and static, which are met in the design and construction of a | SUPF'ONs transmission 'mes

HVDC transmission line.

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- - study of Holstein dairy cow performance and reproduction near a highvoltage DC transmlsslon llnes can Produce AM relle and analog direct. current powerline.]Toxicol Environ Heath |91303-324.

affect the operation of impianted medical devices Such as

TV picture signal interference. This interference is typically limited to within approximately |00 feet of the transmission

line. Due to right-of-way requirements, such noise

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lines without issue. Thus, the possibility of interference with

the operation of such devices is unlikely.

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To Investigate Environmental effects of HVDC versus HVAC Transmission Systems

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ABSTRACT

Alternating current (AC) has few drawbacks which have increased the demand of Direct current (DC) Transmission. The normal HVAC range is between 220-800 kV .This high voltage has to pass different types of terrains including settled area, mountains and water. It is quite clear that human beings and environment will be effected from this huge voltage. The common effects of these huge voltages are magnetic fields, electric fields, corona effects, RF interference, acoustic noise, and electromagnetic interference. This paper discusses the technical details of high voltage DC (HVDC) transmission versus high voltage AC (HVAC) transmission in terms of environmental effectson people and surrounding..

KEYWORDS:HVDC Transmission, High Voltage transmission, Corona effects, Electric fields.

I. INTRODUCTION

Due to generation of electricity, Electric and magnetic fields (EMF) are created. Magnetic fields and Electric fields are formed due to motion and presence of electric charges .These time varying fields are influenced by number of parameters such as magnitude, phase frequency and direction. Electric transmission is basically the transfer of electrical power in bulk form from generating units to substations located near to Load centers. The interconnection of Transmission lines forms together HVAC transmission networks. The transmission Network is named as "power grids" in the USA, while in the UK these networks is called "national grid." It is a usual practice to step up voltage above 110 kV in order to reduce the loss in energy during far away transmission.

An electromagnetic field consists of electric and the magnetic fields. The electric field does not depends on the amount of current flowing through conductors but depends on potential difference between charge-carrying bodies where as magnetic field has a relation with the amount of electric current passing through the conductor irrespective of the presence of voltage.

Electric field strength is normally measured in (Volt/meter) or in kv per meter (1 kilovolt/meter = 1000 V/m). Magnetic fields are normally represented by magnetic flux density (B) or magnetic field strength (H); both have a direct proportion to the magnitude of the current. B is calculated in the centimeter-gram-second unit, the gauss (G), or the unit of the System International (SI), the tesla (T); 1 mG = 1 x 10^{-3} G = 0.1 μT. H is calculated in SI units of (Amperes/meter). B and H forms a relationship: B = μ0H, where μ0 = 1.26 x 10^{-6} H/meter is the magnetic permeability of a vacuum. Normally, μ0 remains the same for air and human tissues, and only one of the variables, B or H, need to be calculated. Magnetic field refers to the magnetic flux density in microtesla (μT; 1 μT = 1 x 10^{-6} T), current voltage, and magnetic flux are taken in (root mean square value) as shown in eqt (A).

$$B_{rms} = \sqrt{1/T \int_{t=0}^{t=T} B(t)^2 \, dt} \qquad (A)$$

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

Typical 60 Hz or 50 Hz electric fields are less than 100 V/m in homes and are not greater than 10 kV/m beneath a high voltage Power line i.e. 500 Kv. However the Line staff and those people who work very close to high power line can experience internal electric fields in the range of 10^{-3} V/m [1].

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This research paper examines the effects of HVDC versus HVAC Transmission systems on environment and people.

II. PROBLEM STATEMENT

Nancy Wertheimer and ED Leeper were the first authors to show a possible relation between childhood cancer and High Electric lines (HVAC) when they published their paper in 1979 [9].They observed that due to high power lines childhood cancer might increases. After that other authors from different countries including USA, Canada, New Zealand, have investigated the effects of Low Frequency Magnetic Fields (ELF - MF) on childhood diseases. Although difference diseases' like central nervous system tumor, Leukemia in children were deeply investigated but acute lymphoblast leukemia (ALL) in children was their main focus.

In order to estimate the intensity of Electromagnetic fields Scandinavian authors Feychting and Ahlbom (1993) [10], Olsen et al (1993) [11], Verkasallo et al (1993) [12], and Tynes and Haldorsen (1997) [13], used calculations based methods. As according to early findings which indicated an increased danger of childhood diseases (Wertheimer 1979) and other Authors concluded that there is a decreased risk of Cancer related diseases' among children exposed to Magnetic field generated by Low Electric lines inside homes (Olsen 1993, Verkasalo 1993, Tynes 1997).However Children living in developing countries in industrial cities are directly exposed to High voltage Power lines due to negligence in housing safety precautions is very dangerous to their health. [2].

In Paper [2-3] it is clearly investigated that there is increased danger of ALL (acute lymphocytic leukemia) due to residing near high voltage overhead Electric lines. Risk factor has a direct relationship with the magnitude of voltage of the Electric lines i.e 132 KV, 230 KV ,400 KV and 800 KV. Normally Distance of 600 m away from Electric lines lower the danger of ALL (acute lymphocytic leukemia) by 0.61folds. Draper investigates that distance of 600 meter is the thresh hold value for measuring risk factor (Draper et al., 2005) [14].It is clear that distances $\leq$ 500 meter and Magnetic Fields > 0.45 μT are two important threshold limits specially for the risk of acute leukemia's in children.

Table 1, shows number of cases of Leukemia and central nervous system tumor among people living close to (220- 400) kV electric lines in Sweden is shown [4].

Table 1.Number of cases
in Sweden 1960-1985.

Diagnosis	Number
Leukemia	325
AML	72
CML	57
ALL	14
CLL	132
Other	50
CNS Tumor	223

*AML = acute myeloid,CML=chronic myeloid leukemia , ALL =acute lymphocytic leukemia , CLL= chronic lymphocytic leukemia.

III. HIGH VOLTAGE DC VERSUS HIGH VOLTAGE AC IN TERMS OF ENVIRONMENTAL EFFECTS

High Voltage Direct Current (HVDC) technology is suitable for certain applications due to its certain advantages. It is mostly suitable for long-distance, weak link interconnections and underwater crossings. . Due to availability of polyphase circuits and Induction Motors in 1880s and 1890s DC lost its initial supremacy and alternating current (AC) defeated the DC due to its greater use.The HVDC projects implemented or under consideration around the world have raised showing interest in the ability of this modern technology

HVDC transmission systems uses two technologies one is voltage sourced converters (VSC). And other is current source converters (CSC).

High voltage Transmission line has two important parameters Current and voltage .Due to skin effect phenomena the conductor DC resistance is less than conductor AC resistance which results in greater loss for AC transmission [5-6].

The combine effects of high voltage transmission systems which include acoustic noise, magnetic fields, corona effects, RF interference, electric fields, and electromagnetic interference, is compared with respect to AC and DC transmissionin the following section.

A. MAGNETIC FIELD:

The magnetic flux density is in inverse proportion to the distance from the conductor. For ± 450 kVDC transmissions line the flux density is about 25 μT, whereas the magnetic field strength of an AC Electric line changes from 10 to 50 μT.

B. ELECTRIC FIELD:

The AC Conductor has its peak electric field beneath the conductor around 20 kV/meter for a ± 450 kV Electric line. The electric field normally changes according to weather and also increases and decreases with humid temperature. DC has fewer electric field problems compare with that of AC because of the constant current phenomena; thus HVDC needs less right-of way (ROW) than horizontal HVAC apparatus and lower Tower height compare with HVAC Electric line of similar rating.To find the ionic current passing through a human being standing beneath an HVDC line at voltage level of ±1000 kV (kilo-Volts) and the capacitive current beneath an HVAC line at a voltage 1150 kV measurements were calculated. These tests concluded that difference in current between the two systems was approximately 100-fold (2-3 μA for the HVDC line and 0.2 mA for the HVAC line) [6-7].

C. CORONA:

Corona effects generated on the surface of Electric power lines produces radiated noise. Corona process depends on the magnitude of the electric field strength, its surface characteristics, the diameter of the line, and weather conditions. Corona effect is produced only by conductors having positive poles in HVDC Systems whereas in an HVAC transmission systems Corona is produced by three phases of A.

D. RADIO, TV, AND TELEPHONE INTERFERENCE:

Parasitic current which is produced due to fast switching process of Thyristor valves (High voltage DC Converters) involving voltage changes and commutation process produces harmonics in the kilohertz and megahertz area of the radio-frequency spectrum. Due to Converter Transformers these high frequencies transfer to the Electric lines. Radio interference is normally lowered by electromagnetic shielding of the Thyristor valves. The radio-interference level of an HVDC over head Electric line is less compare with HVAC overhead Electric line. The value is 40 dB (μV/m) for 0.5MHz, 300 meter away from a conductor for HVDC, and it is 50 dB (μV/m) for 380 kV HVAC overhead Electric line [6-7].

E. ACOUSTIC NOISE:

The allowable limit of the acoustic noise is generally between 35 and 45 dB (A) but it depends on the local atmosphere for any industrial plant .The HVDC transmission system is composed of many equipments and parts which can create noise. Transformer is the main source for the production of noise, and this noise is due to the core flux density. Due to converter transformers, sum of load noises is approximately 10 dB (A) higher than the no load noises, and the frequency content of the emitted noise is evenly spread over 300 to 3000 Hz. The noise problem can be solved with the help of best quality standard equipments, to shield a room or separate the noise producing equipment by a distance. A common HVDC system has a noise intensity less than 10 dB (A) at a distance around 350 m .Bad weather can decrease the Noise levels in a HVDC Electric lines, unlike the noise levels on HVAC Electric lines [8].

IV. CONCLUSION AND FUTURE WORK

This paper clearly shows that there is little risk of magnetic fields by ordinary domestic electric lines but high voltage Electric power lines is a great danger in this regard. High Electric lines above 132Kv can be potential hazards to human beings and children if proper safety distance and

precautions are not maintained. The HVDC and HVAC comparison shows that former has fewer effects on the human beings and environment, thus making HVDC systems friendlier and less hazards to environmen.

In future, we are interrested to inverstigate the hazards discussed in this work using sensors [15] and [16].

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BioInitiative 2012

A Rationale for Biologically-based Exposure Standards for Low-Intensity Electromagnetic Radiation

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BioInitiative Report: A Rationale for Biologically-based Public Exposure Standards for Electromagnetic Radiation at www.bioinitiative.org, December 31, 2012

SECTION I

Preface

Prepared for the BioInitiative Working Group
December 2012

PREFACE

Today, the BioInitiative 2012 Report updates five years of science, public health, public policy and global response to the growing health issue of chronic exposure to electromagnetic fields and radiofrequency radiation in the daily life of billions of people around the world.

The BioInitiative 2012 Report has been prepared by 29 authors from ten countries*, ten holding medical degrees (MDs), 21 PhDs, and three MsC, MA or MPHs. Among the authors are three former presidents of the Bioelectromagnetics Society, and five full members of BEMS. One distinguished author is the Chair of the Russian National Committee on Non-Ionizing Radiation. Another is a Senior Advisor to the European Environmental Agency. As in 2007, each author is responsible for their own chapter.

The great strength of the BioInitiative Report (www.bioinitiative.org) is that it has been done independent of governments, existing bodies and industry professional societies that have clung to old standards. Precisely because of this, the BioInitiative Report presents a solid scientific and public health policy assessment that is evidence-based.

The BioInitiative Report was first posted in August 2007. It still has a significant international viewing audience. Each year, about 100,000 people visit the site. In the five years since it's publication, the BioInitiative website has been accessed over 10.5 million times, or four times every minute. Every five minutes on the average, a person somewhere in the world has logged on. More than 5.2 million files and 1 million pages of information has been downloaded. That is equivalent to more than 93,000 full copies of the 650+ page report (288.5 million kbytes).

The global conversation on why public safety limits for electromagnetic and radiofrequency fields remain thousands of time higher than exposure levels that health studies consistently show to be associated with serious health impacts has intensified since 2007. Roughly, 1800 new studies have been published in the last five years reporting effects at exposure levels ten to hundreds or thousands of times lower than allowed under safety limits in most countries of the world. Yet, no government has instituted comprehensive reforms. Some actions have been taken that highlight partial solutions. The Global Actions chapter presents milestone events that characterize the international 'sea change' of opinion that has taken place, and reports on precautionary advice and actions from around the world.

* Sweden (6), USA (10), India (2), Italy (2), Greece (2), Canada (2), Denmark (1), Austria (2), Slovac Republic (1), Russia (1)

The world's populations – from children to the general public to scientists and physicians – are increasingly faced with great pressures from advertising urging the incorporation of the latest wireless device into their everyday lives. This is occurring even while an elementary understanding the possible health consequences is beyond the ability of most people to grasp. The exposures are invisible, the testing meters are expensive and technically difficult to operate, the industry promotes new gadgets and generates massive advertising and lobbying campaigns that silence debate, and the reliable, non-wireless alternatives (like wired telephones and utility meters) are being discontinued against public will. There is little labeling, and little or no informed choice. In fact there is often not even the choice to stay with safer, wired solutions, as in the case of the 'smart grid' and smart wireless utility metering, an extreme example of a failed corporate-governmental partnership strategy, ostensibly for energy conservation.

A collision of the wireless technology rollout and the costs of choosing unwisely is beginning and will grow. The groundwork for this collision is being laid as a result of increased exposure, especially to radiofrequency fields, in education, in housing, in commerce, in communications and entertainment, in medical technologies and imaging, and in public and private transportation by air, bus, train and motor vehicles. Special concerns are the care of the fetus and newborn, the care for children with learning disabilities, and consideration of people under protections of the Americans With Disabilities Act, which includes people who have become sensitized and physiologically intolerant of chronic exposures. The 2012 Report now addresses these issues as well as presenting an update of issues previously discussed.

Signed: _____ Signed: _____

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I. SUMMARY FOR THE PUBLIC

A. Introduction

You cannot see it, taste it or smell it, but it is one of the most pervasive environmental exposures in industrialized countries today. Electromagnetic radiation (EMR) or electromagnetic fields (EMFs) are the terms that broadly describe exposures created by the vast array of wired and wireless technologies that have altered the landscape of our lives in countless beneficial ways. However, these technologies were designed to maximize energy efficiency and convenience; not with biological effects on people in mind. Based on new studies, there is growing evidence among scientists and the public about possible health risks associated with these technologies.

Human beings are bioelectrical systems. Our hearts and brains are regulated by internal bioelectrical signals. Environmental exposures to artificial EMFs can interact with fundamental biological processes in the human body. In some cases, this can cause discomfort and disease. Since World War II, the background level of EMF from electrical sources has risen exponentially, most recently by the soaring popularity of wireless technologies such as cell phones (two billion and counting in 2006), cordless phones, WI-FI and WI-MAX networks. Several decades of international scientific research confirm that EMFs are biologically active in animals and in humans, which could have major public health consequences.

In today's world, everyone is exposed to two types of EMFs: (1) extremely low frequency electromagnetic fields (ELF) from electrical and electronic appliances and power lines and (2) radiofrequency radiation (RF) from wireless devices such as cell phones and cordless phones, cellular antennas and towers, and broadcast transmission towers. In this report we will use the term EMFs when referring to all electromagnetic fields in general; and the terms ELF and RF when referring to the specific type of exposure. They are both types of non-ionizing radiation, which means that they do not have sufficient energy to break off electrons from their orbits around atoms and ionize (charge) the atoms, as do x-rays, CT scans, and other forms of ionizing radiation. A glossary and definitions are provided in Section 18 to assist you. Some handy definitions you will probably need when reading about ELF and RF in this summary section (the language for measuring it) are shown with the references for this section.

B. Purpose of the Report

This report has been written by 14 (fourteen) scientists, public health and public policy experts to document the scientific evidence on electromagnetic fields. Another dozen outside reviewers have looked at and refined the Report.

The purpose of this report is to assess scientific evidence on health impacts from electromagnetic radiation below current public exposure limits and evaluate what changes in these limits are warranted now to reduce possible public health risks in the future.

Not everything is known yet about this subject; but what is clear is that the existing public safety standards limiting these radiation levels in nearly every country of the world look to be thousands of times too lenient. Changes are needed.

New approaches are needed to educate decision-makers and the public about sources of exposure and to find alternatives that do not pose the same level of possible health risks, while there is still time to make changes.

A working group composed of scientists, researchers and public health policy professionals (The BioInitiative Working Group) has joined together to document the information that must be considered in the international debate about the adequacy (or inadequacy) of existing public exposure standards.

This Report is the product of an international research and public policy initiative to give an overview of what is known of biological effects that occur at low-intensity EMFs exposures (for both radiofrequency radiation RF and power-frequency ELF, and various forms of combined exposures that are now known to be bioactive). The Report examines the research and current standards and finds that these standards are far from adequate to protect public health.

Recognizing that other bodies in the United States, United Kingdom, Australia, many European Union and eastern European countries as well as the World Health Organization are actively debating this topic, the BioInitiative Working Group has conducted a independent science and public health policy review process. The report presents solid science on this issue, and makes recommendations to decision-makers and the public. Conclusions of the individual authors, and overall conclusions are given in Table 2-1 (BioInitiative Overall Summary Chart).

Eleven (11) chapters that document key scientific studies and reviews identifying low-intensity effects of electromagnetic fields have been written by members of the BioInitiative Working Group. Section 16 and 17 have been prepared by public health and policy experts. These sections discusses the standard of evidence which should be applied in public health planning, how the scientific information should be evaluated in the context of prudent public health policy, and identifies the basis for taking precautionary and preventative actions that are proportionate to the knowledge at hand. They also evaluate the evidence for ELF that leads to a recommendation for new public safety limits (not precautionary or preventative actions, as need is demonstrated).

Other scientific review bodies and agencies have reached different conclusions than we have by adopting standards of evidence so unreasonably high as to exclude any conclusions likely to lead to new public safety limits. Some groups are actually recommending a relaxation of the existing (and inadequate) standards. Why is this happening? One reason is that exposure limits for ELF and RF are developed by bodies of scientists and engineers that belong to professional societies who have traditionally developed recommendations; and then government agencies have adopted those recommendations. The standard-setting processes have little, if any, input from other stakeholders outside professional engineering and closely-related commercial interests. Often, the industry view of allowable risk and proof of harm is most influential, rather than what public health experts would determine is acceptable.

Main Reasons for Disagreement among Experts

1) Scientists and public health policy experts use very different definitions of the standard of evidence used to judge the science, so they come to different conclusions about what to do. Scientists do have a role, but it is not exclusive and other opinions matter.
2) We are all talking about essentially the same scientific studies, but use a different way of measuring when "enough is enough" or "proof exists".
3) Some experts keep saying that all studies have to be consistent (turn out the same way every time) before they are comfortable saying an effect exists.
4) Some experts think that it is enough to look only at short-term, acute effects.
5) Other experts say that it is imperative we have studies over longer time (showing the effects of chronic exposures) since that is what kind of world we live in.
6) Some experts say that everyone, including the very young, the elderly, pregnant women, and people with illnesses have to be considered – others say only the average person (or in the case of RF, a six-foot tall man) matter.
7) There is no unexposed population, making it harder to see increased risk of diseases.
8) The lack of consensus about a single biological mechanism of action.
9) The strength of human epidemiological studies reporting risks from ELF and RF exposures, but animal studies don't show a strong toxic effect.
10) Vested interests have a substantial influence on the health debate.

Public Policy Decisions

Safety limits for public exposure to EMFs need to be developed on the basis of interaction among not only scientists, but also public health experts, public policy makers and the general public.

"In principle, the assessment of the evidence should combine with judgment based on other societal values, for example, costs and benefits, acceptability of risks, cultural preferences, etc. and result in sound and effective decision-making. Decisions on these matters are eventually taken as a function of the views, values and interests of the stakeholders participating in the process, whose opinions are then weighed depending on several factors. Scientific evidence perhaps carries, or should carry, relatively heavy weight, but grants no exclusive status; decisions will be evidence-based but will also be based on other factors." (1)

The clear consensus of the BioInitiative Working Group members is that the existing public safety limits are inadequate for both ELF and RF.

These proposals reflect the evidence that a positive assertion of safety with respect to chronic exposure to low-intensity levels of ELF and RF cannot be made. As with many other standards for environmental exposures, these proposed limits may not be totally protective, but more stringent standards are not realistic at the present time. Even a small increased risk for cancer and neurodegenerative diseases translates into an enormous public health consequence. Regulatory action for ELF and preventative actions for RF are warranted at this time to reduce exposures and inform the public of the potential for increased risk; at what levels of chronic exposure these risks may be present; and what measures may be taken to reduce risks.

C. Problems with Existing Public Health Standards (Safety Limits)

Today's public exposure limits for telecommunications are based on the presumption that heating of tissue (for RF) or induced electric currents in the body (for ELF) are the only concerns when living organisms are exposed to RF. These exposures can create tissue heating that is well known to be harmful in even very short-term doses. As such, thermal limits do serve a purpose. For example, for people whose occupations require them to work around radar facilities or RF heat-sealers, or for people who install and service wireless antenna tower, thermally-based limits are necessary to prevent damage from heating (or, in the case of power-frequency ELF from induced current flow in tissues). In the past, scientists and engineers developed exposure standards for electromagnetic radiation based what we now believe are faulty assumptions that the right way to measure how much non-ionizing energy humans can tolerate (how much exposure) without harm is to measure only the heating of tissue (RF) or induced currents in the body (ELF).

In the last few decades, it has been established beyond any reasonable doubt that bioeffects and some adverse health effects occur at far lower levels of RF and ELF exposure where no heating (or induced currents) occurs at all; some effects are shown to occur at several hundred thousand times below the existing public safety limits where heating is an impossibility.

It appears it is the INFORMATION conveyed by electromagnetic radiation (rather than heat) that causes biological changes - some of these biological changes may lead to loss of wellbeing, disease and even death.

Effects occur at non-thermal or low-intensity exposure levels thousands of times below the levels that federal agencies say should keep the public safe. For many new devices operating with wireless technologies, the devices are exempt from any regulatory standards. The existing standards have been proven to be inadequate to control against harm from low-intensity, chronic exposures, based on any reasonable, independent assessment of the scientific literature. It means that an entirely new basis (a biological basis) for new exposure standards is needed. New standards need to take into account what we have learned about the effects of ELF and RF (all non-ionizing electromagnetic radiation and to design new limits based on biologically-

demonstrated effects that are important to proper biological function in living organisms. It is vital to do so because the explosion of new sources has created unprecedented levels of artificial electromagnetic fields that now cover all but remote areas of the habitable space on earth. Mid-course corrections are needed in the way we accept, test and deploy new technologies that expose us to ELF and RF in order to avert public health problems of a global nature.

Recent opinions by experts have documented deficiencies in current exposure standards. There is widespread discussion that thermal limits are outdated, and that biologically-based exposure standards are needed. Section 4 describes concerns expressed by WHO, 2007 in its ELF Health Criteria Monograph; the SCENIHR Report, 2006 prepared for the European Commission; the UK SAGE Report, 2007; the Health Protection Agency, United Kingdom in 2005; the NATO Advanced Research Workshop in 2005; the US Radiofrequency Interagency Working Group in 1999; the US Food and Drug Administration in 2000 and 2007; the World Health Organization in 2002; the International Agency for Cancer Research (IARC, 2001), the United Kingdom Parliament Independent Expert Group Report on Mobile Phones – Stewart Report, 2000) and others.

A pioneer researcher, the late Dr. Ross Adey, in his last publication in Bioelectromagnetic Medicine (P. Roche and M. Markov, eds. 2004) concluded:

> *"There are major unanswered questions about possible health risks that may arise from exposures to various man-made electromagnetic fields where these human exposures are intermittent, recurrent, and may extend over a significant portion of the lifetime of the individual."*
>
> *"Epidemiological studies have evaluated ELF and radiofrequency fields as possible risk factors for human health, with historical evidence relating rising risks of such factors as progressive rural electrification, and more recently, to methods of electrical power distribution and utilization in commercial buildings. Appropriate models describing these bioeffects are based in non-equilibrium thermodynamics, with nonlinear electrodynamics as an integral feature. Heating models, based in equilibrium thermodynamics, fail to explain an impressive new frontier of much greater significance. ..... Though incompletely understood, tissue free radical interactions with magnetic fields may extend to zero field levels." (2)*

There may be no lower limit at which exposures do not affect us. Until we know if there is a lower limit below which bioeffects and adverse health impacts do not occur, it is unwise from a public health perspective to continue "business-as-usual" deploying new technologies that increase ELF and RF exposures, particularly involuntary exposures.

II. SUMMARY OF THE SCIENCE

A. Evidence for Cancer

1. Childhood Leukemia

The evidence that power lines and other sources of ELF are consistently associated with higher rates of childhood leukemia has resulted in the International Agency for Cancer Research (an arm of the World Health Organization) to classify ELF as a Possible Human Carcinogen (in the Group 2B carcinogen list). Leukemia is the most common type of cancer in children.

There is little doubt that exposure to ELF causes childhood leukemia.

The exposure levels for increased risk are quite low – just above background or ambient levels and much lower than current exposure limits. The existing ICNIRP limit is 1000 mG (904 mG in the US) for ELF. Increased risk for childhood leukemia starts at levels almost one thousand times below the safety standard. Leukemia risks for young boys are reported in one study to double at only 1.4 mG and above (7) Most other studies combine older children with younger children (0 to 16 years) so that risk levels do not reach statistical significance until exposure levels reach 2 mG or 3 mG. Although some reviews have combined studies of childhood leukemia in ways that indicate the risk level starts at 4 mG and above; this does not reflect many of the studies reporting elevated risks at the lower exposure levels of 2 mG and 3 mG.

2. Other Childhood Cancers

Other childhood cancers have been studied, including brain tumors, but not enough work has been done to know if there are risks, how high these risks might be or what exposure levels might be associated with increased risks. The lack of certainty about other childhood cancers should not be taken to signal the "all clear"; rather it is a lack of study.

The World Health Organization ELF Health Criteria Monograph No 322 (2007) says that other childhood cancers "cannot be ruled out". (8)

There is some evidence that other childhood cancers may be related to ELF exposure but not enough studies have been done.

Several recent studies provide even stronger evidence that ELF is a risk factor for childhood leukemia and cancers later in life. In the first study (9), children who were recovering in high-ELF environments had poorer survival rates (a 450% increased risk of dying if the ELF fields were 3 mG and above). In the second study, children who were recovering in 2 mG and above ELF environments were 300% more likely to die than children exposed to 1 mG and below. In

this second study, children recovering in ELF environments between 1 and 2 mG also had poorer survival rates, where the increased risk of dying was 280%. (10) These two studies give powerful new information that ELF exposures in children can be harmful at levels above even 1 mG. The third study looked what risks for cancer a child would have later in life, if that child was raised in a home within 300 meters of a high-voltage electric power line. (11) For children who were raised for their first five years of life within 300 meters, they have a life-time risk that is 500% higher for developing some kinds of cancers.

Children who have leukemia and are in recovery have poorer survival rates if their ELF exposure at home (or where they are recovering) is between 1mG and 2 mG in one study; over 3 mG in another study.

Given the extensive study of childhood leukemia risks associated with ELF, and the relatively consistent findings that exposures in the 2 mG to 4 mG range are associated with increased risk to children, a 1 mG limit for habitable space is recommended for new construction. While it is difficult and expensive to retrofit existing habitable space to a 1 mG level, and is also recommended as a desirable target for existing residences and places where children and pregnant women may spend prolonged periods of time.

New ELF public exposure limits are warranted at this time, given the existing scientific evidence and need for public health policy intervention and prevention.

3. Brain Tumors and Acoustic Neuromas

Radiofrequency radiation from cell phone and cordless phone exposure has been linked in more than one dozen studies to increased risk for brain tumors and/or acoustic neuromas (a tumor in the brain on a nerve related to our hearing).

People who have used a cell phone for ten years or more have higher rates of malignant brain tumor and acoustic neuromas. It is worse if the cell phone has been used primarily on one side of the head.

For brain tumors, people who have used a cell phone for 10 years or longer have a 20% increase in risk (when the cell phone is used on both sides of the head). For people who have used a cell phone for 10 years or longer predominantly on one side of the head, there is a 200% increased risk of a brain tumor. This information relies on the combined results of many brain tumor/cell phone studies taken together (a meta-analysis of studies).

People who have used a cordless phone for ten years or more have higher rates of malignant brain tumor and acoustic neuromas. It is worse if the cordless phone has been used primarily on one side of the head.

The risk of brain tumor (high-grade malignant glioma) from cordless phone use is 220% higher (both sides of the head). The risk from use of a cordless phone is 470% higher when used mostly on only one side of the head.

For acoustic neuromas, there is a 30% increased risk with cell phone use at ten years and longer; and a 240% increased risk of acoustic neuroma when the cell phone is used mainly on one side of the head. These risks are based on the combined results of several studies (a meta-analysis of studies).

For use of cordless phones, the increased risk of acoustic neuroma is three-fold higher (310%) when the phone is mainly used on one side of the head.

The current standard for exposure to the emissions of cell phones and cordless phones is not safe considering studies reporting long-term brain tumor and acoustic neuroma risks.

Other indications that radiofrequency radiation can cause brain tumors comes from exposures to low-level RF other than from cell phone or cordless phone use. Studies of people who are exposed in their work (occupational exposure) show higher brain tumor rates as well. Kheifets (1995) reported a 10% to 20% increased risk of brain cancer for those employed in electrical occupations. This meta-analysis surveyed 29 published studies of brain cancer in relation to occupational EMFs exposure or work in electrical occupations. (6). The evidence for a link between other sources of RF exposure like working at a job with EMFs exposure is consistent with a moderately elevated risk of developing brain tumors.

4. *Other Adult Cancers*

There are multiple studies that show statistically significant relationships between occupational exposure and leukemia in adults (see Chapter 11), in spite of major limitations in the exposure assessment. A very recent study by Lowenthal et al. (2007) investigated leukemia in adults in relation to residence near to high-voltage power lines. While they found elevated risk in all adults living near to the high voltage power lines, they found an OR of 3.23 (95% CI = 1.26-8.29) for individuals who spent the first 15 years of life within 300 m of the power line. This study provides support for two important conclusions: adult leukemia is also associated with EMF exposure, and exposure during childhood increases risk of adult disease.

A significant excess risk for adult brain tumors in electrical workers and those adults with occupational EMF exposure was reported in a meta-analysis (review of many individual studies) by Kheifets et al., (1995). This is about the same size risk for lung cancer and secondhand smoke (US DHHS, 2006). A total of 29 studies with populations from 12 countries were included in this meta-analysis. The relative risk was reported as 1.16 (CI = 1.08 – 1.24) or a 16% increased risk

for all brain tumors. For gliomas, the risk estimate was reported to be 1.39 (1.07 – 1.82) or a 39% increased risk for those in electrical occupations. A second meta-analysis published by Kheifets et al., ((2001) added results of 9 new studies published after 1995. It reported a new pooled estimate (OR = 1.16, 1.08 – 1.01) that showed little change in the risk estimate overall from 1995.

The evidence for a relationship between exposure and breast cancer is relatively strong in men (Erren, 2001), and some (by no means all) studies show female breast cancer also to be elevated with increased exposure (see Chapter 12). Brain tumors and acoustic neuromas are more common in exposed persons (see Chapter 10). There is less published evidence on other cancers, but Charles et al. (2003) report that workers in the highest 10% category for EMF exposure were twice as likely to die of prostate cancer as those exposed at lower levels (OR 2.02, 95% CI = 1.34-3.04). Villeneuve et al. (2000) report statistically significant elevations of non-Hodgkin's lymphoma in electric utility workers in relation to EMF exposure, while Tynes et al. (2003) report elevated rates of malignant melanoma in persons living near to high voltage power lines. While these observations need replication, they suggest a relationship between exposure and cancer in adults beyond leukemia.

In total the scientific evidence for adult disease associated with EMF exposure is sufficiently strong for adult cancers that preventive steps are appropriate, even if not all reports have shown exactly the same positive relationship. This is especially true since many factors reduce our ability to see disease patterns that might be related to EMF exposure: there is no unexposed population for comparison, for example, and other difficulties in exposure assessment, The evidence for a relationship between EMF exposure and adult cancers and neurodegenerative diseases is sufficiently strong at present to merit preventive actions to reduce EMF exposure.

5. Breast Cancer

There is rather strong evidence from multiple areas of scientific investigation that ELF is related to breast cancer. Over the last two decades there have been numerous epidemiological studies (studies of human illness) on breast cancer in both men and women, although this relationship remains controversial among scientists. Many of these studies report that ELF exposures are related to increased risk of breast cancer (not all studies report such effects, but then, we do not expect 100% or even 50% consistency in results in science, and do not require it to take reasonable preventative action).

The evidence from studies on women in the workplace rather strongly suggests that ELF is a risk factor for breast cancer for women with long-term exposures of 10 mG and higher.

Breast cancer studies of people who work in relatively high ELF exposures (10 mG and above) show higher rates of this disease. Most studies of workers who are exposed to ELF have defined high exposure levels to be somewhere between 2 mG and 10 mG; however this kind of mixing of relatively low to relatively high ELF exposure just acts to dilute out real risk levels. Many of the occupational studies group exposures so that the highest group is exposed to 4 mG and above. What this means is that a) few people are exposed to much higher levels and b) illness patterns show up at relatively low ELF levels of 4 mG and above. This is another way of demonstrating

that existing ELF limits that are set at 933-1000 mG are irrelevant to the exposure levels reporting increased risks.

Laboratory studies that examine human breast cancer cells have shown that ELF exposure between 6 mG and 12 mG can interfere with protective effects of melatonin that fights the growth of these breast cancer cells. For a decade, there has been evidence that human breast cancer cells grow faster if exposed to ELF at low environmental levels. This is thought to be because ELF exposure can reduce melatonin levels in the body. The presence of melatonin in breast cancer cell cultures is known to reduce the growth of cancer cells. The absence of melatonin (because of ELF exposure or other reasons) is known to result in more cancer cell growth.

Laboratory studies of animals that have breast cancer tumors have been shown to have more tumors and larger tumors when exposed to ELF and a chemical tumor promoter at the same time. These studies taken together indicate that ELF is a likely risk factor for breast cancer, and that ELF levels of importance are no higher than many people are exposed to at home and at work. A reasonable suspicion of risk exists and is sufficient evidence on which to recommend new ELF limits; and to warrant preventative action.

Given the very high lifetime risks for developing breast cancer, and the critical importance of prevention; ELF exposures should be reduced for all people who are in high ELF environments for prolonged periods of time.

Reducing ELF exposure is particularly important for people who have breast cancer. The recovery environment should have low ELF levels given the evidence for poorer survival rates for childhood leukemia patients in ELF fields over 2 mG or 3 mG. Preventative action for those who may be at higher risk for breast cancer is also warranted (particularly for those taking tamoxifen as a way to reduce the risk of getting breast cancer, since in addition to reducing the effectiveness of melatonin, ELF exposure may also reduce the effectiveness of tamoxifen at these same low exposure levels). There is no excuse for ignoring the substantial body of evidence we already have that supports an association between breast cancer and ELF exposure; waiting for conclusive evidence is untenable given the enormous costs and societal and personal burdens caused by this disease.

Studies of human breast cancer cells and some animal studies show that ELF is likely to be a risk factor for breast cancer. There is supporting evidence for a link between breast cancer and exposure to ELF that comes from cell and animal studies, as well as studies of human breast cancers.

These are just some of the cancer issues to discuss. It may be reasonable now to make the assumption that all cancers, and other disease endpoints might be related to, or worsened by exposures to EMFs (both ELF and RF).

If one or more cancers are related, why would not all cancer risks be at issue? It can no longer be said that the current state of knowledge rules out or precludes risks to human health. The

enormous societal costs and impacts on human suffering by not dealing proactively with this issue require substantive public health policy actions; and actions of governmental agencies charged with the protection of public health to act on the basis of the evidence at hand.

B. Changes in the Nervous System and Brain Function

Exposure to electromagnetic fields has been studies in connection with Alzheimer's disease, motor neuron disease and Parkinson's disease. (4) These diseases all involve the death of specific neurons and may be classified as neurodegenerative diseases. There is evidence that high levels of amyloid beta are a risk factor for Alzheimer's disease, and exposure to ELF can increase this substance in the brain. There is considerable evidence that melatonin can protect the brain against damage leading to Alzheimer's disease, and also strong evidence that exposure to ELF can reduce melatonin levels. Thus it is hypothesized that one of the body's main protections against developing Alzheimer's disease (melatonin) is less available to the body when people are exposed to ELF. Prolonged exposure to ELF fields could alter calcium (Ca2+) levels in neurons and induce oxidative stress (4). It is also possible that prolonged exposure to ELF fields may stimulate neurons (particularly large motor neurons) into synchronous firing, leading to damage by the buildup of toxins.

Evidence for a relationship between exposure and the neurodegenerative diseases, Alzheimer's and amyotrophic lateral sclerosis (ALS), is strong and relatively consistent (see Chapter 12). While not every publication shows a statistically significant relationship between exposure and disease, ORs of 2.3 (95% CI = 1.0-5.1 in Qio et al., 2004), of 2.3 (95% CI = 1.6-3.3 in Feychting et al., 2003) and of 4.0 (95% CI = 1.4-11.7 in Hakansson et al., 2003) for Alzheimer's Disease, and of 3.1 (95% CI = 1.0-9.8 in Savitz et al., 1998) and 2.2 (95% CI = 1.0-4.7 in Hakansson et al., 2003) for ALS cannot be simply ignored.

Alzheimer's disease is a disease of the nervous system. There is strong evidence that long-term exposure to ELF is a risk factor for Alzheimer's disease.

Concern has also been raised that humans with epileptic disorders could be more susceptible to RF exposure. Low-level RF exposure may be a stressor based on similarities of neurological effects to other known stressors; low-level RF activates both endogenous opioids and other substances in the brain that function in a similar manner to psychoactive drug actions. Such effects in laboratory animals mimic the effects of drugs on the part of the brain that is involved in addiction.

Laboratory studies show that the nervous system of both humans and animals is sensitive to ELF and RF. Measurable changes in brain function and behavior occur at levels associated with new technologies including cell phone use. Exposing humans to cell phone radiation can change brainwave activity at levels as low as 0.1 watt per kilogram SAR (W/Kg)*** in comparison to the US allowable level of 1.6 W/Kg and the International Commission for Non-ionizing Radiation Protection (ICNIRP) allowable level of 2.0 W/Kg. It can affect memory and learning. It can affect normal brainwave activity. ELF and RF exposures at low levels are able to change behavior in animals.

There is little doubt that electromagnetic fields emitted by cell phones and cell phone use affect electrical activity of the brain.

Effects on brain function seem to depend in some cases on the mental load of the subject during exposure (the brain is less able to do two jobs well simultaneously when the same part of the brain is involved in both tasks). Some studies show that cell phone exposure speeds up the brain's activity level; but also that the efficiency and judgment of the brain are diminished at the same time. One study reported that teenage drivers had slowed responses when driving and exposed to cell phone radiation, comparable to response times of elderly people. Faster thinking does not necessarily mean better quality thinking.

Changes in the way in which the brain and nervous system react depend very much on the specific exposures. Most studies only look at short-term effects, so the long-term consequences of exposures are not known.

Factors that determine effects can depend on head shape and size, the location, size and shape of internal brain structures, thinness of the head and face, hydration of tissues, thickness of various tissues, dialectric constant of the tissues and so on. Age of the individual and state of health also appear to be important variables. Exposure conditions also greatly influence the outcome of studies, and can have opposite results depending on the conditions of exposure including frequency, waveform, orientation of exposure, duration of exposure, number of exposures, any pulse modulation of the signal, and when effects are measured (some responses to RF are delayed). There is large variability in the results of ELF and RF testing, which would be expected based on the large variability of factors that can influence test results. However, it is clearly demonstrated that under some conditions of exposure, the brain and nervous system functions of humans are altered. The consequence of long-term or prolonged exposures have not been thoroughly studied in either adults or in children.

The consequence of prolonged exposures to children, whose nervous systems continue to develop until late adolescence, is unknown at this time. This could have serious implications to adult health and functioning in society if years of exposure of the young to both ELF and RF result in diminished capacity for thinking, judgment, memory, learning, and control over behavior.

People who are chronically exposed to low-level wireless antenna emissions report symptoms such as problems in sleeping (insomnia), fatigue, headache, dizziness, grogginess, lack of concentration, memory problems, ringing in the ears (tinnitus), problems with balance and orientation, and difficulty in multi-tasking. In children, exposures to cell phone radiation have resulted in changes in brain oscillatory activity during some memory tasks. Although scientific studies as yet have not been able to confirm a cause-and-effect relationship; these complaints are

widespread and the cause of significant public concern in some countries where wireless technologies are fairly mature and widely distributed (Sweden, Denmark, France, Germany, Italy, Switzerland, Austria, Greece, Israel). For example, the roll-out of the new 3rd Generation wireless phones (and related community-wide antenna RF emissions in the Netherlands) caused almost immediate public complaints of illness.(5)

Conflicting results from those few studies that have been conducted may be based on the difficulty in providing non-exposed environments for testing to compare to environments that are intentionally exposed. People traveling to laboratories for testing are pre-exposed to a multitude of RF and ELF exposures, so they may already be symptomatic prior to actual testing. Also complicating this is good evidence that RF exposures testing behavioral changes show delayed results; effects are observed after termination of RF exposure. This suggests a persistent change in the nervous system that may be evident only after time has passed, so is not observed during a short testing period.

The effects of long-term exposure to wireless technologies including emissions from cell phones and other personal devices, and from whole-body exposure to RF transmissions from cell towers and antennas is simply not known yet with certainty. However, the body of evidence at hand suggests that bioeffects and health impacts can and do occur at exquisitely low exposure levels: levels that can be thousands of times below public safety limits.

The evidence reasonably points to the potential for serious public health consequences (and economic costs), which will be of global concern with the widespread public use of, and exposure to such emissions. Even a small increase in disease incidence or functional loss of cognition related to new wireless exposures would have a large public health, societal and economic consequences. Epidemiological studies can report harm to health only after decades of exposure, and where large effects can be seen across "average" populations; so these early warnings of possible harm should be taken seriously now by decision-makers.

C. Effects on Genes (DNA)

Cancer risk is related to DNA damage, which alters the genetic blueprint for growth and development. If DNA is damaged (the genes are damaged) there is a risk that these damaged cells will not die. Instead they will continue to reproduce themselves with damaged DNA, and this is one necessary pre-condition for cancer. Reduced DNA repair may also be an important part of this story. When the rate of damage to DNA exceeds the rate at which DNA can be repaired, there is the possibility of retaining mutations and initiating cancer. Studies on how ELF and RF may affect genes and DNA is important, because of the possible link to cancer.
Even ten years ago, most people believed that very weak ELF and RF fields could not possibly have any effect at all on DNA and how cells work (or are damaged and cannot do their work properly). The argument was that these weak fields are do not possess enough energy (are not physically strong enough) to cause damage. However, there are multiple ways we already know about where energy is not the key factor in causing damage. For example, exposure to toxic chemicals can cause damage. Changing the balance of delicate biological processes, including

hormone balances in the body, can damage or destroy cells, and cause illness. In fact, many chronic diseases are directly related to this kind of damage that does not require any heating at all. Interference with cell communication (how cells interact) may either cause cancer directly or promote existing cancers to grow faster.

Using modern gene-testing techniques will probably give very useful information in the future about how EMFs targets and affects molecules in the body. At the gene level, there is some evidence now that EMFs (both ELF and RF) can cause changes in how DNA works. Laboratory studies have been conducted to see whether (and how) weak EMFs fields can affect how genes and proteins function. Such changes have been seen in some, but not all studies.

Small changes in protein or gene expression might be able to alter cell physiology, and might be able to cause later effects on health and well-being. The study of genes, proteins and EMFs is still in its infancy, however, by having some confirmation at the gene level and protein level that weak EMFs exposures do register changes may be an important step in establishing what risks to health can occur.

What is remarkable about studies on DNA, genes and proteins and EMFs is that there should be no effect at all if it were true that EMFs is too weak to cause damage. Scientists who believe that the energy of EMFs is insignificant and unlikely to cause harm have a hard time explaining these changes, so are inclined to just ignore them. The trouble with this view is that the effects are occurring. Not being able to explain these effects is not a good reason to consider them imaginary or unimportant.

The European research program (REFLEX) documented many changes in normal biological functioning in tests on DNA (3). The significance of these results is that such effects are directly related to the question of whether human health risks might occur, when these changes in genes and DNA happen. This large research effort produced information on EMFs effects from more than a dozen different researchers. Some of the key findings included:

> *"Gene mutations, cell proliferation and apoptosis are caused by or result in altered gene and protein expression profiles. The convergence of these events is required for the development of all chronic diseases."* (3)
>
> *"Genotoxic effects and a modified expression of numerous genes and proteins after EMF exposure could be demonstrated with great certainty."* (3)
>
> *"RF-EMF produced genotoxic effects in fibroblasts, HL-60 cells, granulosa cells of rats and neural progenitor cells derived from mouse embryonic stem cells."* (Participants 2, 3 and 4). (3)
>
> *"Cells responded to RF exposure between SAR levels of 0.3 and 2 W/Kg with a significant increase in single- and double-strand DNA breaks and in micronuclei frequency."* (Participants 2, 3 and 4). (3)
>
> *"In HL-60 cells an increase in intracellular generation of free radicals accompanying RF-EMF exposure could clearly be demonstrated."* (Participant 2). (3)
>
> *"The induced DNA damage was not based on thermal effects and arouses consideration about the environmental safety limits for ELF-EMF exposure." (3)*

"The effects were clearly more pronounced in cells from older donors, which could point to an age-related decrease of DNA repair efficiency of ELF-EMF induced DNA strand breaks." (3)

Both ELF and RF exposures can be considered genotoxic (will damage DNA) under certain conditions of exposure, including exposure levels that are lower than existing safety limits.

D. Effects on Stress Proteins (Heat Shock Proteins)

In nearly every living organism, there is a special protection launched by cells when they are under attack from environmental toxins or adverse environmental conditions. This is called a stress response, and what are produced are stress proteins (also known as heat shock proteins). Plants, animals and bacteria all produce stress proteins to survive environmental stressors like high temperatures, lack of oxygen, heavy metal poisoning, and oxidative stress (a cause of premature aging). We can now add ELF and RF exposures to this list of environmental stressors that cause a physiological stress response.

Very low-level ELF and RF exposures can cause cells to produce stress proteins, meaning that the cell recognizes ELF and RF exposures as harmful. This is another important way in which scientists have documented that ELF and RF exposures can be harmful, and it happens at levels far below the existing public safety standards.

An additional concern is that if the stress goes on too long, the protective effect is diminished. There is a reduced response if the stress goes on too long, and the protective effect is reduced. This means the cell is less protected against damage, and it is why prolonged or chronic exposures may be quite harmful, even at very low intensities.

The biochemical pathway that is activated is the same for ELF and for RF exposures, and it is non-thermal (does not require heating or induced electrical currents, and thus the safety standards based on protection from heating are irrelevant and not protective). ELF exposure levels of only 5 to 10 mG have been shown to activate the stress response genes (Table 2, Section 6). The specific absorption rate or SAR is not the appropriate measure of biological threshold or dose, and should not be used as the basis for a safety standard, since SAR only regulates against thermal damage.

E. Effects on the Immune System

The immune system is another defense we have against invading organisms (viruses, bacteria, and other foreign molecules). It protects us against illness, infectious diseases, and tumor cells.

There are many different kinds of immune cells; each type of cell has a particular purpose, and is launched to defend the body against different kinds of exposures that the body determines might be harmful.

There is substantial evidence that ELF and RF can cause inflammatory reactions, allergy reactions and change normal immune function at levels allowed by current public safety standards.

The body's immune defense system senses danger from ELF and RF exposures, and targets an immune defense against these fields, much like the body's reaction in producing stress proteins. These are additional indicators that very low intensity ELF and RF exposures are a) recognized by cells and b) can cause reactions as if the exposure is harmful. Chronic exposure to factors that increase allergic and inflammatory responses on a continuing basis are likely to be harmful to health. Chronic inflammatory responses can lead to cellular, tissue and organ damage over time. Many chronic diseases are thought to be related to chronic problems with immune system function.

The release of inflammatory substances, such as histamine, are well-known to cause skin reactions, swelling, allergic hypersensitivity and other conditions that are normally associated with some kind of defense mechanism. The human immune system is part of a general defense barrier that protects against harmful exposures from the surrounding environment. When the immune system is aggravated by some kind of attack, there are many kinds of immune cells that can respond. Anything that triggers an immune response should be carefully evaluated, since chronic stimulation of the immune system may over time impair the system's ability to respond in the normal fashion.

Measurable physiological changes (mast cell increases in the skin, for example that are markers of allergic response and inflammatory cell response) are triggered by ELF and RF at very low intensities. Mast cells, when activated by ELF or RF, will break (degranulate) and release irritating chemicals that cause the symptoms of allergic skin reactions.

There is very clear evidence that exposures to ELF and RF at levels associated with cell phone use, computers, video display terminals, televisions, and other sources can cause these skin reactions. Changes in skin sensitivity have been measured by skin biopsy, and the findings are remarkable. Some of these reactions happen at levels equivalent to those of wireless technologies in daily life. Mast cells are also found in the brain and heart, perhaps targets of immune response by cells responding to ELF and RF exposures, and this might account for some of the other symptoms commonly reported (headache, sensitivity to light, heart arrhythmias and other cardiac symptoms). Chronic provocation by exposure to ELF and RF can lead to immune dysfunction, chronic allergic responses, inflammatory diseases and ill health if they occur on a continuing basis over time.

These clinical findings may account for reports of persons with electrical hypersensitivity, which is a condition where there is intolerance for any level of exposure to ELF and/or RF. Although there is not yet a substantial scientific assessment (under controlled conditions, if that is even possible); anecdotal reports from many countries show that estimates range from 3% to perhaps 5% of populations, and it is a growing problem. Electrical hypersensitivity, like multiple

chemical sensitivity, can be disabling and require the affected person to make drastic changes in work and living circumstances, and suffer large economic losses and loss of personal freedom. In Sweden, electrohypersensitivity (EHS) is officially recognized as fully functional impairment (i.e., it is not regarded as a disease – see Section 6, Appendix A).

F. Plausible Biological Mechanisms

Plausible biological mechanisms are already identified that can reasonably account for most biological effects reported for exposure to RF and ELF at low-intensity levels (oxidative stress and DNA damage from free radicals leading to genotoxicity; molecular mechanisms at very low energies are plausible links to disease, e.g., effect on electron transfer rates linked to oxidative damage, DNA activation linked to abnormal biosynthesis and mutation). It is also important to remember that traditional public health and epidemiological determinations do not require a proven mechanism before inferring a causal link between EMFs exposure and disease (12). Many times, proof of mechanism is not known before wise public health responses are implemented.

"Obviously, melatonin's ability to protect DNA from oxidative damage has implications for many types of cancer, including leukemia, considering that DNA damage due to free radicals is believed to be the initial oncostatic event in a majority of human cancers [Cerutti et al., 1994]. In addition to cancer, free radical damage to the central nervous system is a significant component of a variety of neurodegenerative diseases of the aged including Alzheimer's disease and Parkinsonism. In experimental animal models of both of these conditions, melatonin has proven highly effective in forestalling their onset, and reducing their severity [Reiter et al., 2001]." (13)

Oxidative stress through the action of free radical damage to DNA is a plausible biological mechanism for cancer and diseases that involve damage from ELF to the central nervous system.

G. Another Way of Looking at EMFs: Therapeutic Uses

Many people are surprised to learn that certain kinds of EMFs treatments actually can heal. These are medical treatments that use EMFs in specific ways to help in healing bone fractures, to heal wounds to the skin and underlying tissues, to reduce pain and swelling, and for other post-surgical needs. Some forms of EMFs exposure are used to treat depression.

EMFs have been shown to be effective in treating conditions of disease at energy levels far below current public exposure standards. This leads to the obvious question. How can scientists dispute the harmful effects of EMF exposures while at the same time using forms of EMF treatment that are proven to heal the body?

Medical conditions are successfully treated using EMFs at levels below current public safety standards, proving another way that the body recognizes and responds to low-intensity EMF signals. Otherwise, these medical treatments could not work. The FDA has approved EMFs medical treatment devices, so is clearly aware of this paradox.

Random exposures to EMFs, as opposed to EMFs exposures done with clinical oversight, could lead to harm just like the unsupervised use of pharmaceutical drugs. This evidence forms a strong warning that indiscriminate EMF exposure is probably a bad idea.

No one would recommend that drugs used in medical treatments and prevention of disease be randomly given to the public, especially to children. Yet, random and involuntary exposures to EMFs occur all the time in daily life.

The consequence of multiple sources of EMFs exposures in daily life, with no regard to cumulative exposures or to potentially harmful combinations of EMFs exposures means several things. First, it makes it very difficult to do clinical studies because it is almost impossible to find anyone who is not already exposed. Second, people with and without diseases have multiple and overlapping exposures – this will vary from person to person.

Just as ionizing radiation can be used to effectively diagnose disease and treat cancer, it is also a cause of cancer under different exposure conditions. Since EMFs are both a cause of disease, and also used for treatment of disease, it is vitally important that public exposure standards reflect our current understanding of the biological potency of EMF exposures, and develop both new public safety limits and measures to prevent future exposures.

III. EMF EXPOSURE AND PRUDENT PUBLIC HEALTH PLANNING

- **The scientific evidence is sufficient to warrant regulatory action for ELF; and it is substantial enough to warrant preventative actions for RF.**
- **The standard of evidence for judging the emerging scientific evidence necessary to take action should be proportionate to the impacts on health and well-being**
- **The exposures are widespread.**
- **Widely accepted standards for judging the science are used in this assessment.**

Public exposure to electromagnetic radiation (power-line frequencies, radiofrequency and microwave) is growing exponentially worldwide. There is a rapid increase in electrification in developing countries, even in rural areas. Most members of society now have and use cordless phones, cellular phones, and pagers. In addition, most populations are also exposed to antennas in communities designed to transmit wireless RF signals. Some developing countries have even given up running land lines because of expense and the easy access to cell phones. Long-term and cumulative exposure to such massively increased RF has no precedent in human history. Furthermore, the most pronounced change is for children, who now routinely spend hours each day on the cell phone. Everyone is exposed to a greater or lesser extent. No one can avoid exposure, since even if they live on a mountain-top without electricity there will likely be exposure to communication-frequency RF exposure. Vulnerable populations (pregnant women, very young children, elderly persons, the poor) are exposed to the same degree as the general population. Therefore it is imperative to consider ways in which to evaluate risk and reduce exposure. Good public health policy requires preventative action proportionate to the potential risk of harm and the public health consequence of taking no action.

IV. RECOMMENDED ACTIONS

A. Defining new exposure standards for ELF

This chapter concludes that new ELF limits are warranted based on a public health analysis of the overall existing scientific evidence. The public health view is that new ELF limits are needed now. They should reflect environmental levels of ELF that have been demonstrated to increase risk for childhood leukemia, and possibly other cancers and neurological diseases. ELF limits should be set below those exposure levels that have been linked in childhood leukemia studies to increased risk of disease, plus an additional safety factor. It is no longer acceptable to build new power lines and electrical facilities that place people in ELF environments that have been determined to be risky. These levels are in the 2 to 4 milligauss* (mG) range, not in the 10s of mG or 100s of mG. The existing ICNIRP limit is 1000 mG (904 mG in the US) for ELF is outdated and based on faulty assumptions. These limits are can no longer be said to be protective of public health and they should be replaced. A safety buffer or safety factor should also be applied to a new, biologically-based ELF limit, and the conventional approach is to add a safety factor lower than the risk level.

While new ELF limits are being developed and implemented, a reasonable approach would be a 1 mG planning limit for habitable space adjacent to all new or upgraded power lines and a 2 mG limit for all other new construction. It is also recommended for that a 1 mG limit be established for existing habitable space for children and/or women who are pregnant (because of the possible link between childhood leukemia and *in utero* exposure to ELF). This recommendation is based on the assumption that a higher burden of protection is required for children who cannot protect themselves, and who are at risk for childhood leukemia at rates that are traditionally high enough to trigger regulatory action. This situation in particular warrants extending the 1 mG limit to existing occupied space. "Establish" in this case probably means formal public advisories from relevant health agencies. While it is not realistic to reconstruct all existing electrical distribution

systems, in the short term; steps to reduce exposure from these existing systems need to be initiated, especially in places where children spend time, and should be encouraged. These limits should reflect the exposures that are commonly associated with increased risk of child hood leukemia (in the 2 to 5 mG range for all children, and over 1.4 mG for children age 6 and younger). Nearly all of the occupational studies for adult cancers and neurological diseases

report their highest exposure category is 4 mG and above, so that new ELF limits should target the exposure ranges of interest, and not necessarily higher ranges.

Avoiding chronic ELF exposure in schools, homes and the workplace above levels associated with increased risk of disease will also avoid most of the possible bioactive parameters of ELF discussed in the relevant literature.

B. Defining preventative actions for reduction in RF exposures

Given the scientific evidence at hand (Chapter 17), the rapid deployment of new wireless technologies that chronically expose people to pulsed RF at levels reported to cause bioeffects, which in turn, could reasonably be presumed to lead to serious health impacts, is of public health concern. Section 17 summarizes evidence that has resulted in a public health recommendation that preventative action is warranted to reduce or minimize RF exposures to the public. There is suggestive to strongly suggestive evidence that RF exposures may cause changes in cell membrane function, cell communication, cell metabolism, activation of proto-oncogenes and can trigger the production of stress proteins at exposure levels below current regulatory limits. Resulting effects can include DNA breaks and chromosome aberrations, cell death including death of brain neurons, increased free radical production, activation of the endogenous opioid system, cell stress and premature aging, changes in brain function including memory loss, retarded learning, slower motor function and other performance impairment in children, headaches and fatigue, sleep disorders, neurodegenerative conditions, reduction in melatonin secretion and cancers (Chapters 5, 6, 7, 8, 9, 10, and 12).

As early as 2000, some experts in bioelectromagnetics promoted a 0.1 μW/cm2 limit (which is 0.614 Volts per meter) for ambient outdoor exposure to pulsed RF, so generally in cities, the public would have adequate protection against involuntary exposure to pulsed radiofrequency (e.g., from cell towers, and other wireless technologies). The Salzburg Resolution of 2000 set a target of 0.1 μW/cm2 (or 0.614 V/m) for public exposure to pulsed radiofrequency. Since then, there are many credible anecdotal reports of unwellness and illness in the vicinity of wireless transmitters (wireless voice and data communication antennas) at lower levels. Effects include sleep disruption, impairment of memory and concentration, fatigue, headache, skin disorders,

visual symptoms (floaters), nausea, loss of appetite, tinnitus, and cardiac problems (racing heartbeat), There are some credible articles from researchers reporting that cell tower -level RF exposures (estimated to be between 0.01 and 0.5 μW/cm2) produce ill-effects in populations living up to several hundred meters from wireless antenna sites.

This information now argues for thresholds or guidelines that are substantially below current FCC and ICNIPR standards for whole body exposure. Uncertainty about how low such standards might have to go to be prudent from a public health standpoint should not prevent reasonable efforts to respond to the information at hand. No lower limit for bioeffects and adverse health effects from RF has been established, so the possible health risks of wireless WLAN and WI-FI systems, for example, will require further research and no assertion of safety at any level of wireless exposure (chronic exposure) can be made at this time. The lower limit for reported human health effects has dropped 100-fold below the safety standard (for mobile phones and PDAs); 1000- to 10,000-fold for other wireless (cell towers at distance; WI-FI and WLAN devices). The entire basis for safety standards is called into question, and it is not unreasonable to question the safety of RF at any level.

A cautionary target level for pulsed RF exposures for ambient wireless that could be applied to RF sources from cell tower antennas, WI-FI, WI-MAX and other similar sources is proposed. The recommended cautionary target level is 0.1 microwatts per centimeter squared (μW/cm2)** (or 0.614 Volts per meter or V/m)** for pulsed RF where these exposures affect the general public; this advisory is proportionate to the evidence and in accord with prudent public health policy. A precautionary limit of 0.1 μW/cm2 should be adopted for outdoor, cumulative RF exposure. This reflects the current RF science and prudent public health response that would reasonably be set for pulsed RF (ambient) exposures where people live, work and go to school. This level of RF is experienced as whole-body exposure, and can be a chronic exposure where there is wireless coverage present for voice and data transmission for cell phones, pagers and PDAs and other sources of radiofrequency radiation. An outdoor precautionary limit of 0.1 μW/cm2 would mean an even lower exposure level inside buildings, perhaps as low as 0.01 μW/cm2. Some studies and many anecdotal reports on ill health have been reported at lower levels than this; however, for the present time, it could prevent some of the most disproportionate burdens placed on the public nearest to such installations. Although this RF target level does not preclude further rollout of WI-FI technologies, we also recommend that wired alternatives to WI-FI be implemented, particularly in schools and libraries so that children are not subjected to

elevated RF levels until more is understood about possible health impacts. This recommendation should be seen as an interim precautionary limit that is intended to guide preventative actions; and more conservative limits may be needed in the future.

Broadcast facilities that chronically expose nearby residents to elevated RF levels from AM, FM and television antenna transmission are also of public health concern given the potential for very high RF exposures near these facilities (antenna farms). RF levels can be in the 10s to several 100's of μW/cm2 in residential areas within half a mile of some broadcast sites (for example, Lookout Mountain, Colorado and Awbrey Butte, Bend, Oregon). Such facilities that are located in, or expose residential populations and schools to elevated levels of RF will very likely need to be re-evaluated for safety.

For emissions from wireless devices (cell phones, personal digital assistant or PDA devices, etc) there is enough evidence for increased risk of brain tumors and acoustic neuromas now to warrant intervention with respect to their use. Redesign of cell phones and PDAs could prevent direct head and eye exposure, for example, by designing new units so that they work only with a wired headset or on speakerphone mode.

These effects can reasonably be presumed to result in adverse health effects and disease with chronic and uncontrolled exposures, and children may be particularly vulnerable. The young are also largely unable to remove themselves from such environments. Second-hand radiation, like second-hand smoke is an issue of public health concern based on the evidence at hand.

V. CONCLUSIONS

• We cannot afford 'business as usual" any longer. It is time that planning for new power lines and for new homes, schools and other habitable spaces around them is done with routine provision for low-ELF environments. The business-as-usual deployment of new wireless technologies is likely to be risky and harder to change if society does not make some educated decisions about limits soon. Research must continue to define what levels of RF related to new wireless technologies are acceptable; but more research should not prevent or delay substantive changes today that might save money, lives and societal disruption tomorrow.

• New regulatory limits for ELF are warranted. ELF limits should be set below those exposure levels that have been linked in childhood leukemia studies to increased risk of disease, plus an additional safety factor. It is no longer acceptable to build new power lines and electrical facilities that place people in ELF environments that have been determined to be risky (at levels generally at 2 mG and above).

• While new ELF limits are being developed and implemented, a reasonable approach would be a 1 mG planning limit for habitable space adjacent to all new or upgraded power lines and a 2 mG limit for all other new construction, It is also recommended for that a 1 mG limit be established for existing habitable space for children and/or women who are pregnant . This recommendation is based on the assumption that a higher burden of protection is required for children who cannot protect themselves, and who are at risk for childhood leukemia at rates that are traditionally high enough to trigger regulatory action. This situation in particular warrants extending the 1 mG limit to existing occupied space. "Establish" in this case probably means formal public advisories from relevant health agencies.

• While it is not realistic to reconstruct all existing electrical distributions systems, in the short term; steps to reduce exposure from these existing systems need to be initiated, especially in places where children spend time, and should be encouraged.

• A precautionary limit of 0.1 (μW/cm2 (which is also 0.614 Volts per meter) should be adopted for outdoor, cumulative RF exposure. This reflects the current RF science and prudent public health response that would reasonably be set for pulsed RF (ambient) exposures where people

live, work and go to school. This level of RF is experienced as whole-body exposure, and can be a chronic exposure where there is wireless coverage present for voice and data transmission for cell phones, pagers and PDAs and other sources of radiofrequency radiation. Some studies and many anecdotal reports on ill health have been reported at lower levels than this; however, for the present time, it could prevent some of the most disproportionate burdens placed on the public nearest to such installations. Although this RF target level does not preclude further rollout of WI-FI technologies, we also recommend that wired alternatives to WI-FI be implemented, particularly in schools and libraries so that children are not subjected to elevated RF levels until more is understood about possible health impacts. This recommendation should be seen as an interim precautionary limit that is intended to guide preventative actions; and more conservative limits may be needed in the future.

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Some Quick Definitions for Units of Measurement of ELF and RF

***Milligauss (mG)**

A milligauss is a measure of ELF intensity and is abbreviated mG. This is used to describe electromagnetic fields from appliances, power lines, interior electrical wiring.

****Microwatts per centimeter squared (μW/cm2)**

Radiofrequency radiation in terms of power density is measured in microwatts per centimeter squared and abbreviated (μW/cm2). It is used when talking about emissions from wireless facilities, and when describing ambient RF in the environment. The amount of allowable RF near a cell tower is 1000 μW/cm2 for some cell phone frequencies, for example.

*****Specific Absorption Rate (SAR is measured in watts per kilogram or W/Kg)**

SAR stands for specific absorption rate. It is a calculation of how much RF energy is absorbed into the body, for example when a cell phone or cordless phone is pressed to the head. SAR is expressed in watts per kilogram of tissue (W/Kg). The amount of allowable energy into 1 gram of brain tissue from a cell phone is 1.6 W/Kg in the US. For whole body exposure, the exposure is 0.8 W/Kg averaged over 30 minutes for the general public. International standards in most countries are similar, but not exactly the same.

Table 1-1 BioInitiative Report Overall Conclusions

OVERALL SUMMARY OF CONCLUSIONS

- The existing ICNIRP and FCC limits for public and occupational exposure to ELF and RF are insufficiently protective of public health.

- Biologically-based public and occupational exposure standards for extra-low frequency and radiofrequency radiation are recommended to address bioeffects and potential adverse health effects of chronic exposure to ELF and RF. These effects are now widely reported to occur at exposure levels significantly below most current national and international limits.

- A biologically-based exposure limit is one that is protective against ELF and RF intensity and modulation factors which, with chronic exposure, can reasonably be presumed to result in significant impacts to health and well-being.

- Research is needed (but should not delay) regulatory action for ELF and substantive *preventative action* for RF proportionate to potential health and wellbeing risks from chronic exposure.

- A biologically-based exposure limit should reflect current scientific knowledge of bioeffects and health effects, and impose new limits based on preventative action as defined by the Precautionary Principle (EEA, 2001).

- Biologically-based exposure standards shall be protective against exposures levels of ELF and RF that affect or change normal biological functioning of organisms (humans). They shall not be based solely on energy absorption or thermal levels of energy input, or resulting tissue heating. They shall be protective against chronic exposure responses.

- The existing standards are based on thermal (heating) limits, and do not address non-thermal (or low-intensity) exposures which are widely reported to cause bioeffects, some likely leading to adverse health effects with chronic exposure.

- Biological effects may include both potential adverse health effects and loss of homeostasis and well-being.

- Biologically-based exposure standards are needed to prevent disruption of normal body processes. Effects are reported for DNS damage (genotoxicity that is directly linked to integrity of the human genome), cellular communication, cellular metabolism and repair, cancer surveillance within the body; and for protection against cancer and neurological diseases. Also reported are neurological effects including impairment of sleep and sleep architecture, cognitive function and memory; depression; cardiac effects; pathological leakage of the blood-brain barrier; and impairment of normal immune function, fertility and reproduction.

- Frequency, intensity, exposure duration, and the number of exposure episodes can affect the response, and these factors can interact with each other to produce different effects. In addition, in order to understand the biological consequences of EMF exposure, one must know whether the effect is cumulative, whether compensatory responses result, and when homeostasis will break down.

- Plausible biological mechanisms that can account for genotoxicity (DNA damage) are already well known (oxidative damage via free-radical actions) although it should also be said that there is not yet proof. *However, proof of mechanism is not required to set prudent public health policy, nor is it mandatory to set new guidelines or limits if adverse health effects occur at lower-than-existing IEEE and ICNIRP standards.*

Table 1-1 BioInitiative Report Overall Conclusions

OVERALL SUMMARY OF CONCLUSIONS (continued

• The SCENIHR report (2007) states that "for breast cancer and cardiovascular disease, recent research has indicated that an association with EMF is unlikely." The WHO ELF Health Criteria Monograph (2007) states "The evidence does not support an association between ELF exposure and cardiovascular disease" and "(T)he evidence for breast cancer was also considered to be effectively negative, while for other diseases it was judged to be inadequate." Neither conclusion is supported by any finding by IARC that would classify EMF as Class 4 (Not A Carcinogen), so it is premature for either group to dismiss the evidence for EMF as a potential risk factor for either breast cancer or for cardiovascular disease.

• The standard for taking action should be precautionary; action should not be deferred while waiting for final proof or causal evidence to be established that EMF is harmful to health and well-being.

• There is great public concern over increasing levels of involuntary exposure to radiofrequency and ELF-modulated radiofrequency exposures from new wireless technologies; there is widespread public resistance to radiofrequency and extra-low frequency radiation exposures which are allowable under current, thermally-based exposure standards.

• There is inadequate warning and notice to the public about possible risks from wireless technologies in the marketplace, which is resulting in adoption and use of technologies that may have adverse health consequences which are still unknown to the public. There is no "informed consent".

• No positive assertion of safety can be made by governments that continue to support and enforce exposure limits for RF and ELF based on ICNIRP or IEEE criteria (or the equivalent). Governments that are considering proposals to relax existing RF and ELF standards should reject these proposals given the weight of scientific evidence that is available; and the clear disconnect between existing public safety limits and their responsibility to provide safe and healthful living environments for all segments of affected populations.

Section 5 Genotoxicity Based on Proteomics

• EMF exposure can change gene and/or protein expression in certain types of cells, even at intensities lower than ICNIRP recommended values.

• The biological consequences of most of the changed genes/proteins are still unclear, and need to be further explored.

• The EMF research community should pay equal attention to the negative reports as to the positive ones. Not only the positive findings need to be replicated, all the negative ones are also needed to be validated.

• The IEEE and WHO data bases do not include the majority of ELF studies (only 6 of 14 in the WHO; 0 of 16 in IEEE); they do include the majority of the RF studies (14 of 16).

Table 1-1 BioInitiative Report Overall Conclusions

Section 6 Genotoxicity (DNA Damage from RF and ELF)

• Toxicity to the genome can lead to a change in cellular functions, cancer, and cell death. One can conclude that under certain conditions of exposure RF is genotoxic. Data available are mainly applicable only to cell phone radiation exposure. One study reports that RF at levels equivalent to the vicinity of base stations and RF- transmission towers is genotoxic and could cause DNA damage (Phillips et al., 1998).

• RF may be considered genotoxic (cause DNA damage). Of 28 total studies on radiofrequency radiation (RF) and DNA damage, 14 studies reported effects (50%) and 14 reported no significant effect (50%). Of 29 total studies on radiofrequency radiation and micronucleation, 16 studies reported effects (55%) and 13 reported no significant effect (45%). Of 21 total studies on chromosome and genome damage from radiofrequency radiation, 13 studies (62%) reported effects and 8 studies (38%) reported no significant effects.

• During cell phone use, a relatively constant mass of tissue in the brain is exposed to radiation at relatively high intensity (peak SAR of 4 - 8 W/kg). Several studies have reported DNA damage at lower than 4 W/kg.

• Since critical genetic mutations in one single cell are sufficient to lead to cancer and there are millions of cells in a gram of tissue, *it is **inconceivable*** that the base of the IEEE SAR standard was changed from averaged over 1 gram of tissue to 10 grams.

• Frequency, intensity, exposure duration, and the number of exposure episodes can affect the response, and these factors can interact with each other to produce different consequences. In order to understand the biological consequence of exposure, one must understand whether the effect is cumulative, whether compensatory responses result and when homeostasis will break down. The choice of cell type or organism studied can also influence the outcome.

• Extremely-low frequency (ELF) has also been shown to be genotoxic and cause DNA damage. Of 41 relevant studies of genotoxicity and ELF exposure, 27 studies (66%) report DNA damage and 14 studies (44%) report no significant effect.

Table 1-1 BioInitiative Report Overall Conclusions

Section 7: Stress Response

- Scientific research on stress proteins has shown that the public is not being protected from potential damage that can be caused by exposure to EMF, both power frequency (ELF) and radio frequency (RF).
- Cells react to an EMF as potentially harmful by producing stress proteins (heat shock proteins or hsp).
- Direct interaction of ELF and RF with DNA has been documented and both activate the synthesis of stress proteins.
- The biochemical pathway that is activated is the same pathway in both ELF and RF and it is non-thermal.
- Many biological systems are affected by EMFs (meaning both ELF and RF trigger stress proteins).
- Many frequencies are active. Field strength and exposure duration thresholds are very low.
- Molecular mechanisms at very low energies are plausible links to disease (e.g., effect on electron transfer rates linked to oxidative damage, DNA activation linked to abnormal biosynthesis and mutation). Cells react to an EMF as potentially harmful.
- Many lines of research now point to changes in DNA electron transfer as a plausible mechanism of action as a result of non-thermal ELF and RF.
- The same biological reaction (production of stress proteins) to an EMF can be activated in more than one division of the EM spectrum.
- Direct interaction of ELF and RF with DNA has been documented and both activate the synthesis of stress proteins.
- Thresholds triggering stress on biological systems occur at environment levels on the order of 0.5 to 1.0 μT for ELF.
- DNA damage (e.g., strand breaks), a cause of cancer, occurs at levels of ELF and RF that are below the safety limits. Also, there is no protection against cumulative effects stimulated by different parts of the EM spectrum.
- The scientific basis for EMF safety limits is flawed when the same biological mechanisms are activated in ELF and RF ranges at vastly different levels of the Specific Absorption Rate (SAR). Activation of DNA to synthesize stress proteins (the stress response) is stimulated in the ELF at a non-thermal SAR level that is over a billion times lower than the same process activated by RF at the thermal level.
- There is a need for a biological standard to replace the thermal standard and to also protect against cumulative effects across the EM spectrum.
- Based on studies of stress proteins, the specific absorption rate (SAR) is not the appropriate measure of biological threshold or dose, and should not be used as a basis for a safety standard since it regulates against thermal effects only.

Table 1-1 BioInitiative Report Overall Conclusions

Section 8 Effects on Immune Function

• Both human and animal studies report large immunological changes with exposure to environmental levels of electromagnetic fields (EMFs). Some of these exposure levels are equivalent to those of e.g. wireless technologies in daily life.

• Measurable physiological changes (mast cells increases, for example) that are bedrock indicators of allergic response and inflammatory conditions are stimulated by EMF exposures.

• Chronic exposure to such factors that increase allergic and inflammatory responses on a continuing basis may be harmful to health.

• It is possible that chronic provocation by exposure to EMF can lead to immune dysfunction, chronic allergic responses, inflammatory responses and ill health if they occur on a continuing basis over time. This is an important area for future research.

• Specific findings from studies on exposures to various types of modern equipment and/or EMFs report over-reaction of the immune system; morphological alterations of immune cells; profound increases in mast cells in the upper skin layers, increased degranulation of mast cells and larger size of mast cells in electrohypersensitive individuals; presence of biological markers for inflammation that are sensitive to EMF exposure at non-thermal levels; changes in lymphocyte viability; decreased count of NK cells; decreased count of T lymphocytes; negative effects on pregnancy (uteroplacental circulatory disturbances and placental dysfunction with possible risks to pregnancy); suppressed or impaired immune function; and inflammatory responses which can ultimately result in cellular, tissue and organ damage.

• Electrical hypersensitivity is reported by individuals in the United States, Sweden, Switzerland, Germany, Denmark and many other countries of the world. Estimates range from 3% to perhaps 10% of populations, and appears to be a growing condition of ill-health leading to lost work and productivity.

• The WHO and IEEE literature surveys do not include all of the relevant papers cited here, leading to the conclusion that evidence has been ignored in the current WHO ELF Health Criteria Monograph; and the proposed new IEEE C95.1 RF public exposure limits (April 2006).

• The current international public safety limits for EMFs do not appear to be sufficiently protective of public health at all, based on the studies of immune function. New, biologically-based public standards are warranted that take into account low-intensity effects on immune function and health that are reported in the scientific literature.

Table 1-1 BioInitiative Report Overall Conclusions

Section 9 Neurology and Behavioral Effects

• Effects on neurophysiological and cognitive functions are quite well established.

• Studies on EEG and brain evoked-potentials in humans exposed to cellular phone radiation predominantly showed positive effects (i.e., positive means the exposure has the ability to change brainwave activity even at exposure levels where no effect would be expected, based on traditional understanding and safety limits).

• There is little doubt that electromagnetic fields emitted by cell phones and cell phone use affect electrical activity in the brain.

• The behavioral consequences of these neuroelectrophysiological changes are not always predictable and research on electrophysiology also indicates that effects are dependent on the mental load of the subjects during exposure, e.g., on the complexity of the task that a subject is carrying out.

• Most of the studies carried out so far are short-term exposure experiments, whereas cell phone use causes long-term repeated exposure of the brain.

• In most of the behavioral experiments, effects were observed after the termination of RF exposure. In some experiments, tests were made days after exposure. This suggests a persistent change in the nervous system after exposure to RF.

• In many instances, neurological and behavioral effects were observed at a SAR less than 4 W/kg. This directly contradicts the basic assumption of the IEEE guideline criterion.

• Caution should be taken in concluding that a neurological effect resulted solely from the action of RF on the central nervous system because it is well known that the functions of the central nervous system can be affected by activity in the peripheral nervous system.

Table 1-1 BioInitiative Report Overall Conclusions

Section 10 Brain Tumors and Acoustic Neuromas

- Studies on brain tumors and use of mobile phones for ≥ 10 years gave a consistent pattern of an increased risk for acoustic neuroma and glioma.

- Cell phone use > 10 years give a consistent pattern of an increased risk for acoustic neuroma and glioma, most pronounced for high-grade glioma. The risk is highest for ipsilateral exposure.

Section 10 Brain Tumors and RF - Epidemiology

- Only a few studies of long-term exposure to low levels of RF fields and brain tumors exist, all of which have methodological shortcomings including lack of quantitative exposure assessment. Given the crude exposure categories and the likelihood of a bias towards the null hypothesis of no association, *the body of evidence is consistent with a moderately elevated risk.*

- Occupational studies indicate that long-term exposure at workplaces may be associated with an elevated brain tumor risk.

- Although the population attributable risk is low (likely below 4%), still more than 1,000 cases per year in the US can be attributed to RF exposure at workplaces alone. Due to the lack of conclusive studies of environmental RF exposure and brain tumors the potential of these exposures to increase the risk cannot be estimated.

- Overall, the evidence suggests that long-term exposure to levels generally below current guideline levels still carry the risk of increasing the incidence of brain tumors.

- Epidemiological studies as reviewed in the IEEE C95.1 revision (2006) are deficient to the extent that the entire analysis is professionally unsupportable. IEEEs dismissal of epidemiological studies that link RF exposure to cancer endpoints should be disregarded, as well as any IEEE conclusions drawn from this flawed analysis of epidemiological studies.

Table 1-1 BioInitiative Report Overall Conclusions

Brain Tumors and Acoustic Neuromas

Additional Data from Section 10

• Mobile phone use increases the risk of acoustic neuroma for persons using a mobile phone 10 years or longer by 30% (when used on both sides of head) to 240% (habitually used on one side of head). This information relies on a meta-analysis of several major studies. For acoustic neuroma studies by Lönn et al., (2004), Christensen et al., (2004) Schoemaker et al., (2005) and Hardell et al., (2006a) all giving results for at least 10 years latency period or more. Overall OR = 1.3, 95 % CI = 0.6-2.8 was obtained increasing to OR = 2.4, 95 % CI = 1.1-5.3 for ipsilateral mobile phone use (Lönn et al., 2004, Schoemaker et al., 2005, Hardell et al., 2006).

• There is observational support for the association between acoustic neuroma and the use of mobile phones since some studies report that the tumor is often located in an anatomical area with high exposure during calls with cellular or cordless phones (Hardell et al., 2003).

• Mobile phone use increases the risk of brain tumors (glioma) for persons using a mobile phone 10 years or longer by 20% (when used on both sides of head) to 200% (habitually used on one side of head). This information relies on a meta-analysis of several major studies. For glioma OR = 1.2, [95 % CI = 0.8-1.9] was calculated (Lönn et al., 2005, Christensen et al., 2005, Hepworth et al., 2006, Schüz et al., 2006, Hardell et al., 2006b, Lahkola et al., 2007). Ipsilateral use yielded OR = 2.0, [95 % CI = 1.2-3.4](Lönn et al., 2005, Hepworth et al., 2006, Hardell et al., 2006b, Lahkola et al., 2007).

• Cordless phone use is also associated with an increased risk for acoustic neuromas and brain tumors (both low-and high-grade gliomas (Hardell et al., 2006 a,b).

• The increased risk of acoustic neuroma from use of a cordless phone for ten years or more was reported to be 310% higher risk (when the cordless phone habitually used on the same-side of the head) in Hardell et al., 2006a.

• The increased risk of high-grade glioma from use of a cordless phone for ten years or more was reported to be 220% higher risk (when cordless used on both sides of head) to 470% higher risk (when cordless used habitually on same side of head) in Hardell et al., 2006b.

• The increased risk of low-grade glioma from use of a cordless phone for ten years or more was reported to be 60% higher risk (when cordless used on both sides of head) to 320% higher risk (when cordless used habitually on same side of head) in Hardell et al., 2006b.

• The current standard for exposure to microwaves during mobile phone use and for cordless phone use is not safe considering studies reporting long-term brain tumor risk.

Table 1-1 BioInitiative Report Overall Conclusions

Section 11 Leukemia

- The balance of evidence suggests that childhood leukemia is associated with exposure to power frequency EMFs either during early life or pregnancy.

- Considering only average ELF (MF flux densities) the population attributable risk is low to moderate. However there is a possibility that other exposure metrics are much more strongly related to childhood leukemia and may account for a substantial proportion of cases. The population attributable fraction ranges between 1-4% (Kheifets et al., 2007); 2-4% (Greenland & Kheifets 2006); and 3.3% (Greenland, 2001) assuming only exposures above 3 to 4 mG (0.3 – 0.4 μT) are relevant. However, if it is not average ELF (average MF flux density) that is the metric causally related to childhood leukemia the attributable fraction can be much higher. Up to 80% of childhood leukemia may be caused by exposure to ELF.

- Other childhood cancers except leukemia have not been studied in sufficient detail to allow conclusions about the existence and magnitude of the risk.

- IEEE guideline levels are designed to protect from short-term immediate effects, long-term effects, such as cancer are evoked by levels several orders of magnitudes below current guideline levels.

- Measures should be implemented to guarantee that exposure due to transmission and distribution lines is below an average of about 1 mG (0.1 μT) and precautionary measures are warranted that can reduce all aspects of exposure.

Table 1-1 BioInitiative Report Overall Conclusions

Section 12 Melatonin, Alzheimers Disease and Breast Cancer

- There is strong epidemiologic evidence that long-term exposure to ELF magnetic field (MF) is a risk factor for Alzheimers disease.

- There is now evidence that 1) high levels of peripheral amyloid beta are a risk factor for AD and 2) medium to high MF exposure can increase peripheral amyloid beta. High brain levels of amyloid beta are also a risk factor for AD and medium to high MF exposure to brain cells likely also increases these cells' production of amyloid beta.

- There is considerable *in vitro* and animal evidence that melatonin protects against Alzheimer's disease. Therefore it is certainly possible that low levels of melatonin production are associated with an increase in the risk of AD.

- There are insufficient studies to formulate an opinion as to whether radiofrequency MF exposure is a risk factor for AD.

- Some studies on EMF show reduced melatonin levels, There is sufficient evidence from *in vitro* and animal studies, from human biomarker studies, from occupational and light-at-night studies, and a single longitudinal study with appropriate collection of urine samples to conclude that high MF exposure may be a risk factor for breast cancer.

- There is rather strong evidence from case-control studies that longterm, high occupational exposure ($\geq$ 10 mG or 1.0 μT)) to ELF magnetic fields is a risk factor for breast cancer.

- Seamstresses are, in fact, one of the most highly MF exposed occupations, with exposure levels generally above 10 mG (1.0 μT) over a significant proportion of the workday. They have also been consistently found to be at higher risk of Alzheimer's disease and (female) breast cancer. This occupation deserves attention in future studies.

- There are no studies of RF magnetic fields on breast cancer that do not exclude ELF magnetic field, so that predictions of RF magnetic field alone on breast cancer cannot be assessed at this time.

Table 1-1 BioInitiative Report Overall Conclusions

Section 13 Melatonin – Cell and Animal Studies

• An association between power-frequency electromagnetic fields (ELF) and breast cancer is strongly supported in the scientific literature by a constellation of relevant scientific papers providing mutually-reinforcing evidence from cell and animal studies.

• ELF at environmental levels negatively affects the oncostatic effects of both melatonin and tamoxifen on human breast cancer cells at common environmental levels of ELF exposure at 6 to 12 mG (0.6 to 1.2 μT). Epidemiological studies over the last two decades have reported increased risk of male and female breast cancer with exposures to residential and occupational levels of ELF. Animal studies have reported increased mammary tumor size and incidence in association with ELF exposure.

• ELF limits for public exposure should be revised to reflect increased risk of breast cancer at environmental levels possibly as low as 2 mG or 3 mG (o.2 to 0.3 μT); certainly as low as 4 mG (0.4 μT).

Section 14 Effects of Modulation of Signal

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

• Modulation signals may interfere with normal, non-linear biological processes.

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

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

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

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

Table 1-1 BioInitiative Report Overall Conclusions

Section 14 **Effects of Modulation of Signal** (continued)

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

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

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

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

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

Section 15 **Therapeutic Uses of EMF at Low-Intensity Levels**

• EMFs are both a cause of disease, and also used for treatment of disease (at levels far below existing public exposure standards).

• Electromagnetic fields are widely used in therapeutic medical applications.

• Proof of effectiveness has been demonstrated in numerous clinical applications of low-intensity ELF and RF.

• EMFs have been shown to be effective in treating conditions of disease at energy levels far below current public exposure standards.

• Indiscriminate EMF exposure is ill advised at even at common environmental levels.

• Multiple sources of EMF exposure in daily life, and cumulative exposures to potentially harmful combinations of EMF are ignored – we don't even study it properly yet.

Table 1-1 BioInitiative Report Overall Conclusions

Section 16 The Precautionary Principle

• The Precautionary Principle has been developed to help justify public policy action on the protection of health where there are plausible, serious and irreversible hazards from current and future exposures and where there are many uncertainties and much scientific ignorance. EMF is characterized by such circumstances.

• The lessons from the histories of most well known hazards show that precautionary- based yet proportionate measures taken in response to robust early warnings can avoid the kinds of costs incurred by asbestos, smoking, PCBs ,X rays etc. Such lessons are relevant to the EMF issue.

• Policymakers need to be aware of the systematic biases within the environmental health science against finding a true hazard, in order to not compromise scientific integrity. However, this bias can lead to the health of people or environments being compromised.

• The Precautionary Principle introduces the use of different levels of proof (or strengths of evidence) to justify actions to reduce exposure, where the level of proof chosen depends upon the nature and distribution of the costs of being wrong in acting, or not acting; the benefits of the agent or substance in question; the availability of alternatives, etc. Waiting for high levels of scientific proof of causality, or for knowledge about mechanisms of action, can be very expensive in terms of compensation, health care, job losses, reductions in public trust of scientists etc.

• The level of proof chosen to justify action does not determine any particular policy measure, or type of action. This is dependent on factors such as the costs of different measures, equity, the origins of the risk, ie voluntary or imposed, etc.

• There is a need to involve stakeholders in helping to frame problems for risk assessments and to choose appropriate levels of proof and types of actions to reduce exposure.

Table 1-1 BioInitiative Report Overall Conclusions

Section 17: Key Scientific Evidence and Public Health Policy Recommendations

• We cannot afford 'business as usual" any longer. It is time that planning for new power lines and for new homes, schools and other habitable spaces around them is done with provision for low-ELF environments. The business-as-usual deployment of new wireless technologies is likely to be risky and harder to change if society does not make some educated decisions about limits soon. Research must continue to define what levels of RF related to new wireless technologies are acceptable; but more research should not prevent or delay substantive changes today that might save money, lives and societal disruption tomorrow.

• New regulatory limits for ELF are warranted. ELF limits should be set below those exposure levels that have been linked in childhood leukemia studies to increased risk of disease, plus an additional safety factor. It is no longer acceptable to build new power lines and electrical facilities that place people in ELF environments that have been determined to be risky (at levels generally at 2 mG (0.2 μT) and above).

• While new ELF limits are being developed and implemented, a reasonable approach would be a 1 mG (0.1 μT) planning limit for habitable space adjacent to all new or upgraded power lines and a 2 mG (0.2 μT) limit for all other new construction, It is also recommended for that a 1 mG (0,1 μT) limit be established for existing habitable space for children and/or women who are pregnant . This recommendation is based on the assumption that a higher burden of protection is required for children who cannot protect themselves, and who are at risk for childhood leukemia at rates that are traditionally high enough to trigger regulatory action. This situation in particular warrants extending the 1 mG (0.1 μT) limit to existing occupied space. "Establish" in this case probably means formal public advisories from relevant health agencies.

• While it is not realistic to reconstruct all existing electrical distributions systems, in the short term; steps to reduce exposure from these existing systems need to be initiated, especially in places where children spend time, and should be encouraged.

• A precautionary limit of 0.1 μW/cm2 (which is also 0.614 Volts per meter) should be adopted for outdoor, cumulative RF exposure. This reflects the current RF science and prudent public health response that would reasonably be set for pulsed RF (ambient) exposures where people live, work and go to school. This level of RF is experienced as whole-body exposure, and can be a chronic exposure where there is wireless coverage present for voice and data transmission for cell phones, pagers and PDAs and other sources of radiofrequency radiation. Some studies and many anecdotal reports on ill health have been reported at lower levels than this; however, for the present time, it could prevent some of the most disproportionate burdens placed on the public nearest to such installations. Although this RF target level does not preclude further rollout of WI-FI technologies, we also recommend that wired alternatives to WI-FI be implemented, particularly in schools and libraries so that children are not subjected to elevated RF levels until more is understood about possible health impacts. This recommendation should be seen as an interim precautionary limit that is intended to guide preventative actions; and more conservative limits may be needed in the future.

Table 1-1 BioInitiative Report Overall Conclusions

Section 17: Key Scientific Evidence and Public Health Policy Recommendations (continued)

• New public safety limits should be developed and implemented for ELF (50 Hz and 60 Hz electrical power frequencies). ELF limits should be set below those exposure levels that have been linked in childhood leukemia studies to increased risk of disease, plus an additional safety factor.

• Guidance should be provided to electric utilities on the need to reduce ELF exposures in siting and construction of new power lines and substations. Mitigation of existing sources of ELF over 1 mG (0.1 μT) should be encouraged, particularly where children and women who are pregnant, or who may be come pregnant spend significant portions of their time.

• Requests for measurement and monitoring of ELF and RF should be provided by utilities (for power line and household ELF) and by employers (for workplace ELF and RF) ,and those who request information should receive full results of such surveys on request.

• International health organizations and agencies should issue public health advisories for those exposed to levels of ELF and RF implicated with increased risks from cancer/neurodegenerative diseases and memory/learning/immune/stress responses. These advisories should address both residential and occupational exposures.

• Reliable, unbiased information should be developed and distributed through a clearinghouse that is available to the public. Scientific, public health and policy option information should be provided for independent review at an affordable cost to the public. Research articles and prudent avoidance strategies should be made available in many languages.

• Cell phones and other wireless devices should be redesigned to operate only on speaker-phone mode or text message mode.

• Restrictions should be placed on the sale and advertising of cell phones and other wireless devices to children age 0 to 18 years.

• All countries should continue to provide wired phone service; and should be strongly discouraged from phasing it out; including pay telephones in public places.

• Manufacturers of devices that operate with wireless features should be required to carry SAR level information and warning labels on the outside packaging (not hidden inside). Wireless devices that create elevated RF levels for the user should be required to warn the user of possible adverse effects on memory and learning, cognitive function, sleep disruption and insomnia, mood disorders, balance, headache, fatigue, ringing in the ears (tinnitus), immune function, and other adverse symptoms of use.

• Warning labels on cell phones and PDAs (personal digital assistant devices) and other wireless devices are needed to alert users to excessively high ELF emissions from the switching battery pack, and require labels to list mitigation measures to reduce exposure (do not wear on or near body in "ON-Receive" position; use only with earpiece or on speaker mode, etc).

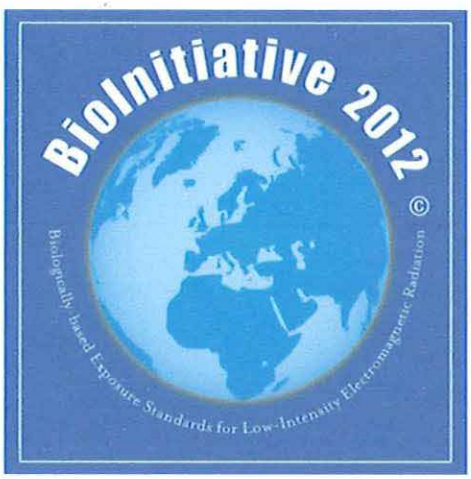
• Disclosure should be provided to the public on the location and operating characteristics of all wireless antenna sites in a fashion easily accessible to the public so informed choices can be made about where to live, shop, work and go to school. Such information should mandatorily include cumulative RF/MW exposures based on calculations from FCC OET Bulletin 65 (or equivalent) at ground level and second story level in increments of 50 feet outward from the facility to a power density of 0.1 μW/cm2 or 0.614 V/m. Signage for the public should be a mandatory condition of approval for all sites, and should be kept current. Public agencies that approve and monitor wireless sites should require the applicant to identify locations of wireless facilities.

Table 1-1 BioInitiative Report Overall Conclusions

Section 17: Key Scientific Evidence and Public Health Policy Recommendations (continued)

• Mobile phone - free and WI-FI-free public areas should be established in areas where the public congregates and can have a reasonable expectation of safety; including airports, public shopping, hospitals, libraries, medical clinics, convalescent homes and assisted living facilities, theatres, restaurants, parks, etc.

• Health agencies and school districts should strongly discourage or prohibit cell towers on or near (within 1000' of) school properties, should delay any new WLAN installations in school classrooms, pre-schools and day-care facilities; and should either remove or disable existing wireless facilities, or be required to offer classrooms with no RF exposure to those families who choose not to have their children involuntarily exposed.



SECTION 1

Summary for the Public
(2012 Supplement)

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I. SUMMARY FOR THE PUBLIC

A. Introduction

The BioInitiative Working Group concluded in 2007 that existing public safety limits were inadequate to protect public health, and agreed that new, biologically-based public safety limits were needed five years ago. The BioInitiative Report was been prepared by more than a dozen world-recognized experts in science and public health policy; and outside reviewers also contributed valuable content and perspective.

From a public health standpoint, experts reasoned that it was not in the public interest to wait. In 2007, the evidence at hand coupled with the enormous populations placed at possible risk was argued as sufficient to warranted strong precautionary measures for RFR, and lowered safety limits for ELF-EMF. The ELF recommendations were biologically-based and reflected the ELF levels consistently associated with increased risk of childhood cancer, and further incorporated a safety factor that is proportionate to others used in similar circumstances. The public health cost of doing nothing was judged to be unacceptable in 2007.

What has changed in 2012? In twenty-four technical chapters, the contributing authors discuss the content and implications of about 1800 new studies. Overall, these new studies report abnormal gene transcription (Section 5); genotoxicity and single-and double-strand DNA damage (Section 6); stress proteins because of the fractal RF-antenna like nature of DNA (Section 7); chromatin condensation and loss of DNA repair capacity in human stem cells (Sections 6 and 15); reduction in free-radical scavengers - particularly melatonin (Sections 5, 9, 13, 14, 15, 16 and 17); neurotoxicity in humans and animals (Section 9); carcinogenicity in humans (Sections 11, 12, 13, 14, 15, 16 and 17); serious impacts on human and animal sperm morphology and function (Section 18); effects on the fetus, neonate and offspring (Section 18 and 19); effects on brain and cranial bone development in the offspring of animals that are exposed to cell phone radiation during pregnancy (Sections 5 and 18); and findings in autism spectrum

disorders consistent with EMF/RFR exposure. This is only a snapshot of the evidence presented in the BioInitiative 2012 updated report.

There is reinforced scientific evidence of risk from chronic exposure to low-intensity electromagnetic fields and to wireless technologies (radiofrequency radiation including microwave radiation). The levels at which effects are reported to occur is lower by hundreds of times in comparison to 2007. The range of possible health effects that are adverse with chronic exposures has broadened. There has been a big increase in the number of studies looking at the effects of cell phones (on the belt, or in the pocket of men radiating only on standby mode) and from wireless laptops on impacts to sperm quality and motility; and sperm death (fertility and reproduction). In other new studies of the fetus, infant and young child, and child-in-school – there are a dozen or more new studies of importance. There is more evidence that such exposures damage DNA, interfere with DNA repair, evidence of toxicity to the human genome (genes), more worrisome effects on the nervous system (neurology) and more and better studies on the effects of mobile phone base stations (wireless antenna facilities or cell towers) that report lower RFR levels over time can result in adverse health impacts.

Importantly, some very large studies were completed on brain tumor risk from cell phone use. The 13-country World Health Organization Interphone Final study (2010) produced evidence (although highly debated among fractious members of the research committee) that cell phone use at 10 years or longer, with approximately 1,640 hours of cumulative use of a cell and/or cordless phone approximately doubles glioma risk in adults. Gliomas are aggressive, malignant tumors where the average life-span following diagnosis is about 400 days. That brain tumors should be revealed in epidemiological studies at ONLY 10 or more years is significant; x-ray and other ionizing radiation exposures that can also cause brain tumors take nearly 15-20 years to appear making radiofrequency/microwave radiation from cell phones a very effective cancer-causing agent. Studies by Lennart Hardell and his research team at Orebro University in Sweden later showed that children who start using a mobile phone in early years have more than a 5-fold (more than a 500%) risk for developing a glioma by the time they are in the 20-29

year age group. This has significant ramifications for public health intervention.

In short order, in 2011 the World Health Organization International Agency on Cancer Research (IARC) classified radiofrequency radiation as a Group 2B Possible Human Carcinogen, joining the IARC classification of ELF-EMF that occurred in 2001. The evidence for carcinogenicity for RFR was primarily from cell phone/brain tumor studies but by IARC rules, applies to all RFR exposures (it applies to the exposure, not just to devices like cell phones or cordless phones that emit RFR).

B. Why We Care?

The stakes are very high. Exposure to electromagnetic fields (both extremely low-frequency ELF-EMF from power frequency sources like power lines and appliances; and radiofrequency radiation or RFR) has been linked to a variety of adverse health outcomes that may have significant public health consequences. The most serious health endpoints that have been reported to be associated with extremely low frequency (ELF) and/or radiofrequency radiation (RFR) include childhood and adult leukemia, childhood and adult brain tumors, and increased risk of the neurodegenerative diseases, Alzheimer's and amyotrophic lateral sclerosis (ALS). In addition, there are reports of increased risk of breast cancer in both men and women, genotoxic effects (DNA damage, chromatin condensation, micronucleation, impaired repair of DNA damage in human stem cells), pathological leakage of the blood–brain barrier, altered immune function including increased allergic and inflammatory responses, miscarriage and some cardiovascular effects. Insomnia (sleep disruption) is reported in studies of people living in very low-intensity RF environments with WI-FI and cell tower-level exposures. Short-term effects on cognition, memory and learning, behavior, reaction time, attention and concentration, and altered brainwave activity (altered EEG) are also reported in the scientific literature. Biophysical mechanisms that may account for such effects can be found in various articles and reviews (Sage, 2012).

Traditional scientific consensus and scientific method is but one contributor to deciding when to take public health action; rather, it is one of several voices that are important in determining when new actions are warranted to protect public health. Certainly it is important, but not the exclusive purview of scientists alone to determine for all of society when changes are in the public health interest and welfare of children.

C. Do We Know Enough To Take Action?

Human beings are bioelectrical systems. Our hearts and brains are regulated by internal bioelectrical signals. Environmental exposures to artificial EMFs can interact with fundamental biological processes in the human body. In some cases, this may cause discomfort, or sleep disruption, or loss of well-being (impaired mental functioning and impaired metabolism) or sometimes, maybe it is a dread disease like cancer or Alzheimer's disease. It may be interfering with one's ability to become pregnant, or to carry a child to full term, or result in brain development changes that are bad for the child. It may be these exposures play a role in causing long-term impairments to normal growth and development of children, tipping the scales away from becoming productive adults. The use of common wireless devices like wireless laptops and mobile phones requires urgent action simply because the exposures are everywhere in daily life; we need to define whether and when these exposures can damage health, or the children of the future who will be born to parents now immersed in wireless exposures.

Since World War II, the background level of EMF from electrical sources has risen exponentially, most recently by the soaring popularity of wireless technologies such as cell phones (six billion in 2011-12, up from two billion in 2006), cordless phones, WI-FI ,WI-MAX and LTE networks. Some countries are moving from telephone landlines (wired) to wireless phones exclusively, forcing wireless exposures on uninformed populations around the world. These wireless exposures at the same time are now classified by the world's highest authority on cancer assessment, the World Health Organization International Agency for Research on Cancer. to be a possible risk to health. Several decades of international scientific research confirm that EMFs are biologically active in animals and in humans. Now, the balance has clearly shifted to one

of 'presumption of possible adverse effects' from chronic exposure. It is difficult to conclude otherwise, when the bioeffects that are clearly now occurring lead to such conditions as pathological leakage of the blood-brain barrier (allowing toxins into the brain tissues); oxidative damage to DNA and the human genome, preventing normal DNA repair in human stem cells; interfering with health sperm production; producing poor quality sperm or low numbers of healthy sperm, altering fetal brain development that may be fundamentally tied to epidemic rates of autism and problems in school children with memory, attention, concentration, and behavior; and leading to sleep disruptions that undercut health and healing in numerous ways.

In today's world, everyone is exposed to two types of EMFs: (1) extremely low frequency electromagnetic fields (ELF) from electrical and electronic appliances and power lines and (2) radiofrequency radiation (RFR) from wireless devices such as cell phones and cordless phones, cellular antennas and towers, and broadcast transmission towers. In this report we will use the term EMFs when referring to all electromagnetic fields in general; and the terms ELF or RFR when referring to the specific type of exposure. They are both types of non-ionizing radiation, which means that they do not have sufficient energy to break off electrons from their orbits around atoms and ionize (charge) the atoms, as do x-rays, CT scans, and other forms of ionizing radiation. A glossary and definitions are provided in this report to assist you. Some handy definitions you will probably need when reading about ELF and RF in this summary section (the language for measuring it) are shown in Section 26 – Glossary.

II. SUMMARY OF THE SCIENCE

A. Evidence for Damage to Sperm and Reproduction

Several international laboratories have replicated studies showing adverse effects on sperm quality, motility and pathology in men who use and particularly those who wear a cell phone, PDA or pager on their belt or in a pocket (See Section 18 for references - Agarwal et al, 2008; Agarwal et al, 2009; Wdowiak et al, 2007; De Iuliis et al, 2009; Fejes et al, 2005; Aitken et al, 2005; Kumar, 2012). Other studies conclude that usage of

cell phones, exposure to cell phone radiation, or storage of a mobile phone close to the testes of human males affect sperm counts, motility, viability and structure (Aitken et al, 2004; Agarwal et al, 2007; Erogul et al, 2006). Animal studies have demonstrated oxidative and DNA damage, pathological changes in the testes of animals, decreased sperm mobility and viability, and other measures of deleterious damage to the male germ line (Dasdag et al, 1999; Yan et al, 2007; Otitoloju et al, 2010; Salama et al, 2008; Behari et al, 2006; Kumar et al, 2012). There are fewer animal studies that have studied effects of cell phone radiation on female fertility parameters. Panagopoulous et al (2012) report decreased ovarian development and size of ovaries, and premature cell death of ovarian follicles and nurse cells in *Drosophila melanogaster*. Gul et al (2009) reported rats exposed to stand-by level RFR (phones on but not transmitting calls) had a decrease in the number of ovarian follicles in pups born to these exposed dams. Magras and Xenos (1997) reported irreversible infertility in mice after five (5) generations of exposure to RFR at cell phone tower exposure levels of less than one microwatt per centimeter squared (μW/cm2). See Section 18 for references.

HUMAN SPERM AND THEIR DNA ARE DAMAGED

Human sperm are damaged by cell phone radiation at very low intensities (0.00034 – 0.07 μW/cm2). There is a veritable flood of new studies reporting sperm damage in humans and animals, leading to substantial concerns for fertility, reproduction and health of the offspring (unrepaired de novo mutations in sperm). Exposure levels are similar to those resulting from wearing a cell phone on the belt, or in the pants pocket, or using a wireless laptop computer on the lap. Sperm lack the ability to repair DNA damage.

B. Evidence that Children are More Vulnerable: Many studies demonstrate that children are more sensitive to environmental toxins of various kinds (See Section 24 for references - Barouki et al, 2012; Preston, 2004; WHO, 2002; Gee, 2009; Sly and Carpenter, 2012). Some studies report that the fetus and young children are at greater risk than are adults from exposure to environmental toxins. This is consistent with a large body of information showing that the fetus and young child are more vulnerable than older persons are to chemicals and ionizing radiation. The US Environmental Protection Agency (EPA) proposes a 10-fold risk adjustment for the first 2 years of life exposure to

carcinogens, and a 3-fold adjustment for years 3 to 5. These adjustments do not deal with fetal risk, and the possibility of extending this protection to the fetus should be examined, because of fetus' rapid organ development.

> The Presidential Cancer Panel (2010) found that children "*are at special risk due to their smaller body mass and rapid physical development, both of which magnify their vulnerability to known carcinogens, including radiation.*"

> The American Academy of Pediatrics, in a letter to Congressman Dennis Kucinich dated 12 December 2012 states: "*Children are disproportionately affected by environmental exposures, including cell phone radiation. The differences in bone density and the amount of fluid in a child's brain compared to an adult's brain could allow children to absorb greater quantities of RF energy deeper into their brains than adults. It is essential that any new standards for cell phones or other wireless devices be based on protecting the youngest and most vulnerable populations to ensure thay are safeguarded through their lifetimes.*"

The issue around exposure of children to RFR is of critical importance. There is overwhelming evidence that children are more vulnerable than adults to many different exposures (Sly and Carpenter, 2012), including RFR, and that the diseases of greatest concern are cancer and effects on neurodevelopment. Yet parents place RFR-emitting baby monitors in cribs, provide very young children with wireless toys, and give cell phones to young children, usually without any knowledge of the potential dangers. A growing concern is the movement to make all student computer laboratories in schools wireless. A wired computer laboratory will not increase RFR exposure, and will provide safe access to the internet (Section, Sage and Carpenter, BioInitiative 2012 Report).

C. Evidence for Fetal and Neonatal Effects: Effects on the developing fetus from *in-utero* exposure to cell phone radiation have been observed in both human and animal studies since 2006. Sources of fetal and neonatal exposures of concern include cell phone radiation (both paternal use of wireless devices worn on the body and maternal use of wireless phones during pregnancy). Sources include exposure to whole-body RFR from base stations and WI-FI, use of wireless laptops, use of incubators for newborns with excessively high ELF-EMF levels resulting in altered heart rate variability and reduced melatonin levels in newborns, fetal exposures to MRI of the pregnant

mother, and greater susceptibility to leukemia and asthma in the child where there have been maternal exposures to ELF-EMF. Divan et al (2008) found that children born to mothers who used cell phones during pregnancy develop more behavioral problems by the time they have reached school age than children whose mothers did not use cell phones during pregnancy. Children whose mothers used cell phones during pregnancy had 25% more emotional problems, 35% more hyperactivity, 49% more conduct problems and 34% more peer problems (Divan et al, 2008). Aldad et al (2012) showed that cell phone radiation significantly altered fetal brain development and produced ADHD-like behavior in the offspring of pregnant mice. Exposed mice had a dose-dependent impaired glutamatergic synaptic transmission onto Layer V pyramidal neurons of the prefrontal cortex. The authors conclude the behavioral changes were the result of altered neuronal developmental programming *in utero*. Offspring mice were hyperactive and had impaired memory function and behavior problems, much like the human children in Divan et al (2008). See Sections 19 and 20 for references. Fragopoulou et al (2012) reports that brain astrocyte development followed by proteomic studies is adversely affected by DECT (cordless phone radiation) and mobile phone radiation.

Fetal (*in-utero*) and early childhood exposures to cell phone radiation and wireless technologies in general may be a risk factor for hyperactivity, learning disorders and behavioral problems in school.

Common sense measures to limit both ELF-EMF and RF EMF in these populations is needed, especially with respect to avoidable exposures like incubators that can be modified; and where education of the pregnant mother with respect to laptop computers, mobile phones and other sources of ELF-EMF and RF EMF are easily instituted.

A precautionary approach may provide the frame for decision-making where remediation actions have to be realized to prevent high exposures of children and pregnant woman.

(Bellieni and Pinto, 2012 – Section 19)

D. Evidence for Effects on Autism (Autism Spectrum Disorders)

Physicians and health care practitioners should raise the visibility of EMF/RFR as a plausible environmental factor in ASD clinical evaluations and treatment protocols. Reducing or removing EMF and wireless RFR stressors from the environment is a reasonable precautionary action given the overall weight of evidence for a link to ASDs.

Several thousand scientific studies over four decades point to serious biological effects and health harm from EMF and RFR. These studies report genotoxicity, single- and double-strand DNA damage, chromatin condensation, loss of DNA repair capacity in human stem cells, reduction in free-radical scavengers (particularly melatonin), abnormal gene transcription, neurotoxicity, carcinogenicity, damage to sperm morphology and function, effects on behavior, and effects on brain development in the fetus of human mothers that use cell phones during pregnancy. Cell phone exposure has been linked to altered fetal brain development and ADHD-like behavior in the offspring of pregnant mice.

Many disrupted physiological processes and impaired behaviors in people with ASDs closely resemble those related to biological and health effects of EMF/RFR exposure. Biomarkers and indicators of disease and their clinical symptoms have striking similarities. At the cellular and molecular level many studies of people with ASDs have identified oxidative stress and evidence of free-radical damage, as well as deficiencies of antioxidants such as glutathione. Elevated intracellular calcium in ASDs can be associated with genetic mutations but more often may be downstream of inflammation or chemical exposures. Lipid peroxidation of cell membranes, disruption of calcium metabolism, altered brain wave activity and consequent sleep, behavior and immune disfunction, pathological leakage of critical barriers between gut and blood or blood and brain may also occur. Mitochondria may function poorly, and immune system disturbances of various kinds are common. Changes in brain and autonomic nervous system electrophysiology can be measured and seizures are far more common than in the population at large. Sleep disruption and high levels of stress are close to universal. All

of these phenomena have also been documented to result from or be modulated by EMF/RFR exposure.

- Children with existing neurological problems that include cognitive, learning, attention, memory, or behavioral problems should as much as possible be provided with wired (not wireless) learning, living and sleeping environments.
- Special education classrooms should observe 'no wireless' conditions to reduce avoidable stressors that may impede social, academic and behavioral progress.
- All children should reasonably be protected from the physiological stressor of significantly elevated EMF/RFR (wireless in classrooms, or home environments).
- School districts that are now considering all-wireless learning environments should be strongly cautioned that wired environments are likely to provide better learning and teaching environments, and prevent possible adverse health consequences for both students and faculty in the long-term.
- Monitoring of the impacts of wireless technology in learning and care environments should be performed with sophisticated measurement and data analysis techniques that are cognizant of the non-linear impacts of EMF/RFR and of data techniques most appropriate for discerning these impacts.
- There is sufficient scientific evidence to warrant the selection of wired internet, wired classrooms and wired learning devices, rather than making an expensive and potentially health-harming commitment to wireless devices that may have to be substituted out later.
- Wired classrooms should reasonably be provided to all students who opt-out of wireless environments. (Herbert and Sage, 2012 – Section 20)

The public needs to know that these risks exist, that transition to wireless should not be presumed safe, and that it is very much worth the effort to minimize exposures that still provide the benefits of technology in learning, but without the threat of health risk and development impairments to learning and behavior in the classroom.

Broader recommendations also apply, related to reducing the physiological vulnerability to exposures, reduce allostatic load and build physiological resiliency through high quality nutrition, reducing exposure to toxicants and infectious agents, and reducing stress, all of which can be implemented safely based upon presently available knowledge.

E. Evidence for Electrohypersensitivity: The contentious question of whether electrohypersensitivity exists as a medical conditon and what kinds of testing might reveal biomarkers for diagnosis and treatment has been furthered by several new studies presented in Section 24 – Key Scientific Evidence and Public Health Policy Recommendations. What is evident is that a growing number of people world-wide have serious and debilitating symptoms that key to various types of EMF and RFR exposure. Of this there is little doubt. The continued massive rollout of wireless technologies, in particular the wireless 'smart' utility meter, has triggered thousands of complaints of ill-health and disabling symptoms when the installation of these meters is in close proximity to family home living spaces.

McCarty et al (2011) studied electrohypersensitivity in a patient (a female physician). The patient was unable to detect the presence or absence of EMF exposure, largely ruling out the possibility of bias. In multiple trials with the fields either on or not on, the subject experienced and reported temporal pain, feeling of unease, skipped heartbeats, muscle twitches and/or strong headache when the pulsed field (100 ms, duration at 10 Hz) was on, but no or mild symptoms when it was off. Symptoms from continuous fields were less severe than with pulsed fields. The differences between field on and sham exposure were significant at the $p < 0.05$ level. The authors conclude that electromagnetic hypersensitivity is a neurological syndrome, and statistically reliable somatic reactions can be provoked in this patient by exposure to 60-Hz electric fields at 300 volts per meter (V/m). Marino et al (2012) responded to comments on his study with McCarty saying *"EMF hypersensitivity can occur as a bona fide environmentally inducible neurological syndrome. We followed an empirical approach and demonstrated a cause-and-effect relationship ($p < 0.05$) under conditions that permitted us to infer the existence of electromagnetic hypersensitivity (EHS), a novel neurological syndrome."*

The team of Sandstrom, Hansson Mild and Lyskov produced numerous papers between 1994 and 2003 involving people who are electrosensitive (See Section 24 - Lyskov et al, 1995; Lyskov et al, 1998; Sandstrom et al, 1994; Sandstrom et al, 1995;

Sandstrom et al, 1997; Sandstrom et al, 2003). Sandstrom et al (2003) presented evidence that heart rate variability is impaired in people with electrical hypersensitivity and showed a dysbalance of the autonomic nervous system.

> *"EHS patients had a disturbed pattern of circadian rhythms of HRF and showed a relatively 'flat' representation of hourly-recorded spectral power of the HF component of HRV".* This research team also found that *"EHS patients have a dysbalance of the autonomic nervous system (ANS) regulation with a trend to hyper-sympathotonia, as measured by heart rate (HR) and electrodermal activity, and a hyperreactivity to different external physical factors, as measured by brain evoked potentials and sympathetic skin responses to visual and audio stimulation."* (Lyskov et al, 2001 a,b; Sandstrom et al, 1997).

The reports referenced above provide evidence that persons who report being electrosensitive differ from others in having some abnormalities in the autonomic nervous system, reflected in measures such as heart rate variability.

F. Evidence for Effects from Cell Tower-Level RFR Exposures

Very low exposure RFR levels are associated with bioeffects and adverse health effects. At least five new cell tower studies are reporting bioeffects in the range of 0.001 to 0.05 μW/cm2 at lower levels than reported in 2007 (0.05 to 0.1 uW/cm2 was the range below which, in 2007, effects were not observed). Researchers report headaches, concentration difficulties and behavioral problems in children and adolescents; and sleep disturbances, headaches and concentration problems in adults. Public safety standards are 1,000 – 10,000 or more times higher than levels now commonly reported in mobile phone base station studies to cause bioeffects.

Since 2007, five new studies of base-station level RFR at intensitites ranging from less than 0.001 uW/cm2 to 0.05 uW/cm2 report headaches, concentration difficulties and behavioral problems in children and adolescents; and sleep disturbances, headaches and concentration problems in adults.

G. Evidence for Effects on the Blood-brain Barrier (BBB): The Lund University (Sweden) team of Leif Salford, Bertil Persson and Henrietta Nittby has done pioneering work on effects of very low level RFR on the human brain's protective lining – the barrier that protects the brain from large molecules and toxins that are in the blood.

THE BLOOD-BRAIN BARRIER IS AT RISK

> *The BBB is a protective barrier that prevents the flow of toxins into sensitive brain tissue. Increased permeability of the BBB caused by cell phone RFR may result in neuronal damage. Many research studies show that very low intensity exposures to RFR can affect the blood-brain barrier (BBB) (mostly animal studies). Summing up the research, it is more probable than unlikely that non-thermal EMF from cell phones and base stations do have effects upon biology. A single 2-hr exposure to cell phone radiation can result in increased leakage of the BBB, and 50 days after exposure, neuronal damage can be seen,* and at the later time point also albumin leakage is demonstrated. *The levels of RFR needed to affect the BBB have been shown to be as low as 0.001 W/kg, or less than holding a mobile phone at arm's length. The US FCC standard is 1.6 W/kg; the ICNIRP standard is 2 W/kg of energy (SAR) into brain tissue from cell/cordless phone use. Thus, BBB effects occur at about 1000 times lower RFR exposure levels than the US and ICNIRP limits allow.* (Salford et al, 2012 - Section 10)

H. Evidence for Effects on Brain Tumors: The Orebro University (Sweden) team led by Lennart Hardell, MD, an oncologist and medical researcher, has produced an extraordinary body of work on environmental toxins of several kinds, including the effects of radiofrequency/microwave radiation and cancer. Their 2012 work concludes:

> *"Based on epidemiological studies there is a consistent pattern of increased risk for glioma and acoustic neuroma associated with use of mobile phones and cordless phones. The evidence comes mainly from two study centres, the Hardell group in Sweden and the Interphone Study Group. No consistent pattern of an increased risk is seen for meningioma. A systematic bias in the studies that explains the results would also have been the case for meningioma. The different risk pattern for tumor type strengthens the findings regarding glioma and acoustic neuroma. Meta-analyses of the Hardell group and Interphone studies show an increased risk for glioma and acoustic neuroma. Supportive evidence comes also from anatomical localisation of the tumor to the most exposed area of the brain, cumulative exposure in hours and latency time that all add to the biological relevance of an increased risk. In addition risk calculations based on estimated absorbed dose give strength to the findings.* (Hardell et al, 2012 – Section 11)

"There is reasonable basis to conclude that RF-EMFs are bioactive and have a potential to cause health impacts. There is a consistent pattern of increased risk for glioma and acoustic neuroma associated with use of wireless phones (mobile phones and cordless phones) mainly based on results from case-control studies from the Hardell group and Interphone Final Study results. Epidemiological evidence gives that RF-EMF should be classified as a human carcinogen. Based on our own research and review of other evidence the existing FCC/IEE and ICNIRP public safety limits and reference levels are not adequate to protect public health. New public health standards and limits are needed.

I. Evidence for Genotoxic Effects (Genotoxicity)

Genetic Damage (Genotoxicity Studies): There are at least several hundred published papers that report EMF (ELF/RFR) can affect cellular oxidative processes (oxidative damage). Increased free radical activity and changes in enzymes involved in cellular oxidative processes are the most consistent effects observed in cells and animals after EMF exposure. Aging may make an individual more susceptible to the detrimental effects of ELF EMF from oxidative damage, since anti-oxidants may decline with age. Clearly, the preponderance of genetic studies report DNA damage and failure to repair DNA damage.

Eighty six (86) new papers on genotoxic effects of RFR published between 2007 and mid-2012 are profiled. Of these, 54 (63%) showed effects and 32 (37%) showed no effects (Lai, 2012)

Forty three (43) new ELF-EMF papers and two static magnetic field papers that report on genotoxic effects of ELF-EMF published between 2007 and mid-2012 are profiled. Of these, 35 (81%) show effects and 8 (19%) show no effect. (Lai, 2012 – Section 6).

K. Evidence for Effects on the Nervous System: Factors that act directly or indirectly on the nervous system can cause morphological, chemical, or electrical changes in the nervous system that can lead to neurological effects. Both RF and ELF EMF affect neurological functions and behavior in animals and humans.

One hundred fifty five (155) new papers that report on neurological effects of RFR published between 2007 and mid-2012 are profiled. Of these, 98 (63%) showed effects and 57 (37%) showed no effects.

Sixty nine (69) new ELF-EMF papers (including two static field papers) that report on genotoxic effects of ELF-EMF published between 2007 and mid-2012 are profiled. Of these, 64 (93%) show effects and 5 (7%) show no effect. (Lai, 2012 – Section 9)

K. Evidence for Cancer (Childhood Leukemia): With overall 42 epidemiological studies published to date power frequency EMFs are among the most comprehensively studied environmental factors. Except ionizing radiation no other environmental factor has been as firmly established to increase the risk of childhood leukemia.

Sufficient evidence from epidemiological studies of an increased risk from exposure to EMF (power frequency magnetic fields) that cannot be attributed to chance, bias or confounding. Therefore, according to the rules of IARC such exposures can be classified as a **Group 1 carcinogen (Known Carcinogen).** (Kundi, 2012 – Section 12)

There is no other risk factor identified so far for which such unlikely conditions have been put forward to postpone or deny the necessity to take steps towards exposure reduction. As one step in the direction of precaution, measures should be implemented to guarantee that exposure due to transmission and distribution lines is below an average of about 1 mG. This value is arbitrary at present and only supported by the fact that in many studies this level has been chosen as a reference. (Kundi, 2012 – Section 12)

L. Melatonin, Breast Cancer and Alzheimer's Disease: Eleven (11) of the 13 published epidemiologic residential and occupational studies are considered to provide (positive) evidence that high ELF magnetic fields (MF) exposure can result in decreased melatonin production. The two negative studies had important deficiencies that may certainly have biased the results. There is sufficient evidence to conclude that long-term relatively high ELF MF exposure can result in a decrease in melatonin production. It has not been determined to what extent personal characteristics, e.g., medications, interact with ELF MF exposure in decreasing melatonin production.

MELATONIN AND BREAST CANCER: There is sufficient evidence to conclude that long-term relatively high ELF MF exposure can result in a decrease in melatonin production. It has not been determined to what extent personal characteristics, e.g., medications, interact with ELF MF exposure in decreasing melatonin production. New research indicates that ELF MF exposure, in vitro, can significantly decrease melatonin activity through effects on MT1, an important melatonin receptor. Five longitudinal studies have now been conducted of low melatonin production as a risk factor for breast cancer. There is increasingly strong longitudinal evidence that low melatonin production is a risk factor for at least post-menopausal breast cancer.

(Davanipour and Sobel, 2012 – Section 13)

ALZHEIMER'S DISEASE: There is now evidence that a) high levels of peripheral amyloid beta are a risk factor for AD and b) medium to high ELF MF exposure can increase peripheral amyloid beta. High brain levels of amyloid beta are also a risk factor for AD and medium to high ELF MF exposure to brain cells likely also increases these cells' production of amyloid beta. There is considerable in vitro and animal evidence that melatonin protects against AD. Therefore it is certainly possible that low levels of melatonin production are associated with an increase in the risk of AD.

There is strong epidemiologic evidence that exposure to ELF MF is a risk factor for AD. There are now twelve (12) studies of ELF MF exposure and AD or dementia. Nine (9) of these studies are considered positive and three (3) are considered negative. The three negative studies have serious deficiencies in ELF MF exposure classification that results in subjects with rather low exposure being considered as having significant exposure. There are insufficient studies to formulate an opinion as to whether radiofrequency MF exposure is a risk or protective factor for AD.

There is now evidence that (i) high levels of peripheral amyloid beta are a risk factor for AD and (ii) medium to high ELF MF exposure can increase peripheral amyloid beta. High brain levels of amyloid beta are also a risk factor for AD and medium to high ELF MF exposure to brain cells likely also increases these cells' production of amyloid beta.

There is considerable in vitro and animal evidence that melatonin protects against AD. Therefore it is certainly possible that low levels of melatonin production are associated with an increase in the risk of AD.

(Davanipour and Sobel, 2012 – Section 13)

M. Stress, Stress Proteins and DNA as a Fractal Antenna: Any agent (EMF, ionizing radiation, chemicals, heavy metals, etc) that continuously generates stress proteins is not adaptive, and is harmful, if it is a constant provocation. The work of Martin Blank and Reba Goodman of Columbia University has established that stress proteins are produced by ELF-EMF and RFR at levels far below current safety standards allow. Further, they think DNA is actually a very good fractal RF-antenna which is very sensitive to low doses of EMF, and may induce the cellular processes that result in chronic 'unrelenting' stress. That daily environmental levels of ELF-EMF and RFR can and do throw the human body into stress protein response mode (out of homeostasis) is a fundamental and continuous insult. Chronic exposures can then result in chronic ill-health.

> *"It appears that the DNA molecule is particularly vulnerable to damage by EMF because of the coiled-coil configuration of the compacted molecule in the nucleus. The unusual structure endows it with the self similarity of a fractal antenna and the resulting sensitivity to a wide range of frequencies. The greater reactivity of DNA with EMF, along with a vulnerability to damage, underscores the urgent need to revise EMF exposure standards in order to protect the public. Recent studies have also exploited the properties of stress proteins to devise therapies for limiting oxidative damage and reducing loss of muscle strength associated with aging."* *(Blank, 2012- Section 7)*

DNA acts as a 'fractal antenna' for EMF and RFR. The coiled-coil structure of DNA in the nucleus makes the molecule react like a fractal antenna to a wide range of frequencies.

The structure makes DNA particularly vulnerable to EMF damage.

The mechanism involves direct interaction of EMF with the DNA molecule (claims that there are no known mechanisms of interaction are patently false).

Many EMF frequencies in the environment can and do cause DNA changes.

The EMF-activated cellular stress response is an effective protective mechanism for cells exposed to a wide range of EMF frequencies.

EMF stimulates stress proteins (indicating an assault on the cell).

EMF efficiently harms cells at a billion times lower levels than conventional heating.
(Blank, 2012- Section 7)

Safety standards based on heating are irrelevant to protect against EMF-levels of exposure. There is an urgent need to revise EMF exposure standards. Research has shown thresholds are very low (safety standards must be reduced to limit biological responses). Biologically-based EMF safety standards could be developed from the research on the stress response.
(Blank, 2012- Section 7)

N. Effects of Weak-Field Interactions on Non-Linear Biological Oscillators and Synchronized Neural Activity

A unifying hypothesis for a plausible biological mechanism to account for very weak field EMF bioeffects other than cancer may lie with weak field interactions of pulsed RFR and ELF-modulated RFR as disrupters of synchronized neural activity. Electrical rhythms in our brains can be influenced by external signals. This is consistent with established weak field effects on coupled biological oscillators in living tissues. Biological systems of the heart, brain and gut are dependent on the cooperative actions of cells that function according to principles of non-linear, coupled biological oscillations for their synchrony, and are dependent on exquisitely timed cues from the environment at vanishingly small levels (Buzsaki, 2006; Strogatz, 2003). The key to synchronization is the joint actions of cells that co-operate electrically - linking populations of biological oscillators that couple together in large arrays and synchronize spontaneously. Synchronous biological oscillations in cells (pacemaker cells) can be disrupted by artificial, exogenous environmental signals, resulting in desynchronization of neural activity that regulates critical functions (including metabolism) in the brain, gut and heart and circadian rhythms governing sleep and hormone cycles (Strogatz, 1987). The brain contains a population of oscillators with distributed natural frequencies, which pull one another into synchrony (the circadian pacemaker cells). Strogatz has addressed the unifying mathematics of biological cycles and external factors disrupt these cycles (Strogatz, 2001, 2003). *"Rhythms can be altered by a wide variety of agents and that these perturbations must seriously alter brain performance"* (Buzsaki, 2006).

III. EMF EXPOSURE AND PRUDENT PUBLIC HEALTH PLANNING

Chronic exposure to low-intensity RFR and to ELF-modulated RFR at today's environmental levels in many cities will exceed thresholds for increased risk of many diseases and causes of death (Sage and Huttunen, 2012). RFR exposures in daily life alter homeostasis in human beings. These exposures can alter and damage genes, trigger epigenetic changes to gene expression and cause de novo mutations that prevent genetic recovery and healing mechanisms. These exposures may interfere with normal cardiac and brain function; alter circadian rhythms that regulate sleep, healing, and hormone balance; impair short-term memory, concentration, learning and behavior; provoke aberrant immune, allergic and inflammatory responses in tissues; alter brain metabolism; increase risks for reproductive failure (damage sperm and increase miscarriage risk); and cause cells to produce stress proteins. Exposures now common in home and school environments are likely to be physiologically addictive and the effects are particularly serious in the young (Sage and Huttunen, 2012).

IV. RECOMMENDED ACTIONS

A. Defining preventative actions for reduction in RFR exposures

ELF-EMF AND RFR ARE CLASSIFIED AS POSSIBLE CANCER-CAUSING AGENTS – WHY ARE GOVERNMENTS NOT ACTING?

The World Health Organization International Agency for Research on Cancer has classified wireless radiofrequency as a Possible Human Carcinogen (May, 2011)*. The designation applies to low-intensity RFR in general, covering all RFR-emitting devices and exposure sources (cell and cordless phones, WI-FI, wireless laptops, wireless hotspots, electronic baby monitors, wireless classroom access points, wireless antenna facilities, etc). The IARC Panel could have chosen to classify RFR as a Group 4 – Not A Carcinogen if the evidence was clear that RFR is not a cancer-causing agent. It could also have found a Group 3 designation was a good interim choice (Insufficient Evidence). IARC did neither.

NEW SAFETY LIMITS MUST BE ESTABLISHED – HEALTH AGENCIES SHOULD ACT NOW

Existing public safety limits (FCC and ICNIRP public safety limits) do not sufficiently protect public health against chronic exposure from very low-intensity exposures. If no mid-course corrections are made to existing and outdated safety limits, such delay will magnify the public health impacts with even more applications of wireless-enabled technologies exposing even greater populations around the world in daily life.

SCIENTIFIC BENCHMARKS FOR HARM PLUS SAFETY MARGIN = NEW SAFETY LIMITS THAT ARE VALID

Health agencies and regulatory agencies that set public safety standards for ELF-EMF and RFR should act now to adopt new, biologically-relevant safety limits that key to the lowest scientific benchmarks for harm coming from the recent studies, plus a lower safety margin. Existing public safety limits are too high by several orders of magnitude, if prevention of bioeffects and resulting adverse health effects are to be minimized or eliminated. Most safety standards are a thousand times or more too high to protect healthy populations, and even less effective in protecting sensitive subpopulations.

SENSITIVE POPULATIONS MUST BE PROTECTED

Safety standards for sensitive populations will more likely need to be set at lower levels than for healthy adult populations. Sensitive populations include the developing fetus, the infant, children, the elderly, those with pre-existing chronic diseases, and those with developed electrical sensitivity (EHS).

PROTECTING NEW LIFE - INFANTS AND CHILDREN

Strong precautionary action and clear public health warnings are warranted immediately to help prevent a global epidemic of brain tumors resulting from the use of wireless devices (mobile phones and cordless phones). Common sense measures to limit both ELF-EMF and RFR in the fetus and newborn infant (sensitive populations) are needed, especially with respect to avoidable exposures like baby monitors in the crib and baby

isolettes (incubators) in hospitals that can be modified; and where education of the pregnant mother with respect to laptop computers, mobile phones and other sources of ELF-EMF and RFR are easily instituted.

Wireless laptops and other wireless devices should be strongly discouraged in schools for children of all ages.

STANDARD OF EVIDENCE FOR JUDGING THE SCIENCE

The standard of evidence for judging the scientific evidence should be based on good public health principles rather than demanding scientific certainty before actions are taken.

WIRELESS WARNINGS FOR ALL

The continued rollout of wireless technologies and devices puts global public health at risk from unrestricted wireless commerce unless new, and far lower exposure limits and strong precautionary warnings for their use are implemented.

EMF AND RFR ARE PREVENTABLE TOXIC EXPOSURES

We have the knowledge and means to save global populations from mulit-generational adverse health consequences by reducing both ELF and RFR exposures. Proactive and immediate measures to reduce unnecessary EMF exposures will lower disease burden and rates of premature death.

B. Defining new 'effect level' for RFR

Section 24 concludes that RFR 'effect levels' for bioeffects and adverse health effects justify new and lower precautionary target levels for RFR exposure. New epidemiological and laboratory studies are finding effects on humans at lower exposure levels where studies are of longer duration (chronic exposure studies). Real-world experience is revealing worrisome evidence that sperm may be damaged by cell phones

even on stand-by mode; and people can be adversely affected by placing new wireless pulsed RFR transmitters (utility meters on the sides or interiors of homes), even when the time-weighted average for RFR is miniscule in both cases.

There is increasing reason to believe that the critical factor for biologic significance is the intermittent pulse of RF, not the time-averaged SAR. For example, Hansson Mild et al, (2012) concluded there could be no effect on sleep and testicular function from a GSM mobile phone because the "*exposure in stand-by mode can be considered negligible*". It may be that we, as a species, are more susceptable than we thought to intermittent, very low-intensity pulsed RFR signals that can interact with critical activities in living tissues. It is a mistake to conclude that the effect does not exist because we cannot explain HOW it is happening or it upsets our our mental construct of how things should work.

This highlights the serious limitation of not taking the nature of the pulsed RFR signal (high intensity but intermittent, microsecond pulses of RFR) into account in the safety standards. This kind of signal is biologically active. Even if it is essentially mathematically invisible when the individual RFR pulses are time-averaged, it is apparently NOT invisible to the human body and its proper biological functioning.

For these reasons, and in light of parallel scientific work on non-linear biological oscillators including the accepted mathematics in this branch of science regarding coupled oscillators (Bezsaki, 2006; Strogatz, 2001, 2003), it is essential to think forward about the ramifications of shifting national energy strategies toward ubiquitous wireless systems. And, it is essential to re-think safety standards to take into account the exquisite sensitivity of biological systems and tissue interactions where the exposures are pulsed and cumulatively insignificant over time-scale averaging, but highly relevant to body processes and functioning. If it is true that weak-field effects have

control elements over synchronous activity of neurons in the brain, and other pacemaker cells and tissues in the heart and gut that drive essential metabolic pathways as a result, then this will go far in explaining why living tissues are apparently so reactive to very small inputs of pulsed RFR, and lead to better understanding of what is required for new, biologically-based public exposure standards.

A reduction from the BioInitiative 2007 recommendation of 0.1 uW/cm2 (or one-tenth of a microwatt per square centimeter) for cumulative outdoor RFR down to something three orders of magnitude lower (in the low nanowatt per square centimeter range) is justified on a public health basis. We use the new scientific evidence documented in this Report to identify 'effect levels' and then apply one or more reduction factors to provide a safety margin. A cautionary target level for cumulative, outdoor pulsed RFR exposures for ambient wireless that could be applied to RFR sources from cell tower antennas, WI-FI, WI-MAX and other similar sources is proposed. Research is needed to determine what is biologically damaging about intermittent pulses of RFR, and how to provide for protection in safety limits against it. With this knowledge it might be feasible to recommend a higher time-averaged number.

A scientific benchmark of 0.003 uW/cm2 or three nanowatts per centimeter squared for 'lowest observed effect level' for RFR is based on mobile phone base station-level studies. Applying a ten-fold reduction to compensate for the lack of long-term exposure (to provide a safety buffer for chronic exposure, if needed) or for children as a sensitive subpopulation (if studies are on adults, not children) yields a 300 to 600 picowatts per square centimeter precautionary action level. This equates to a 0.3 nanowatts to 0.6 nanowatts per square centimeter as a reasonable, precautionary action level for chronic exposure to pulsed RFR. Even so, these levels may need to change in the future, as new and better studies are completed. This is what the authors said in 2007

(Carpenter and Sage, 2007, BioInitiative Report) and it remains true today in 2012. We leave room for future studies that may lower or raise today's observed 'effects levels' and should be prepared to accept new information as a guide for new precautionary actions.

BIOINITIATIVE 2012 - CONCLUSIONS Table 1-1

Overall, these 1800 or so new studies report abnormal gene transcription (Section 5); genotoxicity and single-and double-strand DNA damage (Section 6); stress proteins because of the fractal RF-antenna like nature of DNA (Section 7); chromatin condensation and loss of DNA repair capacity in human stem cells (Sections 6 and 15); reduction in free-radical scavengers - particularly melatonin (Sections 5, 9, 13, 14, 15, 16 and 17); neurotoxicity in humans and animals (Section 9), carcinogenicity in humans (Sections 11, 12, 13, 14, 15, 16 and 17); serious impacts on human and animal sperm morphology and function (Section 18); effects on offspring behavior (Section 18, 19 and 20); and effects on brain and cranial bone development in the offspring of animals that are exposed to cell phone radiation during pregnancy (Sections 5 and 18). This is only a snapshot of the evidence presented in the BioInitiative 2012 updated report.

BIOEFFECTS ARE CLEARLY ESTABLISHED

Bioeffects are clearly established and occur at very low levels of exposure to electromagnetic fields and radiofrequency radiation. Bioeffects can occur in the first few minutes at levels associated with cell and cordless phone use. Bioeffects can also occur from just minutes of exposure to mobile phone masts (cell towers), WI-FI, and wireless utility 'smart' meters that produce whole-body exposure. Chronic base station level exposures can result in illness.

BIOEFFECTS WITH CHRONIC EXPOSURES CAN REASONABLY BE PRESUMED TO RESULT IN ADVERSE HEALTH EFFECTS

Many of these bioeffects can reasonably be presumed to result in adverse health effects if the exposures are prolonged or chronic. This is because they interfere with normal body processes (disrupt homeostasis), prevent the body from healing damaged DNA, produce immune system imbalances, metabolic disruption and lower resilience to disease across multiple pathways. Essential body processes can eventually be disabled by incessant external stresses (from system-wide electrophysiological interference) and lead to pervasive impairment of metabolic and reproductive functions.

LOW EXPOSURE LEVELS ARE ASSOCIATED WITH BIOEFFECTS AND ADVERSE HEALTH EFFECTS AT CELL TOWER RFR EXPOSURE LEVELS

At least five new cell tower studies are reporting bioeffects in the range of 0.003 to 0.05 μW/cm2 at lower levels than reported in 2007 (0.05 to 0.1 uW/cm2 was the range below which, in 2007, effects were not observed). Researchers report headaches, concentration difficulties and behavioral problems in children and adolescents; and sleep disturbances, headaches and concentration problems in adults. Public safety standards are 1,000 – 10,000 or more times higher than levels now commonly reported in mobile phone base station studies to cause bioeffects.

EVIDENCE FOR FERTILITY AND REPRODUCTION EFFECTS: HUMAN SPERM AND THEIR DNA ARE DAMAGED

Human sperm are damaged by cell phone radiation at very low intensities in the low microwatt and nanowatt/cm2 range (0.00034 – 0.07 uW/cm2). There is a veritable flood of new studies reporting sperm damage in humans and animals, leading to substantial concerns for fertility, reproduction and health of the offspring (unrepaired de novo mutations in sperm). Exposure levels are similar to those resulting from wearing a cell phone on the belt, or in the pants pocket, or using a wireless laptop computer on the lap. Sperm lack the ability to repair DNA damage.

Studies of human sperm show genetic (DNA) damage from cell phones on standby mode and wireless laptop use. Impaired sperm quality, motility and viability occur at exposures of 0.00034 uW/cm2 to 0.07 uW/cm2 with a resultant reduction in human male fertility. Sperm cannot repair DNA damage.

Several international laboratories have replicated studies showing adverse effects on sperm quality, motility and pathology in men who use and particularly those who wear a cell phone, PDA or pager on their belt or in a pocket (Agarwal et al, 2008; Agarwal et al, 2009; Wdowiak et al, 2007; De Iuliis et al, 2009; Fejes et al, 2005; Aitken et al, 2005; Kumar, 2012). Other studies conclude that usage of cell phones, exposure to cell phone radiation, or storage of a mobile phone close to the testes of human males affect sperm counts, motility, viability and structure (Aitken et al, 2004; Agarwal et al, 2007; Erogul et al., 2006). Animal studies have demonstrated oxidative and DNA damage, pathological changes in the testes of animals, decreased sperm mobility and viability, and other measures of deleterious damage to the male germ line (Dasdag et al, 1999; Yan et al, 2007; Otitoloju et al, 2010; Salama et al, 2008; Behari et al, 2006; Kumar et al, 2012). There are fewer animal studies that have studied effects of cell phone radiation on female fertility parameters. Panagopoulous et al. 2012 report decreased ovarian development and size of ovaries, and premature cell death of ovarian follicles and nurse cells in *Drosophila melanogaster*. Gul et al (2009) report rats exposed to stand-by level RFR (phones on but not transmitting calls) caused decrease in the number of ovarian follicles in pups born to these exposed dams. Magras and Xenos (1997) reported irreversible infertility in mice after five (5) generations of exposure to RFR at cell phone tower exposure levels of less than one microwatt per centimeter squared (μW/cm2).

EVIDENCE THAT CHILDREN ARE MORE VULNERABLE

There is good evidence to suggest that many toxic exposures to the fetus and very young child have especially detrimental consequences depending on when they occur during critical phases of growth and development (time windows of critical development), where such exposures may lay the seeds of health harm that develops even decades later. Existing FCC and ICNIRP public safety limits seem to be not sufficiently protective of public health, in particular for the young (embryo, fetus, neonate, very young child).

The Presidential Cancer Panel (2010) found that children '*are at special risk due to their smaller body mass and rapid physical development, both of which magnify their vulnerability to known carcinogens, including radiation.*'

The American Academy of Pediatrics, in a letter to Congressman Dennis Kucinich dated 12 December 2012 states "*Children are disproportionately affected by environmental exposures, including cell phone radiation. The differences in bone density and the amount of fluid in a child's brain compared to an adult's brain could allow children to absorb greater quantities of RF energy deeper into their brains than adults. It is essential that any new standards for cell phones or other wireless devices be based on protecting the youngest and most vulnerable populations to ensure thay are safeguarded through their lifetimes.*"

FETAL AND NEONATAL EFFECTS OF EMF

Fetal (*in-utero*) and early childhood exposures to cell phone radiation and wireless technologies in general may be a risk factor for hyperactivity, learning disorders and behavioral problems in school.

Fetal Development Studies: Effects on the developing fetus from *in-utero* exposure to cell phone radiation have been observed in both human and animal studies since 2006. Divan et al (2008) found that children born of mothers who used cell phones during pregnancy develop more behavioral problems by the time they have reached school age than children whose mothers did not use cell phones during pregnancy. Children whose mothers used cell phones during pregnancy had 25% more emotional problems, 35% more hyperactivity, 49% more conduct problems and 34% more peer problems
(Divan et al., 2008).

Common sense measures to limit both ELF-EMF and RF EMF in these populations is needed, especially with respect to avoidable exposures like incubators that can be modified; and where education of the pregnant mother with respect to laptop computers, mobile phones and other sources of ELF-EMF and RF EMF are easily instituted.

Sources of fetal and neonatal exposures of concern include cell phone radiation (both paternal use of wireless devices worn on the body and maternal use of wireless phones during pregnancy). Exposure to whole-body RFR from base stations and WI-FI, use of wireless laptops, use of incubators for newborns with excessively high ELF-EMF levels resulting in altered heart rate variability and reduced melatonin levels in newborns, fetal exposures to MRI of the pregnant mother, and greater susceptibility to leukemia and asthma in the child where there have been maternal exposures to ELF-EMF.

A precautionary approach may provide the frame for decision-making where remediation actions have to be realized to prevent high exposures of children and pregnant woman.

(Bellieni and Pinto, 2012 – Section 19)

EMF/RFR AS A PLAUSIBLE BIOLGICAL MECHANISM FOR AUTISM (ASD)

- Children with existing neurological problems that include cognitive, learning, attention, memory, or behavioral problems should as much as possible be provided with wired (not wireless) learning, living and sleeping environments,
- Special education classrooms should observe 'no wireless' conditions to reduce avoidable stressors that may impede social, academic and behavioral progress.
- All children should reasonably be protected from the physiological stressor of significantly elevated EMF/RFR (wireless in classrooms, or home environments).
- School districts that are now considering all-wireless learning environments should be strongly cautioned that wired environments are likely to provide better learning and teaching environments, and prevent possible adverse health consequences for both students and faculty in the long-term.
- Monitoring of the impacts of wireless technology in learning and care environments should be performed with sophisticated measurement and data analysis techniques that are cognizant of the non-linear impacts of EMF/RFR and of data techniques most appropriate for discerning these impacts.
- There is sufficient scientific evidence to warrant the selection of wired internet, wired classrooms and wired learning devices, rather than making an expensive and potentially health-harming commitment to wireless devices that may have to be substituted out later, and
- Wired classrooms should reasonably be provided to all students who opt-out of wireless environments. (Herbert and Sage, 2012 – Section 20)

Many disrupted physiological processes and impaired behaviors in people with ASDs closely resemble those related to biological and health effects of EMF/RFR exposure. Biomarkers and indicators of disease and their clinical symptoms have striking similarities. Broadly speaking, these types of phenomena can fall into one or more of several classes: a) alteration of genes or gene expression, b) induction of change in brain or organismic development, c) alteration of phenomena modulating systemic and brain function on an ongoing basis throughout the life course (which can include systemic pathophysiology as well as brain-based changes), and d) evidence of functional alteration in domains such as behavior, social interaction and attention known to be challenged in ASD.

Several thousand scientific studies over four decades point to serious biological effects and health harm from EMF and RFR. These studies report genotoxicity, single-and double-strand DNA damage, chromatin condensation, loss of DNA repair capacity in human stem cells, reduction in free-radical scavengers (particularly melatonin), abnormal gene transcription, neurotoxicity, carcinogenicity, damage to sperm morphology and function, effects on behavior, and effects on brain development in the fetus of human mothers that use cell phones during pregnancy. Cell phone exposure has been linked to altered fetal brain development and ADHD-like behavior in the offspring of pregnant mice.

Reducing life-long health risks begins in the earliest stages of embryonic and fetal development, is accelerated for the infant and very young child compared to adults, and is not complete in young people (as far as brain and nervous system maturation) until the early 20's. Windows of critical development mean that risk factors once laid down in the cells, or in epigenetic changes in the genome may have grave and life-long consequences for health or illness for every individual.

Scientific Panel on Electromagnetic Field Health Risks: Consensus Points, Recommendations, and Rationales

Scientific Meeting: Seletun, Norway, November 17-21, 2009

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Summary: In November, 2009, a scientific panel met in Seletun, Norway, for three days of intensive discussion on existing scientific evidence and public health implications of the unprecedented global exposures to artificial electromagnetic fields (EMF). EMF exposures (static to 300 GHz) result from the use of electric power and from wireless telecommunications technologies for voice and data transmission, energy, security, military and radar use in weather and transportation. The Scientific Panel recognizes that the body of evidence on EMF requires a new approach to protection of public health; the growth and development of the fetus, and of children; and argues for strong preventative actions. New, biologically-based public exposure standards are urgently needed to protect public health worldwide.

Keywords: EMF, wireless telecommunications technology, radiofrequency, non-ionizing radiation, non-thermal effects, long-term effects, public exposure guidelines, public health

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BACKGROUND

In November, 2009, a scientific panel met in Seletun, Norway, for three days of intensive discussion on existing scientific evidence and public health implications of the unprecedented global exposures to artificial electromagnetic fields (EMF).

EMF exposures (static to 300 GHz) result from the use of electric power and from wireless telecommunications technologies for voice and data transmission, energy, security, military and radar use in weather and transportation.

The Scientific Panel recognizes that the body of evidence on EMF requires a new approach to protection of public health; the growth and development of the fetus, and of children; and argues for strong preventative actions. These conclusions are built upon prior scientific and public health reports /1-6/ documenting the following:

1) *Low-intensity (non-thermal) bioeffects and adverse health effects are demonstrated at levels significantly below existing exposure standards.*
2) *ICNIRP and IEEE/FCC public safety limits are inadequate and obsolete with respect to prolonged, low-intensity exposures.*

3) *New, biologically-based public exposure standards are urgently needed to protect public health world-wide.*
4) *It is not in the public interest to wait.*

Strong concern has been voiced by the public, and by scientists as well as public health and environmental policy experts, that the deployment of technologies that expose billions of people worldwide to new sources of EMF may pose a pervasive risk to public health. Such exposures did not exist before the "age of industry and information". Prolonged exposure appears to disrupt biological processes that are fundamental to plant, animal and human growth and health. Life on earth did not evolve with biological protections or adaptive biological responses to these EMF exposures. Exceptionally small levels of EMF from earth and space existed during the time that all life evolved on earth on the order of less than a billionth to one ten-billionth of a Watt per meter squared. A rapidly accumulating body of scientific evidence of harm to health and well-being constitute warnings that adverse health effects can occur with prolonged exposures to very low-intensity EMF at biologically active frequencies or frequency combinations.

The Seletun Scientific Panel has adopted a Consensus Agreement that recommends preventative and precautionary actions that are warranted now, given the existing evidence for potential global health risks. We recognize the duty of governments and their health agencies to educate and warn the public, to implement measures balanced in favor of the Precautionary Principle, to monitor compliance with directives promoting alternatives to wireless, and to fund research and policy development geared toward prevention of exposures and development of new public safety measures.

POINTS OF AGREEMENT

- Global populations are not sufficiently protected from electromagnetic fields (EMF) from emerging communication and data transmission technologies that are being deployed worldwide, affecting billions of people;
- Sensitive populations (for example, the elderly, the ill, the genetically and/or immunologically challenged) and children and fetuses may be additionally vulnerable to health risks; their exposures are largely involuntary and they are less protected by existing public safety standards;
- It is well established that children are more vulnerable to health risks from environmental toxins in general;
- It is established that the combined effects of chemical toxins and EMF together is greater than either exposure alone;
- The Seletun Scientific Panel takes note of international scientific reviews, resolutions and recommendations documenting scientific and public health evidence on EMF exposures;
- The Seletun Scientific Panel notes that complete *"consistency"* of study findings is not to be expected, and it should not be interpreted as a necessary pre-condition for a consensus linking EMF exposure to health impacts. *"Consistency in nature does not require that all or even a majority of studies find the same effect. If all studies of lead showed the same relationship between variables, one would be startled, perhaps justifiably suspicious"* /7/;
- The Seletun Scientific Panel acknowledges that some, but not all, of these exposures support preventative and precautionary action, and the need for more stringent public health limits;
- The Panel takes note of international scientific resolutions and expressions of concern including the Salzburg, Catania, Freiberger Appeal, Helsinki, Irish Doctors (IDEA), Benevento, Venice, London, and Porto Alegre Resolutions (2000-2009);
- The Panel is guided by previously recommended target limits for EMF exposure

in the BioInitiative Report (2007) and the London Resolution (2009);
- The Panel urges governments to adopt an explicit statement that "the standard for judging and acting on the scientific evidence shall be based on prudent public health planning principles rather than scientific certainty of effect (causal evidence)". Actions are warranted based on limited or weak scientific evidence, or a sufficiency of evidence – rather than a conclusive scientific evidence (causation or scientific certainty) where the consequence of doing nothing in the short term may cause irreparable public health harm, where the populations potentially at risk are very large, where there are alternatives without similar risks, or where the exposures are largely involuntary;
- The Seletun Scientific Panel urges governments to make explicit that the burden of proof of safety rests with the producers and providers of EMF-producing technologies, not with the users and consumers.

THE SELETUN SCIENTIFIC PANEL UNANIMOUSLY ENDORSES THESE GENERAL AGREEMENTS AND GENERAL AND SPECIFIC RECOMMENDATIONS

General Agreements from the Seletun Scientific Panel

- The Seletun Scientific Panel has identified specific scientific and public health benchmarks for numeric limits and preventative action that are justified now based on the existing body of evidence;
- The Panel is relying on scientific evidence as the basis for identifying scientific benchmarks establishing EMF levels associated with adverse health effects. The Panel notes that radiofrequent (RF) levels in some regions may already exceed scientific benchmarks for health harm identified here, but political expediency is not the guiding criterion in this assessment;
- EMF exposures should be reduced now rather than waiting for proof of harm before acting. This recommendation is in keeping with traditional public health principles, and is justified now given abundant evidence that biological effects and adverse health effects are occurring at exposure levels many orders of magnitude below existing public safety standards around the world;
- SAR (Specific Absorption Rate) is not an adequate approach to predict many important biologic effects in studies that report increased risks for cancer, neurological diseases, impairments to immune function, fertility and reproduction, and neurological function (cognition, behaviour, performance, mood status, disruption of sleep, increased risk for auto collisions, etc);
- SAR fails to adequately address known effects from modulation.

General Recommendations from the Seletun Scientific Panel

- The Seletun Scientific Panel recommends an international registry be established to track time-trends in incidence and mortality for cancers and neurological and immune diseases. Tracking effects of EMF on children and sensitive EHS populations is a high priority. There should be open access to this information;
- The Panel recommends existing brain tumour registries provide timely age-specific incidence rates. An early indication of brain tumors from mobile (cell) phone use could be in the younger age-specific incidence rates. Where such brain tumors registries to not exist, they should be established;

- Intervention-related epidemiological studies are needed to track the efficacy of intervention(s) that reduce or eliminate exposures to EMF;
- There is a need for mandatory pre-market assessments of emissions and risks before deployment of new wireless technologies. There should be convincing evidence that products do not cause health harm before marketing;
- For occupational exposures, there has been epidemiological evidence as well as clusters and case reports which state the 'case for action' and stringent control measures based on classic industrial hygiene principles (separation, distancing and enclosure). Further, there is need for surveillance markers of hematologic, immunotoxic and chromosome aberrations;
- The Panel discourages use of more lenient safety standards for workers, as compared to the general public. Separate safety limits are not ethically acceptable. Workers include women of childbearing age and men who wish to retain their fertility. Occupational environments where wireless exposures are common may be potentially hazardous to fertility and reproduction (retail and restaurant workers, transit workers, telecommunications and broadcast workers, medical workers, educators, administrators, etc) and those with other exposures or special health risks;
- The Panel strongly recommends that persons with electrohypersensitivity symptoms (EHS) be classified as functionally impaired rather than with 'idiopathic environmental disease' or similar indistinct categories. This terminology will encourage governments to make adjustments in the living environment to better address social and well-being needs of this subpopulation of highly sensitive members of society.

General Research Recommendations from the Seletun Scientific Panel

- Research funding is urgently needed for assays for biological markers [*EMF bioassays as biological markers of EMF dose*] which show promise to measure adverse health effects, and biological effects that, with prolonged or repetitive exposure, can reasonably be presumed to lead to harmful health consequences (biomarkers from cerebrospinal fluid, saliva, immune function changes, and DNA damage to name some);
- The Scientific Panel recommends research funding for studies on bioactive modulation which may, based on current knowledge, cause major consequences at far lower exposure levels based on different exposure parameters including modulation, frequency windows, intensity windows, duration, geomagnetic field and other factors;
- Research is urgently recommended for effects of prolonged or repetitive wireless exposure on children (cancers, neurological diseases, and impairment of cognition, behavior, performance and mood status, and disruption of sleep, etc) ;
- Research in SAR refinements is given a low priority. The scientific panel is in unanimous agreement that SAR is a poor measurement tool. Yet SARs have been used in many key studies reporting increased risk of DNA damage, increased risk for brain cancer, increased risk for acoustic neuroma, and reduced sperm quality parameters, among others. SAR measures only one aspect of exposure and ignores other critical aspects, such as biologically active frequencies (and modulations) that is essential information needed to understand the biological responses induced by EMF over short and long term exposures (e.g., nervous system response and

tissue/organ development, respectively) that does not cause thermal damage so that effective, biologically protective limits can be developed.

Specific Recommendations from the Seletun Scientific Panel

Extremely Low Frequency (Fields from Electrical Power)

- Based on the available evidence, the Seletun Scientific Panel recommends a 0.1 uT (1 mG) exposure limit for all new installations based on findings of risk for leukemia, brain tumours, Alzheimer's, ALS, sperm damage and DNA strand breaks. This exposure limit does not include a safety margin;
- For all newly installed, or newly upgraded electrical power distribution, the Panel recommends a 0.1 uT (1 mG) set-back distance, from residences, hospitals, schools, parks, and playgrounds schools (and similar locations occupied by children) [A 0.1 uT (1 mG) time-weighted average (TWA) using peak loading for transmission lines to ensure that average is about half of this for typical exposures; or equivalent for long-term exposure in interior EMF environments (wiring, trans-formers, appliances, others).];
- For all newly constructed residences, offices, schools (and other facilities with children), and hospitals there shall be a 0.1 uT (1 mG) max. 24 hour average exposure limit;
- For all new equipment (e.g. transformers, motors, electronic products), where practical, the Panel recommends a 0.1 uT (1 mG) max. 24 hour average exposure limit. Where not practical (e.g. large power transformers), there should be a fence, or boundary marker, with clearly written warning labels that states that within the boundary area the 0.1 uT (1 mG) maximum, 24 hour average exposure limit is exceeded;
- The Panel recommends all countries should adopt electrical code requirements to disallow conduction of high-frequency voltage transients back into electrical wiring systems;
- All new electronic devices including compact fluorescent lamps (CFLs) should be constructed with filters to block high-frequency voltage transients from being conducted back onto electrical wiring systems;
- The Panel recommends electric field reductions from electrical wiring in buildings based on evidence of increased cancer risk from prolonged or repetitive electric field exposure. The United States National Electrical Code (NEC) and other governmental codes relating to building design and construction should be revised so that all new electrical wiring is enclosed in a grounded metal shield;
- The United States NEC and other governmental codes that disallow net current on electrical wiring should be better enforced, and ground fault interrupters (GFIs) should be installed on all electrical circuits in order to reduce net current.

Radiofrequency/Microwave Radiation
Exposure Limit Recommendations

Present guidelines, such as IEEE, FCC, and ICNIRP, are not adequate to protect humans from harmful effects of chronic EMF exposure. The existing scientific knowledge is, however, not sufficient at this stage to formulate final and definite science-based guidelines for all these fields and conditions, particularly for such chronic exposure as well as contributions of the different parameters of the fields, e.g. frequency, modulation, intensity, and window effects. The values suggested below are, thus, provisional and may be altered in the future.

- For whole-body (in vivo experiments) or cell culture-based exposure, the Seletun Scientific Panel finds sufficient evidence to establish a

scientific benchmark for adverse health effect at 0.0166 W/kg based on at least 32 scientific studies reporting low-intensity effects (defined as studies reporting effects at exposures of 0.1 W/kg or lower) /8-39/.

- The Panel recommends a provisional whole-body limit of 0.00033 W/kg by incorporation of an additional 50-fold safety margin applied to the scientific benchmark of 0.0166 W/kg. This is consistent with both ICNIRP and IEEE/FCC safety factors. An additional 10-fold reduction is applied to take prolonged exposure into account (because 29 of the 32 studies are acute exposure only), giving a final whole-body limit of 0.000033 W/kg (33 μW/kg). No further safety margin or provision for sensitive populations is incorporated. This may need to be lowered in the future.
- Based on power density measurements, the Seletun Scientific Panel finds sufficient evidence for a whole-body scientific benchmark for adverse health effect exists down to 85 mW/m^2 (0.0085 mW/cm^2 or 8.5 $\mu W/cm^2$) based on at least 17 scientific studies reporting low-intensity effects on humans. Taking more recent human studies conducted near base stations, or at base-station RF levels, Kundi and Hutter /57/ report that the levels must exceed 0.5-1.0 mW/m^2 (0.05 to 0.1 uW/cm^2) for effects to be seen; /40-57/.
- The Panel recommends a provisional whole-body (far-field) limit of 1.7 mW/m^2 (also = 0.00017 mW/cm^2 = 0.17 $\mu W/cm^2$) by incorporation of an additional 50-fold safety margin applied to the scientific benchmark of 85 mW/m^2. This is consistent with both ICNIRP and IEEE/FCC safety factors. This may need to be lowered in the future.
- It can be argued that a further 10-fold reduction is not justified since 13 of the 17 studies are already testing for long-term RF exposure. However, considering that the latest human population studies as reported by Kundi & Hutter (2009) do not show effects below 0.5-1.0 mW/m^2, it can also then be argued that an additional 10-fold reduction on precautionary grounds is justified. If another 10-fold reduction is applied, the recommended level would then be 0.17 mW/m^2 (also 0.000017 mW/cm^2 = 0.017 $\mu W/cm^2$);
- The Seletun Scientific Panel recommends these numeric limits to governments and health agencies for adoption in place of ICNIRP, IEEE/FCC and other outdated public safety guidelines and limits in use around the world. This approach is based on traditional public health principles that support taking actions to protect public health when sufficient evidence is present. Sufficient scientific evidence and public health concern exist today based on increased risk for cancer, adverse fertility and reproductive outcomes, immune disruption, neurological diseases, increased risk of road collisions and injury-producing events, and impairment of cognition, behaviour, performance, mood status, and disruption of sleep;
- Numeric limits recommended here do not yet take into account sensitive populations (EHS, immune-compromised, the fetus, developing children, the elderly, people on medications, etc). Another safety margin is, thus, likely justified further below the numeric limits for EMF exposure recommended here;
- The Scientific Panel acknowledges that numeric limits derived here for new biologically-based public exposure standards are still a billion times higher than natural EMF levels at which all life evolved.

Specific Recommendations for mobile (cell) and cordless phone use

- The Seletun Scientific Panel recommends that users keep mobile (cell) phones away from head and body;
- The Seletun Scientific Panel recommends that users keep mobile (cell) phones and PDAs* switched off if worn or carried in a pocket or

holster, or on a belt near the body. *PDA is generic for any type of Personal Digital Assistant or hand-held computer device;

- The Panel strongly recommends against the use of mobile (cell) and cordless phones and PDAs by children of any age;
- The Panel strongly recommends against the use of mobile (cell) and cordless phones and PDAs by pregnant women;
- The Panel recommends that use of mobile (cell) and cordless phones and PDAs be curtailed near children or pregnant women, in keeping with preventative and precautionary strategies. The most vulnerable members of society should have access to public places without fear of harm to health;
- Public access to public places and public transportation should be available without undue risk of EMF exposure, particularly in enclosed spaces (trains, airplanes, buses, cars, etc) where the exposure is likely to be involuntary;
- The Panel recommends wired internet access in schools, and strongly recommends that schools do not install wireless internet connections that create pervasive and prolonged EMF exposures for children;
- The Panel recommends preservation of existing land-line connections and public telephone networks;
- The Panel recommends against the use of cordless phones (DECT phones) and other wireless devices, toys and baby monitors, wireless internet, wireless security systems, and wireless power transmitters in SmartGrid-type connections that may produce unnecessary and potentially harmful EMF exposures;
- The Panel recognizes that wired internet access (cable modem, wired Ethernet connections, etc) is available as a substitute;
- The Panel recommends use of wired headsets, preferably with hollow-tube segments;
- The Panel recommends avoidance of wireless (Bluetooth-type) headsets in general;
- The Panel encourages the removal of speakers from headsets on wireless phones and PDAs;
- The Panel encourages 'auto-off switches' for mobiles (cells) and PDAs that automatically turn off the device when placed in a holster;
- The Panel strongly discourages the technology that allows one mobile (cell) phone to act as a repeater for other phones within the general area. This can increase exposures to EMF that are unknown to the person whose phone is "piggy-backed" upon without their knowledge or permission;
- The Panel recommends the use of telephone lines (land-lines) or fiber optic cables for SmartGrid type energy conservation infra-structure. Utilities should choose options that do not create new, community-wide exposures from wireless components of SmartGrid-type projects. Future health risks from prolonged or repetitive wireless exposures of SmartGrid-type systems may be avoided by using telephone lines or fiber-optic cable. The Panel endorses energy conservation but not at the risk of exposing hundreds of millions of families in their homes to a new, involuntary source of wireless radiofrequency radiation.

The undersigned recognize the duty of governments and their health agencies to educate and warn the public, to implement measures balanced in favor of the Precautionary Principle, to monitor compliance with directives promoting alternatives to wireless, and to fund research and policy development geared toward prevention of exposure.

The undersigned urge governments and their health agencies to adopt new interim numeric limits and new timetables for implementation of biologically-based precautionary action to limit exposures to EMF.

Agreed 19 November 2009
(as revised through April 20, 2010)
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Electromagnetic fields stress living cells

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Abstract

Electromagnetic fields (EMF), in both ELF (extremely low frequency) and radio frequency (RF) ranges, activate the cellular stress response, a protective mechanism that induces the expression of stress response genes, e.g., HSP70, and increased levels of stress proteins, e.g., hsp70. The 20 different stress protein families are evolutionarily conserved and act as 'chaperones' in the cell when they 'help' repair and refold damaged proteins and transport them across cell membranes. Induction of the stress response involves activation of DNA, and despite the large difference in energy between ELF and RF, the same cellular pathways respond in both frequency ranges. Specific DNA sequences on the promoter of the HSP70 stress gene are responsive to EMF, and studies with model biochemical systems suggest that EMF could interact directly with electrons in DNA. While low energy EMF interacts with DNA to induce the stress response, increasing EMF energy in the RF range can lead to breaks in DNA strands. It is clear that in order to protect living cells, EMF safety limits must be changed from the current thermal standard, based on energy, to one based on biological responses that occur long before the threshold for thermal changes.

Keywords: DNA; Biosynthesis; Electromagnetic fields; ELF; RF

1. Electromagnetic fields (EMF) alter protein synthesis

Until recently, genetic information stored in DNA was considered essentially invulnerable to change as it was passed on from parent to progeny. Mutations, such as those caused by cosmic radiation at the most energetic end of the EM spectrum, were thought to be relatively infrequent. The model of gene regulation was believed to be that the negatively charged DNA was tightly wrapped up in the nucleus with positively charged histones, and that most genes were 'turned off' most of the time. Of course, different regions of the DNA code are being read more or less all the time to replenish essential proteins that have broken down and those needed during cell division.

New insights into the structure and function of DNA have resulted from numerous, well-done laboratory studies. The demonstration that EMF induces gene expression and the synthesis of specific proteins [1,2] generated considerable controversy from power companies, government agencies, physicists, and most recently, cell phone companies. Physicists have insisted that the reported results were not possible because there was not enough energy in the power frequency range (ELF) to activate DNA. They were thinking solely of mechanical interaction with a large molecule and not of the large hydration energy tied up in protein and DNA structures that could be released by small changes in charge [3]. Of the biologists who accepted such results [4], most thought that the EMF interaction originated at, and was amplified by, the cell membrane and not with DNA.

It is now generally accepted that weak EMF in the power frequency range can activate DNA to synthesize proteins. An EMF reactive sequence in the DNA has been identified [5] and shown to be transferable to other gene promoters [6]. This DNA sequence acts as an EMF sensitive antenna

Abbreviations: EMF, electromagnetic fields; Hz, hertz; ELF, extremely low frequency; RF, radio frequency; MAPK, mitogen activated protein kinase; ERK1\2, extracellular signal regulated kinase; JNK, c-Jun-terminal kinase p38MAPK; SAPK, stress activated protein kinase; NADH, nicotinamide adenine dinucleotide dehydrogenase; ROS, reactive oxygen species.

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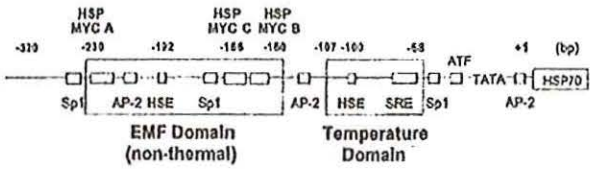

Fig. 1. Diagram of the HSP70 promoter showing the two different DNA sequences that have been identified as activated by EMF (non-thermal) and by thermal stimuli, respectively. The EMF domain contains three nCTCTn consensus sequences (electromagnetic response elements; EMRE), and differs from the consensus sequence (nGAAn) in the temperature or thermal domain.

that responds to EMF when transfected into reporter genes. Research at the more energetic levels of power frequency [7] and in the RF [8] ranges has shown that exposure to EMF can lead to breaks in the DNA strands. Therefore, DNA can no longer be considered unaffected by environmental EMF levels. It can be activated and damaged by EMF at levels that are considered safe [9]. The vulnerability of DNA to environmental influences and the possible dangers associated with EMF, had been underscored by discovery of EMF activation of the cellular stress response in the ELF range [10,11]. The cellular stress response is an unambiguous signal by the cell that EMF is potentially harmful.

2. Physiological stress and cellular stress

Discussions of physiological stress mechanisms usually describe responses of the body to pain, fear, 'oxygen debt' from muscle overexertion. These responses are mediated by organ systems. For example, the nervous system transmits action potentials along a network of nerves to cells, such as adrenal glands, that release rapidly acting agents such as epinephrine and norepinephrine and slower acting mineralocorticoids. These hormones are transported throughout the body by the circulatory system. They mobilize the defenses to cope with the adverse conditions and enable the body to 'fight or flee' from the noxious stimuli. The defensive actions include changes in heart rate, breathing rate, muscle activity, etc.

In addition to the responses of organ systems, there are protective mechanisms at the cellular level known as the cellular stress response. These mechanisms are activated by damage to cellular components such as DNA and protein [12], and the responses are characterized by increased levels of stress proteins [13] indicating that stress response genes have been upregulated in response to the stress.

The first stress response mechanism identified was the cellular reaction to sharp increases in temperature [14] and was referred to as 'heat shock', a term that is still retained in the nomenclature of the protective proteins, the hsps, heat shock proteins. Stress proteins are designated by the prefix 'hsp' followed by a number that gives the molecular weight in kilodaltons. There are about 20 different protein families ranging in molecular weight from a few kilodaltons to over 100 kD, with major groups of proteins around 30 kD, 70 kD and 90 kD.

Research on the 'heat shock' response has shown that hsp synthesis is activated by a variety of stresses that are potentially harmful to cells, including physical stimuli like pH and osmotic pressure changes, as well as chemicals such as alcohol and toxic metal ions like Cd^{2+}. EMF is a recent addition to the list of physical stimuli. It was initially shown in the power frequency (extremely low frequency, ELF) range [13], but shortly afterwards, radio frequency (RF) fields [15] and amplitude modulated RF fields [16] were shown to activate the same stress response.

Studies of stress protein stimulation by low frequency EMF have focused on a specific DNA sequence in the gene promoter that codes for hsp70, a major stress protein. Synthesis of this stress protein is initiated in a region of the promoter (see Fig. 1) where a transcription factor known as heat shock factor 1 (HSF-1) binds to a heat shock element (HSE). This EMF sensitive region on the HSP70 promoter is upstream from the thermal domain of the promoter and is not sensitive to increased temperature. The binding of HSF-1 to HSE occurs at −192 in the HSP70 promoter relative to the transcription initiation site. The EMF domain contains three nCTCTn myc-binding sites −230, −166 and −160 relative to the transcription initiation site and upstream of the binding sites for the heat shock (nGAAn) and serum responsive elements [5,6,17,18]. The electromagnetic response elements (EMREs) have also been identified on the c-*myc* promoter and are also responsive to EMF. The sensitivity of the DNA sequences, nCTCTn, to EMF exposures has been demonstrated by transfecting these sequences into CAT and Luciferase reporter genes [6]. Thus, the HSP70 promoter contains different DNA regions that are specifically sensitive to different stressors, thermal and non-thermal.

Induction of increased levels of the major stress protein, hsp70, by EMF is rapid, within 5 min. Also it occurs at extremely low levels of energy input, 14 orders of magnitude lower than with a thermal stimulus [10]. The far greater sensitivity to EMF than to temperature change in elevating the protective protein, hsp70, has been demonstrated to have potential clinical application, preventing injury from ischemia reperfusion [19–21]. George et al. [22] have shown the non-invasive use of EMF-induced stress proteins improved hemodynamic parameters during reperfusion

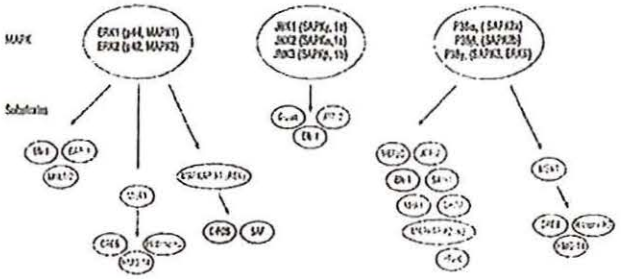

Fig. 2. The four mitogen activated protein kinase (MAPK) signaling cascades identified to date are: extracellular signal regulated kinase 1/2 (ERK), c-Jun-terminal kinase (JNK), p38MAPK and stress activated protein kinase (SAPK). Elements of the three MAPKinase pathways that have been identified as activated by EMF are shown as the shaded circles.

following ischemia. This effect occurred in the absence of measurable increased temperature.

3. EMF interaction with signaling pathways

EMF penetrate cells unattenuated and so can interact directly with the DNA in the cell nucleus, as well as other cell constituents. However, biological agents are impeded by membranes and require special mechanisms to gain access to the cell interior. Friedman et al. [23] have demonstrated that the initial step in transmitting extracellular information from the plasma membrane to the nucleus of the cell occurs when NADH oxidase rapidly generates reactive oxygen species (ROS). These ROS stimulate matrix metalloproteinases that allow them to cleave and release heparin binding epidermal growth factor. This secreted factor activates the epidermal growth receptor, which in turn activates the extracellular signal regulated kinase 1\2 (ERK) cascade. The ERK cascade is one of the four mitogen-activated protein kinase (MAPK) signaling cascades that regulate transcriptional activity in response to extracellular stimuli. The elements of the three MAPK signaling cascades implicated in exposures to ELF and RF are highlighted in Fig. 2.

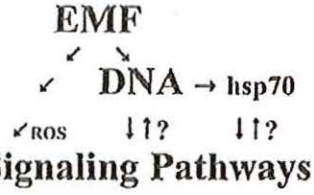

Fig. 3. The signaling pathways and the stress response are activated by EMF. The activation mechanisms discussed in the text are indicated by arrows. In the stress response, DNA activation leads to hsp synthesis and may be due to direct EMF interaction with DNA. The signaling pathways are activated by reactive oxygen species (ROS) that are probably generated by EMF. Possible interactions between the pathways, DNA and hsp are indicated with question marks. In any case, EMF leads to activation of all the processes shown.

The four MAPK cascades are: (1) ERK, (2) c-Jun-terminal kinase (JNK), (3) stress activated protein kinase (SAPK) and (4) p38SAPK. Each of the cascades is composed of three to six tiers of protein kinases, and their signals are transmitted by sequential phosphorylation and activation of the protein kinases in each of the tiers. The result is activation of a large number of regulatory proteins, which include a set of transcription factors, e.g., c-Jun, c-Fos, hsp27 and hsp70. Activation of the stress response is accompanied by activation of specific signal transduction cascades involved in regulating cell proliferation, differentiation and metabolism [24–26]. The MAPK pathways have been characterized in several cell types [24,27–30]. Exposure to non-thermal ELF as well as thermal RF affects the expression of many cellular proteins [23–25] (Fig. 3).

The elevated expression of these protein transcription factors participate in the induction of various cellular processes, including several that are affected by cell phones, e.g., replication and cell-cycle progression [25,31] and apoptosis [32]. RF fields have been shown to activate specific transcription factor binding that stimulate cell proliferation and induce stress proteins [25,33]. It has been reported [31] that within 10 min of cell phone exposures, two MAPKinase cascades, p38 and ERK1\2, are activated. Both ELF and RF activate the upregulation of the HSP70 gene and induction of elevated levels of the hsp70 protein. This effect on RNA transcription and protein stability is controlled by specific protein transcription factors that are elements of the mitogen MAPK cascade.

EMF also stimulate serum response factor which binds to the serum response element (SRE) through ERK MAPK activation and is associated with injury and repair *in vivo* and *in vitro*. The SRE site is on the promoter of an early response gene, c-fos, which under specific cellular circumstances has oncogenic properties. The c-fos promoter is EMF-sensitive; a 20 min exposure to 60 Hz 80mG fields significantly increases c-*fos* gene expression [34]. The SRE accessory protein,

Elk-1, contains a growth-regulated transcriptional activation domain. ERK phosphorylation potentiates Elk-1 and transactivation at the c-*fos* SRE [29].

During the past twenty years, the growing use of cellular phones has aroused great concern regarding the health effects of exposure of the brain to 900 MHz RF waves. Despite claims that the energy level is too low to induce changes in DNA and that the devices are safe, the non-thermal effects that have been demonstrated at both ELF and RF exposure levels can cause physiological changes in cells and tissues even at the level of DNA. Finally, it should be mentioned that some of the pathways described in this section also have roles in protein synthesis via RNA polymerase III, an enzyme in oncogenic pathways [35] and could, therefore, provide a mechanistic link between cancer and EMF exposure.

4. Cells affected by the stress response

Reviews on EMF and the stress response have appeared for the ELF range [13] and for the RF range [36]. The most recent review was published online in section 7 of the Bioinitiative Report [9], and it summarized both ELF and RF studies, mainly at frequencies 50 Hz, 60 Hz, 900 MHz and 1.8 GHz. The citations in that review were not exhaustive, but the different frequencies and biological systems represent the diversity of results on stimulation of DNA and stress protein synthesis in many different cells. It is clear that the stress response does not occur in reaction to EMF in all types of cells, and sometimes because of the use of tissue cultured cell lines, even the same cell line can give opposite results in the same laboratory [37].

Many different types of cells have been shown to respond to EMF, both *in vivo* and *in vitro*, including epithelial, endothelial and epidermal cells, cardiac muscle cells, fibroblasts, yeast, *E. coli*, developing chick eggs, and dipteran cells (see Bioinitiative Report [9], section 7). Tissue cultured cells are less likely to show an effect of EMF, probably because immortalized cells have been changed significantly to enable them to live indefinitely in unnatural laboratory conditions. This may also be true of cancer cells, although some (e.g., MCF7 breast cancer cells) have responded to EMF [38,39], and in HL60 cells, one cell line responds to EMF while another does not [24]. Czyz et al. [16] found that p53-deficient embryonic stem cells showed an increased EMF response, but the wild type did not.

A broad study of genotoxic effects (i.e., DNA damage) in different kinds of cells [40] found no effects with lymphocytes, monocytes and skeletal muscle cells, but did find effects with fibroblasts, melanocytes and rat granulosa cells. Other studies [41,42] have also found that the blood elements, such as lymphocytes and monocytes are natural cells that have not responded. Since mobile cells can easily move away from a stress, there would be little selective advantage and evolutionary pressure for developing the stress response. The lack of response by skeletal muscle cells is related to the need to desensitize the cells to excessive heating during activity. Unlike slow muscle fibers that do synthesize hsp70, cells containing fast muscle fibers do not synthesize hsp70 to protect them from over-reacting to the high temperatures reached a during activity.

Table 1
Biological thresholds in the ELF range.

Biological system	Threshold (μT)[a]	Reference
Acceleration of reaction rates		
Na,K-ATPase	0.2–0.3	Blank and Soo [49]
cytochrome oxidase	0.5–0.6	Blank and Soo [43]
ornithine decarboxylase	~2	Mullins et al. [58]
malonic acid oxidation	<0.5	Blank and Soo [59]
Biosynthesis of stress proteins		
HL60, Sciara, yeast,	<0.8	Goodman et al. [11]
breast (HTB124, MCF7)	<0.8	Lin et al. [39]
chick embryo (anoxia)	~2	DiCarlo et al. [60]
Breast cancer (MCF7) cell growth block melatonin inhibition	0.2 < 1.2	Liburdy et al. [38]
Leukemia epidemiology	0.3–4	Ahlbom et al. [61] Greenland et al. [62]

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

5. EMF–DNA interaction mechanisms: electron transfer

The biochemical compounds in living cells are composed of charges and dipoles that can interact with electric and magnetic fields by various mechanisms. An example discussed earlier is the generation of reactive oxygen species (ROS) in activation of the ERK signaling cascade. The cellular stress response leading to the synthesis of stress proteins is also activated by EMF. However, the specific reaction is not known, except that it is stimulated by very weak EMF. For this reason, our focus has been on molecular processes that are most sensitive to EMF and that could cause the DNA to come apart to initiate biosynthesis. We have suggested that direct EMF interaction with electrons in DNA is likely for the following reasons:

- The largest effects of EMF would be expected on electrons because of their high charge to mass ratio. At the sub-atomic level, one assumes that electrons respond instantaneously compared to protons and heavier atomic nuclei, as in the Born-Oppenheimer Approximation. The very low field strengths and durations that activate the stress response and other reactions (Table 1) suggest interaction with electrons, and make ion-based mechanisms unlikely.
- Weak ELF fields have been shown to affect the rates of electron transfer reactions [43,44]. A 10 μT magnetic field exerts a very small force of only $\sim 10^{-20}$ N on a unit charge,

but this force can move an isolated electron more than a bond length, ~1 nm, in ~1 nanosecond.

- There is a specific EMF responsive DNA sequence that is associated with the response to EMF (Fig. 1), and that retains this property when transfected
- Displacement of electrons in DNA would cause local charging that has been shown to lead to disaggregation of biopolymers [45].
- As the energy in an EMF stimulus increases, there is an increase in single strand breaks, followed by double strand breaks, suggesting an interaction with EMF at all energy levels [46].

Effects of EMF on electrons in chemical reactions were detected indirectly in studies on the Na,K-ATPase [47], a ubiquitous enzyme that establishes the normal Na and K ion gradients across cell membranes. Electric and magnetic fields, each accelerated the reaction only when the enzyme was relatively inactive. It is reasonable to assume that the threshold response occurs when the same charge is affected by the two fields, so the velocity (v) of the charge (q) could be calculated from these measurements and its nature determined. Assuming both fields exert the same force at the threshold, the electric (E) and the magnetic (B) forces should be equal.

$$F = qE = qvB. \quad (1)$$

From this $v = E/B$, the ratio of the threshold fields, and by substituting the measured thresholds [48,49], $E = 5 \times 10^{-4}$ V/m and $B = 5 \times 10^{-7}$T (0.5 μT), we obtain $v = 10^3 m/s$. This very rapid velocity, similar to that of electrons in DNA [50], indicated that electrons were probably involved in the ion transport mechanism of the Na,K-ATPase [47]. An electron moving at a velocity of 10^3 m/s crosses the enzyme ($\sim 10^{-8}$ m) before the ELF field has had a chance to change. This means that a low frequency sine wave signal is effectively a repeated DC pulse. This is true of all low frequency effects on fast moving electrons.

Studies of effects of EMF on electron transfer in cytochrome oxidase, ATP hydrolysis by the Na,K-ATPase, and the Belousov–Zhabotinski (BZ) redox reaction, have led to certain generalizations:

- EMF can accelerate reaction rates, including electron transfer rates
- EMF acts as a force that competes with the chemical forces in a reaction. The effect of EMF varies inversely with the intrinsic reaction rate, so EMF effects are only seen when intrinsic rates are low. (This is in keeping with the therapeutic efficacy of EMF on injured tissue, while there is usually little or no effect on normal tissue.)
- Experimentally determined thresholds are low (~0.5 μT) and comparable to levels found by epidemiology. See Table 1.
- Effects vary with frequency, with different optima for the reactions studied: The two enzymes showed broad frequency optima close to the reaction turnover numbers for Na,K-ATPase (60 Hz) and cytochrome oxidase (800 Hz), suggesting that EMF interacted optimally when in synchrony with the molecular kinetics. This is not true for EMF interactions with DNA, which are stimulated in both ELF and RF ranges and do not appear to involve electron transfer reactions with well-defined kinetics.

Probably the most convincing evidence for a frequency sensitive mechanism that involves stimulation of DNA is activation of protein synthesis in striated muscle. In this natural process, specific muscle proteins are synthesized by varying the rate of the (electrical) action potentials in the attached nerves [51]. The ionic currents of the action potentials that flow along and through the muscle membranes, also pass through the muscle cell nuclei that contain the DNA codes for the muscle proteins. Two frequencies were studied in muscle, high (100 Hz) and low (10 Hz) frequency, corresponding to the frequencies of the fast muscles and slow muscles that have different contraction rates and different muscle proteins. In the experiments, either the fast or slow muscle proteins were synthesized at the high or low frequency stimulation rates corresponding to the frequency of the action potentials. The clear dependence of the protein composition on the frequency of the action potentials indicates a relation between stimulation and activation of DNA in muscle physiology. The process is undoubtedly far more complicated and unlikely to be a simple electron transfer reaction as with cytochrome oxidase. It is more probable that an entire region of DNA coding for a group of related proteins is activated simultaneously.

A mechanism based on electron movement is in keeping with the mV/m electric field and μT magnetic field thresholds that affect the Na,K-ATPase. The very small force on a charge ($\sim 10^{-20}$ N) can affect an electron, but is unlikely to have a direct effect on much more massive ions and molecules, especially if they are hydrated. Ions are affected by the much larger DC electric fields of physiological membrane processes. The low EMF energy can move electrons, cause small changes in charge distribution and release the large hydration energy tied up in protein and DNA structures [3]. Electrons have been shown to move in DNA at great speed [50], and we have suggested that RF and ELF fields initiate the stress response by directly interacting and accelerating electrons moving within DNA [52,53].

A mechanism based on electron movement also provides insight into why the same stress response is stimulated by both ELF and RF even though the energies of the two stimuli differ by orders of magnitude. A typical ELF cycle at 10^2Hz lasts 10^{-2} s and a typical RF cycle at 10^{11} Hz lasts 10^{-11} s. Because the energy is spread over a different number of cycles/second in the two ranges, the energy/cycle is the same in both ELF and RF ranges. Since electron movement occurs much faster than the change of field, both frequencies are seen by rapidly moving electrons as essentially DC pulses. Each cycle contributes to electron movement at both

frequencies, but more rapidly at the higher frequency. The fluctuation of protons between water molecules in solution at a frequency of about 10^{12} Hz [54] gives an indication of the speed of electron movement, and may suggest an upper limit of the frequency in which sine wave EMF act as DC pulses.

6. DNA biology and the EM spectrum

Research on DNA and the stress response has shown that the same biology occurs across divisions of the EM spectrum, and that EMF safety standards based on cellular measures of potential harm should be much stricter. These data also raise questions about the utility of spectrum sub-divisions as the basis for properly assessing biological effects and setting separate safety standards for the different sub-divisions. The frequencies of the EM spectrum form a continuum, and division into frequency bands is only a convenience that makes it easier to assign and regulate different portions of the spectrum for practical uses, such as the different design requirements of devices for EMF generation and measurement. Except for the special case of the visual range, the frequency bands are not based on biology, and the separate bands now appear to be a poor way of dealing with biological responses needed for evaluating safety. The DNA studies indicate the need for an EMF safety standard rooted in biology and a rational basis for assessing health implications.

DNA responses to EMF can be used to create a single scale for evaluation of EMF dose because:

- The same biological responses are stimulated in ELF and RF ranges.
- The intensity of EMF interactions with DNA leads to greater effects on DNA as the energy increases with frequency. In the ELF range, the DNA is only activated to initiate protein synthesis, while single and double strand breaks occur in the more energetic RF and ionizing ranges.

A scale based on DNA biology also makes possible an approach to a quantitative relation between EMF dose and disease. This can be done by utilizing the data banks that have been kept for A-bomb exposure and victims of nuclear accidents, data that link exposure to ionizing radiation and subsequent development of cancer. Utilizing experimental studies of DNA breaks with ionizing radiation, it is possible in principle to relate cancer incidence to EMF exposures. It should be possible to determine single and double strand breaks in a standard preparation of DNA, caused by exposure to EMF for a specified duration, under standard conditions. Although many studies of DNA damage and repair rates under different conditions would be needed, this appears to be a possible experimental approach to assessing the relation between EMF exposure and disease.

7. The stress response and safety standards

Most scientists believe that basic research eventually pays off in practical ways. This has certainly been true of EMF research on the stress response, where EMF stimulated stress proteins have been used to minimize damage to ischemic tissues on reperfusion. However, more importantly, biological effects stimulated by both ELF and RF have shown that the standards used for developing safety guidelines are not protective of cells.

First and foremost, it is important to realize that the stress response occurs in reaction to a potentially harmful environmental influence. The stress response is an unambiguous indication that cells react to EMF as potentially harmful. It is therefore an indication of compromised cell safety, given by the cell, in the language of the cell. The low threshold level of the stress response shows that the current safety standards are much too high to be considered safe.

safety standards set much too high to be safe.

In general, cellular processes are unusually sensitive to fields in the environment. The biological thresholds in the ELF range (Table 1) are in the range of 0.5–1.0 μT—not very much higher than the ELF backgrounds of ~0.1 μT. The relatively low field strengths that can affect biochemical reactions is a further indication that cells are able to sense potential danger long before there is an increase in temperature.

EMF research has also shown that exposure durations do not have to be prolonged to have an effect. Litovitz et al. [55,56], working with the enzyme ornithine decarboxylase, showed an EMF response when cells were exposed for only 10 s to ELF or ELF modulated 915 MHz, providing that the exposure was continuous. Gaps in the sine wave resulted in a reduced response, and interference with the sine wave in the form of superimposed ELF noise also reduced the response [57]. The interfering effect of noise has been shown in the RF range by Lai and Singh [46], who reported that noise interferes with the ability of an RF signal to cause breaks in DNA strands. The decreased effect when noise is added to a signal is yet another indication that EMF energy is not the critical factor in causing a response. In fact, EMF noise appears to offer a technology for mitigating potentially harmful effects of EMF in the environment.

EMF research has shown that the thermal standard used by agencies to measure safety is at best incomplete, and in reality not protective of potentially harmful non-thermal fields. Non-thermal ELF mechanisms are as effective as thermal RF mechanisms in stimulating the stress response and other protective mechanisms. The current safety standard based on thermal response is fundamentally flawed, and not protective.

Finally, since both ELF and RF activate the same biology, simultaneous exposure to both is probably additive and total EMF exposure is important. Safety standards must consider total EMF exposure and not separate standards for ELF and RF ranges.

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FULL PAPER

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Childhood leukaemia close to high-voltage power lines – the Geocap study, 2002–2007

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Background: High-voltage overhead power lines (HVOLs) are a source of extremely low-frequency magnetic fields (ELF-MFs), which are classified as possible risk factors for childhood acute leukaemia (AL). The study was carried out to test the hypothesis of an increased AL incidence in children living close to HVOL of 225–400 kV (VHV-HVOL) and 63–150 kV (HV-HVOL).

Methods: The nationwide Geocap study included all the 2779 cases of childhood AL diagnosed in France over 2002–2007 and 30 000 contemporaneous population controls. The addresses at the time of inclusion were geocoded and precisely located around the whole HVOL network.

Results: Increased odds ratios (ORs) were observed for AL occurrence and living within 50 m of a VHV-HVOL (OR = 1.7 (0.9–3.6)). In contrast, there was no association with living beyond that distance from a VHV-HVOL or within 50 m of a HV-HVOL.

Conclusion: The present study, free from any participation bias, supports the previous international findings of an increase in AL incidence close to VHV-HVOL. In order to investigate for a potential role of ELF-MF in the results, ELF-MF at the residences close to HVOL are to be estimated, using models based on the annual current loads and local characteristics of the lines.

High-voltage overhead power lines (HVOLs) are one of the major sources of extremely low-frequency magnetic fields (ELF-MFs), considered a possible risk factor for childhood leukaemia. In the absence of any underlying biological hypothesis, the International Agency for Research on Cancer (IARC) classified ELF-MF as possible carcinogens (group 2B), based on epidemiological observations over more than two decades (IARC, 2002). The first meta-analyses concluded that exposure to ELF-MF levels of at least 0.3 μT was significantly associated with an increased incidence of childhood acute leukaemia (AL) (odds ratio (OR) = 1.7 (1.2–2.3) for exposures $\geqslant$0.3 μT (Greenland *et al*, 2000) and OR = 2.0 (1.3–3.3) for exposures $\geqslant$0.4 μT (Ahlbom *et al*, 2000)). A recent meta-analysis of the studies published after 2000 (Kheifets *et al*, 2010) generated consistent but weaker results (OR = 1.4 (0.9–2.4) for exposures $\geqslant$0.3 μT). The large British study by Draper *et al* (2005) focused on the proximity of VHV-HVOL and showed an association between AL and residence at birth <200 m from a VHV-HVOL (OR = 1.7 (1.1–2.5)) and, to a lesser extent, between 200 and 600 m from a VHV-HVOL (OR = 1.2 (1.0–1.5)). With the same data, the relative risk was not significantly increased for estimates of ELF-MF $\geqslant$0.4 μT (Kroll *et al*, 2010). High-voltage overhead power lines account for only a fraction of ELF-MF exposure, but, in their near vicinity, constitute the main source of background exposure (Schüz *et al*, 2000; Maslanyj *et al*, 2007).

The aim of the present study was to test whether the risk of AL was increased in the vicinity of HVOL, where children were expected to encounter higher residential exposure to ELF-MF. We followed a two-step approach. The present one aims at investigating the relationship between AL and distance to HVOL. The second step will rely on calculated residential exposure to ELF-EMF based on characteristics of the neighbouring HVOL. The study, the first in France, was based on the geolocation of the last

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address and covered the entire mainland over a recent period (2002–2007), on an exhaustive basis, free from participation bias, and was based on a geographic information system (GIS) using precise and recent databases to locate the dwellings and HVOL.

MATERIALS AND METHODS

The Geocap case-control study. The Geocap case-control study included all the 2779 French childhood AL cases aged <15 years at the end of the year of diagnosis, diagnosed between 1 January 2002 and 31 December 2007, residing in mainland France (excluding Corsica for which HVOL information was not available). The cases were obtained from the French National Registry of Childhood Hematopoietic Malignancies (Lacour *et al*, 2010).

Over the same period (2002–2007), six yearly sets of 5000 control addresses were randomly sampled from the paediatric population of mainland France by the National Institute for Statistics and Economic Studies (INSEE), using the income and council tax databases of the French households. These databases contain the addresses and income information of all the households in France, irrespective of employment status, and list the children in each household by year of birth. The sample was stratified on the 94 French mainland administrative areas (*Départements*). The individual variables available for the controls were the year of birth, number of children in the household and last address. Demographic and socioeconomic characteristics of the municipality (*Commune*) of residence were also used as contextual variables. The sample of 30 000 controls was closely representative of the source population in terms of age and number of children in the household, and in terms of contextual variables, that is, size of the urban unit, median income, proportion of blue-collar workers, proportion of subjects who successfully completed high school (baccalaureate holders) and proportion of homeowners in the *Commune* of residence (Sermage-Faure *et al*, 2012).

Geocoding. The residence considered for geolocation was the residence at the time of diagnosis for the cases and that at the time of inclusion for the controls. Residential histories, particularly addresses at birth, were not available. The method for geocoding the addresses of cases and controls was compiled, checked for consistency and corrected when necessary by GEOCIBLE, an outside service provider, in close cooperation with the epidemiology research team. The addresses were geocoded blind to case/control status, using the MAPINFO GIS, NAVTEQ street databases and detailed vectorized maps from the National Geographic Institute (IGN). Automatic processes were checked and completed by visual inspection of maps when necessary. Ultimately, only 3% of the cases and 1% of the controls could not be located more precisely than by their *Commune* of residence and were allocated the coordinates of their *Commune* town hall.

In the Navteq and IGN databases, the geocodes are given at the middle of the street in front of the number in the street (i.e., the front door, the entrance of the plot or the projection of centre of the plot along the street), generally corresponding to the mailbox residence. Most often in urban areas and in collective housing, the mailbox is attached to the building of residence. However, especially in countryside, the house can be at a distance from the entrance of the plot, where the mailbox is.

Depending on whether the databases enabled location of the home directly or by extrapolation from the nearest or more distant neighbours, the coordinates were assigned a degree of uncertainty along the street ranging from 20 m (exact number in the database) to the size of a *Commune* (Table 1). The scale of uncertainty provided by Geocible had been determined previously, based on the size of the objects to locate and on the mean differences between estimated and measured geocodes. The best geocoded addresses were assigned an uncertainty of 20 m, equal to the mean value of the estimated coordinates given by the GIS and the center of the house. Altogether, 1946 cases (70%) and 23 171 controls (77%) were located by their exact number in the street (best geocoded addresses, uncertainty of 20 m), whereas 303 cases (11%) and 2459 controls (8.6%) were located by a segment of a short street or by a close number (uncertainty of 50–100 m).

Table 1. Distribution of the cases and controls by category of uncertainty of location by geocoding

		Cases		Controls	
Category of accuracy of address location for geocoding	Uncertainty	*N*	%	*N*	%
At the exact number	20 m	1946	70.0	23 171	77.2
In a section of a short street	50 m	173	6.2	1658	5.5
At a close number	100 m	130	4.7	801	2.7
In a medium street or in a hamlet	300 m	394	14.2	3693	12.3
In a long street	500 m	54	1.9	383	1.3
In a Commune		82	3.0	292	1.0
Total		2779	100.0	30 000	100.0

In addition to the coordinates obtained for all the postal addresses of the Geocap sample, another set of coordinates was also estimated using photographic views obtained from Street View (Google Maps), Géoportail (IGN data) and the French cadaster, when available. This was possible for 72% of the cases and 69% of the controls living <200 m from a HVOL, considering the uncertainty, and used to position the building of residence.

HVOL characteristics and distance from the nearest HVOL. There are 77 400 km of HVOL in France. There are five main types: HVOL of 400 kV (13 350 km), 225 kV (21 200 km), 150 kV (1050 km) and 90 or 63 kV (41 800 km). The HVOLs have been precisely mapped by RTE (*Réseau de Transport d'Electricité*), the French utility in charge of electricity transmission, based on the utility's own database, in which pylons and sections of lines are accurately located, and on the most precise local maps of the national geographic institute (IGN). The distances from the closest HVOLs were estimated by GEOCIBLE.

Statistical analysis. All the statistical analyses were performed using the SAS software package (version 9; SAS Institute Inc., Cary, NC, USA). The ORs, their 95% confidence intervals and two-sided *P*-values were estimated by unconditional logistic regression adjusted for age in 5-year categories and *Département*. Additional analyses stratified by age category were adjusted for age in years.

The subjects were classified in terms of their distance from the closest HVOL (<50, 50–99, 100–199, 200–599 and ⩾600 m). The very high voltage lines, 225 and 400 kV (VHV-HVOL), and the high voltage lines, 63, 90 and 150 kV (HV-HVOL), were separated as dwellings located ⩽50 m from VHV-HVOL are expected to be more frequently exposed to higher ELF-MF than those located ⩽50 m from HV-HVOL (Maslanyj *et al*, 2009). The inverse distance function was used to test for the existence of a trend in AL incidence, assigning 0 to the dwellings located at least 600 m from an HVOL.

All the main analyses were conducted on the whole study sample, without any selection by address uncertainty. The analyses

Table 2. Description of the cases included in the study, by the distance between their residence and the closest HVOL and by voltage category (very high (225–400 kV) or high (63–150 kV)) over the period 2002–2007

	Distance from the closest HVOL						
	225–400 kV HVOL			63–150 kV HVOL			
	0–49 m	50–199 m	⩾200 m	0–49 m	50–199 m	⩾200 m	Total
Gender							
Female	4	12	1246	7	26	1229	1262
Male	5	12	1500	7	28	1482	1517
Age							
<5 years	6	11	1291	8	24	1276	1308
5–9 years	3	10	858	2	18	851	871
10–14 years	0	3	597	4	12	584	600
Down's syndrome	0	0	43	0	0	43	43
AL type							
ALL	8	21	2250	13	46	2220	2279
B-cell precursor ALL	6	12	1056	8	25	1041	1074
T-cell ALL	0	0	173	1	4	168	173
Other ALL	2	9	1021	4	17	1011	1032
AML	1	2	428	1	6	424	431
Other AL	0	1	68	0	2	67	69

Abbreviations: AL = acute leukaemia; ALL = acute lymphoblastic leukaemia; AML = acute myeloblastic leukaemia; HVOL = high-voltage overhead power line.

were conducted on all the cases and also stratified by age group – <5 years old covering most of the incidence peak and ⩾5 years old – and for acute lymphoblastic leukaemia (ALL) alone.

All the analyses were performed taking the same baseline as reference category, that is, the group of children who lived in *Communes* with no part of their territory within 600 m of a HVOL, after accounting for geocoding uncertainty. Thus, the baseline included all the residences definitely located ⩾600 m from a HVOL, even if they were geocoded with the highest uncertainty. Additional sensitivity analyses also included the subjects living at least 600 m from a HVOL in the reference category, even when the *Commune* had a part of its territory within 600 m of a HVOL, in order to account for the possibility that the baseline category might select residences in relation with an AL risk factor.

The 67 cases and 203 controls who lived in a *Commune* partially located within 600 m of a line but who could not be individually located better than at the town hall were considered to have missing data for the distances from HVOL.

Supplementary analyses were performed to test the robustness of the results and account for the spatial extent of the house, by restriction to the best geocoded addresses (uncertainty <20 m), or by modifying the distance cutoffs around the *a priori* value of 50 m (30, 40, 60 and 70 m). In addition, for sensitivity analyses, when the distances using the main geocoding and the photographic views were available, the cases and controls were classified in the category '<50 m from a HVOL', either when the distance from photographic views was <50 m, or when at least one of the two estimated distances was <50 m, or when both the estimated distances were <50 m.

The analyses were also stratified by contextual socioeconomic variables extracted from the 1999 census data for the *Commune* of residence, including the urban status of the *Commune*, median income of the households, proportion of blue-collar workers and proportion of baccalaureate holders. Additional analyses were performed after excluding the cases and controls who lived <5 km from a nuclear power plant, in order to rule out possible confounding by residence in the proximity of a nuclear power plant, which was associated with AL in the present study (Sermage-Faure *et al*, 2012).

RESULTS

Table 2 describes the cases registered from 2002 to 2007 by age, gender and leukaemia subtype, on the basis of the distance of their residences from the closest VHV-HVOL or HV-HVOL.

The 610 cases (22.0%) and 7061 controls (23.5%) who were living in a *Commune* entirely located at least 600 m from any HVOL constituted the baseline of the models. Living within 50 m of the closest HVOL, all voltages considered together, was not associated with AL (OR = 1.2 (0.8–1.9)) (Table 3). However, while no association was observed with residences close to HV-HVOL (OR = 1.0 (0.6–1.7)), an association was evidenced for children who lived within 50 m of a VHV-HVOL (OR = 1.7 (0.9–3.6)). In contrast, the ORs were close to one for the residences located ⩾50 m from a HVOL, even a VHV-HVOL, and no statistically significant trend was observed with the inverse of the distance ($P = 0.28$ for distance from VHV-HVOL). The results for ALL were very similar (OR = 1.9 (0.9–4.0) at <50 m from a VHV-HVOL).

Splitting the sample into children aged <5 years and those aged ⩾5 years showed that the association was only observed for the younger group (Table 4). In that age group, living within 50 m of the closest VHV-HVOL was significantly associated with AL (OR = 2.6 (1.0–7.0)), with a significant trend with the inverse of the distance ($P = 0.03$), whereas there was no association for the older group (OR = 1.0 (0.3–3.3) living within 50 m of the closest VHV-HVOL).

Living within 50 m of a VHV-HVOL was not associated with AL in the *Communes* of urban units with a population >100 000

Table 3. Association between childhood acute leukaemia and distance to the closest HVOL by category of voltage (very high (225–400 kV) or high (63–150 kV)) over the period 2002–2007

	Distance to HVOL																	
	225–400 kV HVOL						63–150 kV HVOL						Any HVOL					
	Cases		Controls				Cases		Controls				Cases		Controls			
	n	%	*n*	%	OR[a]	95% CI	*n*	%	*n*	%	OR[a]	95% CI	*n*	%	*n*	%	OR[a]	95% CI
Baseline[b]	610	22.0	7061	23.5	1.0	Reference	610	22.0	7061	23.5	1.0	Reference	610	22.0	7061	23.5	1.0	Reference
Unknown	67		203				67		203				67		203			
⩾600 m	1924	69.2	20896	69.7	1.0	(0.9–1.2)	1792	64.5	19168	63.9	1.1	(1.0–1.2)	1665	59.9	17937	59.8	1.1	(0.9–1.2)
200–599 m	145	5.2	1416	4.7	1.2	(1.0–1.4)	242	8.7	2740	9.1	1.0	(0.8–1.2)	345	12.4	3633	12.1	1.1	(0.9–1.2)
100–199 m	16	0.6	267	0.9	0.7	(0.4–1.2)	33	1.2	461	1.5	0.8	(0.6–1.2)	44	1.6	669	2.2	0.8	(0.5–1.0)
50–99 m	8	0.3	97	0.3	1.0	(0.5–2.1)	21	0.8	203	0.7	1.2	(0.7–1.9)	25	0.9	284	0.9	1.0	(0.7–1.6)
0–49 m	9	0.3	60	0.2	1.7	(0.9–3.6)	14	0.5	164	0.5	1.0	(0.6–1.7)	23	0.8	213	0.7	1.2	(0.8–1.9)
Total	2779		30000				2779		30000				2779		30000			

Abbreviations: CI = confidence interval; HVOL = high-voltage overhead power line; OR = odds ratio.
[a]OR and 95% CIs estimated by logistic regression adjusted for age at the end of the year (5-year age groups for the 0–14-year-old children, 1-year age groups for the 0–4-year-old children) and *Département* of residence.
[b]Residence in a *Commune* entirely located ⩾600 m from an HVOL.

(Table 4), but an association was observed for the less urban categories of *Commune*. The same pattern was observed for the under-5-year age group (data not shown). The association between AL and living <50 m from a VHV-HVOL appeared more marked, although not significantly so, in the *Communes* with less-favorable contextual socioeconomic characteristics: median income or percentage baccalaureate holders lower than the median value for the controls; percentage blue-collar workers greater than the median value for the controls. Adjustments for those contextual variables, either separately or jointly, did not change the estimates.

No case and only two controls lived within 5 km of a nuclear power plant and <200 m from a VHV-HVOL; excluding them did not modify the results.

Sensitivity analyses restricted to the best geocoded subjects (uncertainty ⩽20 m) generated slightly stronger results (OR = 2.1 (0.9–4.7) for living within 50 m of a VHV-HVOL) (Table 5). The results were also unchanged when the cutoffs were 10 and 20 m above or below the *a priori* value of 50 m, and when the baseline was extended to include the subjects living >600 m from a HVOL, even if their *Commune* of residence had parts located <600 m from a line (data not shown). Lastly, in the sensitivity analyses using the main geocoding distance and that based on photographic views when both were available (Table 5), the ORs remained of the same order of magnitude but the associations were no longer significant (OR = 1.3 (0.5–3.7) for distance <50 m based on photographic views, OR = 1.7(0.6–4.8) for both distances <50 m and OR = 1.5 (0.8–3.1) for at least one distance <50 m from a VHV-HVOL). For 0–4-year-old children, this was also the case (OR = 2.5 (0.6–10.5) for distance <50 m based on photographic views, OR = 3.5 (0.8–15.1) for both distances <50 m and OR = 2.3 (0.9–6.0) for at least one distance <50 m).

DISCUSSION

The present analysis of the Geocap nationwide case–control study was carried out to test the hypothesis that living close to HVOL, particularly VHV-HVOL, was associated with an increased incidence of childhood AL. The study focused on HVOL, a major source of exposure to ELF-MF in neighbouring residences (Schüz *et al*, 2000; Maslanyj *et al*, 2007). The proximity of HVOL to the residence of all the subjects was reliably evaluated without any selection and using the same process over all mainland France and over the 2002–2007 period. The results for living <50 m from a 225 or 400 kV HVOL were compatible with the IARC conclusions. There was no association beyond that distance. The association at a short distance was not observed for children aged ⩾5 years or those living in the most urban *Communes*.

The study covered a recent and relatively short period, and historical databases were therefore available for the entire period. One of the main strengths of the Geocap study is that it was designed to avoid selection biases. The cases were identified by the national registry, which complies with the international criteria required for cancer registration and classification, and achieves a high degree of completeness, by active research with almost three sources per case on average (Clavel *et al*, 2004; Lacour *et al*, 2010). Similarly, the recruitment of the controls did not require their active participation, preventing self-selection by socioeconomic status. *De facto*, the control sample was closely representative of the paediatric population on the basis of the sociodemographic contextual criteria (Table 1).

All the cases' and controls' addresses were obtained and geocoded, and the distances were calculated from objective databases free from any recall bias and blind to case/control status. This is another strength of the Geocap study in that it enabled minimisation of differential misclassifications. The distances estimated from the GISs were assumed to rank, as adequately as possible, the cases and controls by the true distance of their dwellings from the HVOL. The databases used to locate the lines were very precise. In particular, pylons were located with an uncertainty of 2.5 m in the RTE database.

Interestingly, the results were strengthened when the analyses were restricted to the best geocoded addresses. The 67 cases and 203 controls (<2% of the subjects) whose addresses were not precise enough to enable their location close to the HVOL probably had no substantial impact on the results, given the expected distribution of the few subjects with respect to the distance from VHV-HVOL (about 0.2% of the controls <50 m from VHV-HVOL). For the association to have been due to the

Table 4. Association between childhood AL and distance from HVOLs over the period 2002–2007, stratified by age and urban status of the *Commune* of residence

	Address-based distance from HVOL											
	225–400 kV HVOL						63–150 kV HVOL					
	Ca		Co		OR[a]	95% CI	Ca		Co		OR[a]	95% CI
	n	%	*n*	%			*n*	%	*n*	%		
Age												
0–4 years												
Baseline[b]	311	23.8	2326	23.9	1.0	Reference	311	23.8	2326	23.9	1.0	Reference
Unknown	35		85				35		85			
⩾600 m	870	66.6	6734	69.3	0.9	(0.8–1.1)	814	62.3	6146	63.2	0.9	(0.8–1.1)
200–599 m	74	5.7	444	4.6	1.2	(0.9–1.6)	115	8.8	902	9.3	0.9	(0.7–1.1)
100–199 m	5	0.4	87	0.9	0.4	(0.2–1.0)	13	1.0	145	1.5	0.6	(0.4–1.2)
50–99 m	6	0.5	27	0.3	1.6	(0.7–4.1)	11	0.8	61	0.6	1.3	(0.7–2.5)
0–49 m	6	0.5	14	0.1	2.6	(1.0–6.9)	8	0.6	52	0.5	1.1	(0.5–2.3)
Total	1307		9717				1307		9717			
5–14 years												
Baseline[b]	299	20.3	4735	23.3	1.0	Reference	299	20.8	4735	23.3	1.0	Reference
Unknown	32		118				32		118			
⩾600 m	1054	71.6	14162	69.8	1.2	(1.0–1.4)	978	66.4	13022	64.2	1.2	(1.0–1.4)
200–599 m	71	4.8	972	4.8	1.2	(0.9–1.5)	127	8.6	1838	9.1	1.1	(0.9–1.4)
100–199 m	11	0.7	180	0.9	1.0	(0.5–1.8)	20	1.4	316	1.6	1.0	(0.6–1.6)
50–99 m	2	0.1	70	0.3	0.5	(0.1–2.0)	10	0.7	142	0.7	1.1	(0.6–2.1)
0–49 m	3	0.2	46	0.2	1.0	(0.3–3.3)	6	0.4	112	0.6	0.9	(0.4–2.1)
Total	1472		20283				1472		20283			
Size of urban unit[c]												
<5000 inhabitants												
Baseline[b]	309	34.1	3415	35.5	1.0	Reference	309	34.1	3415	35.5	1.0	Reference
Unknown	36		67				36		67			
⩾600 m	525	57.9	5630	58.6	1.0	(0.9–1.2)	482	53.1	5221	54.3	1.0	(0.9–1.2)
200–599 m	30	3.3	393	4.1	0.9	(0.6–1.3)	68	7.5	724	7.5	1.0	(0.8–1.4)
100–199 m	2	0.2	71	0.7	0.3	(0.1–1.4)	7	0.8	109	1.1	0.7	(0.3–1.6)
50–99 m	1	0.1	20	0.2	0.6	(0.1–4.6)	4	0.4	45	0.5	1.1	(0.4–3.0)
0–49 m	4	0.4	19	0.2	2.5	(0.8–7.7)	1	0.1	34	0.4	0.4	(0.1–2.9)
Total	907		9615				907		9615			
5000–100 000 inhabitants												
Baseline[b]	71	11.1	756	10.9	1.0	Reference	71	11.1	756	10.9	1.0	Reference
Unknown	18		63				18		63			
⩾600 m	513	80.3	5811	84.1	0.8	(0.6–1.1)	451	72.7	4942	71.6	0.9	(0.7–1.2)
200–599 m	27	4.2	219	3.2	1.2	(0.7–2.0)	72	11.5	876	12.7	0.8	(0.5–1.1)
100–199 m	5	0.8	33	0.5	1.5	(0.5–3.9)	15	2.4	144	2.1	1.0	(0.5–1.8)
50–99 m	1	0.2	19	0.3	0.6	(0.1–4.8)	5	0.8	73	1.1	0.7	(0.3–1.7)
0–49 m	4	0.6	6	0.1	4.9	(1.3–19.2)	7	1.1	53	0.8	1.2	(0.5–2.7)
Total	639		6907				639		6907			
⩾100 000 inhabitants												
Baseline[b]	230	18.7	2890	21.4	1.0	Reference	230	18.7	2890	21.4	1.0	Reference
Unknown	13		73				13		73			
⩾600 m	886	71.9	9455	70.2	1.1	(0.9–1.4)	859	69.7	9005	66.8	1.2	(0.9–1.4)
200–599 m	88	7.1	804	6.0	1.3	(1.0–1.8)	102	8.3	1140	8.5	1.1	(0.8–1.4)
100–199 m	9	0.7	163	1.2	0.7	(0.4–1.4)	11	0.9	208	1.5	0.7	(0.4–1.3)
50–99 m	6	0.5	58	0.4	1.4	(0.6–3.3)	12	1.0	85	0.6	1.7	(0.9–3.3)
0–49 m	1	0.1	35	0.3	0.4	(0.1–2.9)	6	0.5	77	0.6	1.0	(0.4–2.4)
Total	1233		13478				1233		13478			

Abbreviations: AL = acute leukaemia; Ca = number of cases; CI = confidence interval; Co = number of controls; HVOL = high-voltage overhead power line; OR = odds ratio.

[a]ORs and 95% CIs estimated by logistic regression adjusted for age at the end of the year (5-year age groups for the 0–14-year-old children, 1-year age groups for the 0–4-year-old children) and *Département* of residence.

[b]Baseline = residence in a *Commune* entirely located ⩾600 m from any HVOL.

[c]An urban unit is defined by the INSEE (National Institute of Statistics and Economic Studies) as a group of *Communes* in which the distance between dwellings is nowhere more than 200 m.

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Table 5. Sensitivity analyses of the association between childhood acute leukaemia and distance to the closest HVOL by category of voltage (very high (225–400 kV) or high (63–150 kV)) over the period 2002–2007, for all ages and the 0–4-years age group

	Main results				Sensitivity analyses															
	GIS with any uncertainty				(1) GIS with uncertainty of 20 m				(2) Photographic views available											
									Photograph only				<50 m by GIS or photo				<50 m by GIS and photo			
	Ca	Co	OR	95% CI	Ca	Co	OR	95% CI	Ca	Co	OR	95% CI	Ca	Co	OR	95% CI	Ca	Co	OR	95% CI
0–14 years																				
Baseline	610	7061	1.0	Reference	610	7061	1.0	Reference	610	7061	1.0	Reference	610	7061	1.0	Reference	610	7061	1.0	Reference
Any HVOL																				
100–199 m	44	669	0.8	(0.5–1.0)	32	499	0.7	(0.5–1.1)	36	455	0.9	(0.6–1.3)								
50–99 m	25	284	1.0	(0.7–1.6)	20	212	1.1	(0.7–1.8)	22	184	1.4	(0.9–2.2)								
0–49 m	23	213	1.2	(0.8–1.9)	16	152	1.2	(0.7–2.0)	14	158	1.1	(0.6–1.9)	24	243	1.2	(0.7–1.8)	13	128	1.2	(0.7–2.1)
VHV-HVOL																				
100–199 m	16	267	0.7	(0.4–1.2)	13	200	0.8	(0.4–1.3)	18	172	1.2	(0.7–1.9)								
50–99 m	8	97	1.0	(0.5–2.1)	6	68	1.0	(0.4–2.4)	8	74	1.3	(0.6–2.7)								
0–49 m	9	60	1.7	(0.9–3.6)	7	39	2.1	(0.9–4.7)	4	38	1.3	(0.5–3.7)	9	68	1.5	(0.8–3.1)	4	30	1.7	(0.6–4.8)
HV-HVOL																				
100–199 m	33	461	0.8	(0.6–1.2)	22	346	0.7	(0.5–1.1)	24	322	0.9	(0.6–1.3)								
50–99 m	21	203	1.2	(0.7–1.9)	16	155	1.2	(0.7–2.0)	14	121	1.3	(0.7–2.3)								
0–49 m	14	164	1.0	(0.6–1.7)	9	120	0.8	(0.4–1.7)	10	127	0.9	(0.5–1.8)	15	188	0.9	(0.5–1.6)	9	103	1.0	(0.5–2.0)
0–4 years																				
Baseline	311	2326	1.0	Reference	311	2326	1.0	Reference	311	2326	1.0	Reference	311	2326	1.0	Reference	311	2326	1.0	Reference
Any HVOL																				
100–199 m	17	213	0.6	(0.3–1.0)	9	160	0.4	(0.2–0.8)	16	146	0.9	(0.5–1.5)								
50–99 m	14	84	1.2	(0.7–2.1)	11	62	1.2	(0.6–2.4)	13	55	1.7	(0.9–3.3)								
0–49 m	14	62	1.5	(0.8–2.8)	9	42	1.3	(0.6–2.8)	8	38	1.5	(0.6–3.3)	14	66	1.4	(0.8–2.6)	8	34	1.7	(0.8–3.9)
VHV-HVOL																				
100–199 m	5	87	0.4	(0.2–1.0)	4	63	0.5	(0.2–0.4)	9	58	1.3	(0.6–2.8)								
50–99 m	6	27	1.6	(0.7–4.1)	4	19	1.6	(0.5–5.0)	6	21	2.1	(0.8–5.8)								
0–49 m	6	14	2.6	(1.0–6.9)	5	8	4.1	(1.3–13.3)	3	7	2.5	(0.6–10.5)	6	16	2.3	(0.9–6.0)	3	5	3.5	(0.8–15.1)
HV-HVOL																				
100–199 m	13	108	0.6	(0.4–1.2)	6	145	0.4	(0.2–0.9)	10	99	0.7	(0.4–1.4)								
50–99 m	11	45	1.3	(0.7–2.5)	8	61	1.2	(0.5–2.6)	7	35	1.5	(0.6–3.4)								
0–49 m	8	36	1.1	(0.5–2.3)	4	52	0.6	(0.2–1.8)	5	33	1.1	(0.4–2.9)	8	55	1.0	(0.5–2.1)	5	30	1.3	(0.5–3.4)

Abbreviations: Ca = number of cases; CI = confidence interval; Co = number of controls; GIS = geographic information system; HV-HVOL = high voltage high-voltage overhead power lines (63-150 kV); HVOL = high-voltage overhead power line; OR = odds ratio; VHV-HVOL = very high voltage high-voltage overhead power lines (225-400 kV). The first sensitivity analysis (1) is restricted to the addresses best geocoded (GIS obtained with uncertainty of 20 m) and the second one (2) to the addresses for which a photographic view was available. The results shown in Tables 4 and 5 are recalled in the first columns.

Unknown category, the true addresses would have to have been within 50 m of a VHV-HVOL for none of the unclassified cases and for about 15% of the unclassified controls, which is very unlikely. The sensitivity analyses were consistent with the main results.

The Geocap study was designed to avoid selection and differential misclassification biases, which are common shortcomings of case–control studies on environmental factors, particularly ELF-MF (Mezei and Kheifets, 2006; Kheifets and Oksuzyan, 2008; Schüz and Ahlbom, 2008). The study included no individual data other than age and address, which were obtained for all the cases and controls. Therefore, potential AL risk factors such as birth order, breastfeeding, day-care attendance and pesticide exposure were not available. However, conditionally on age and the sociodemographic characteristics of the *Commune* of residence, which were accounted for in adjusted or stratified analyses, known or suspected risk factors are not likely to differ markedly within *vs* outside the 50-m distance from the VHV-HVOL. The study may have suffered from non-differential misclassifications, particularly because of the uncertainty of the geolocation of the homes, or because the period considered, that is, residence at diagnosis or interview, may not belong to the most relevant time window, or because the small numbers did not enable separation of the 400- and 225-kV VHV-HVOL or splitting the smallest category of distance. Therefore, the relationship between living close to VHV-HVOL and AL is probably not overestimated. As a registry-based study, the Geocap study considered the addresses at the time of diagnosis for the cases and at the time of inclusion for the controls. It did not cover the whole residential history since conception, and earlier or longer time windows may be more relevant in childhood AL. In the Escale case–control study (data collected in 2003–2004), the household had not moved during the index pregnancy or childhood for 46% of the controls <15 years, and 60% of those <5 years (Amigou *et al*, 2011). In the present study, the relationship was only observed for children <5 years, which might be compatible with a smaller impact of misclassifications, due to moves, of early exposures related to the proximity of VHV-HVOL. The relationship was not observed in children living in the most populated urban Communes.

The present study exclusively addressed the question, recurrent in France, of the risk of childhood AL close to HVOL. If living <50 m from HVOL is causally related to AL, it is expected to induce an excess of less than one new case <15 years per year in France, under steady conditions of residency close to VHV-HVOL. The distance of the residence from a HVOL is by no means a perfect surrogate for individual exposure to ELF-MF because of the

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proximity of the lines. Individual *in situ* measurements would be more suitable exposure indicators, provided that they were standardized, accurate and precise measurements, and that no selection bias (and no participation bias) limited their interpretation. Residential proximity of a VHV-HVOL was considered an indicator of increased probability of high residential exposure to ELF-MF, with the hypothesis that other sources of exposure to ELF-MF would be independent of the presence of the line and thus would be distributed similarly for the children living <50 m from a VHV-HVOL and those living further away (Schüz *et al*, 2000; Maslanyj *et al*, 2007). The study combined stringent voltage ($\geqslant 225$ kV) and distance (<50 m) conditions with a high degree of accuracy in the geocoding process, in order to identify the individuals who most probably had the highest exposures to ELF-MF in the population study. Exposure to ELF-MF depends on many sources and, regarding power lines, on many other parameters than distance, particularly current load and type of pylon (also related to the line voltage). Conversely, the distance from VHV-HVOL might also be an indicator of environmental exposures and lifestyle factors related to the vicinity of lines other than ELF-MF.

In a descriptive analysis of studies of ELF-MF exposure in 4452 homes in the United Kingdom (UKCCS, 1999) and 1835 homes in Germany (Schüz *et al*, 2000), only a small number of dwellings were located within 50 m of a HVOL (93 homes), 16 of which were close to a 220–400 kV HVOL (Maslanyj *et al*, 2009). Extremely low-frequency magnetic field exposure $\geqslant 0.4\,\mu$T was more prevalent in the latter homes (18.8%) than in those close to 11–132 kV HVOL (6.5%), even though the absolute numbers of dwellings with ELF-MF exposure $\geqslant 0.4\,\mu$T were similar (three and five homes, respectively). Therefore, in this study, the absence of an association close to HV-HVOL lines, where the prevalence of exposed residences is assumed to be lower, is poorly informative with respect to the hypothesis that ELF-MF may have a role in childhood AL.

This hypothesis will be investigated more precisely in a future stage of the Geocap study. RTE is to calculate individual estimates of the exposure to ELF-MF for all the Geocap subjects located close to a HVOL, blind to case/control status. The exposure estimates will take into account the particular characteristics of each of the neighbouring lines (pylons geometry, height and type of cable, ground wires and so on), the average annual current load for each of the identified lines, the time-distribution percentiles of the current load and the particular location of the residence with respect to the closest line spans (Bessou *et al*, 2013).

This is the first French contribution to the issue of ELF-MF, HVOL and childhood AL. The results are compatible with the first meta-analyses published in 2000 (Ahlbom *et al*, 2000; Greenland *et al*, 2000), the recent review by Schüz and Ahlbom (2008) and the most recent meta-analysis summarizing the studies of the last decade (Kheifets *et al*, 2010). While no underlying biological mechanism has been advanced to date in support of the epidemiological observation (WHO, 2007), the IARC classification of ELF-MF as a possible carcinogen (IARC, 2002) has not been strongly challenged. The study by Draper *et al* (2005) based on residence at birth and covering more than three decades (1962–1995) revealed associations with longer distances from power lines than previously envisaged, far above the threshold usually recognised as generating ELF-MF greater than background exposures, and with a positive trend with decreasing distance. Extremely low-frequency magnetic fields were estimated secondarily in the same study, and then considered unlikely to be the only explanation (Swanson, 2008; Kroll *et al*, 2010) for the observed relationship with distance. Overall, the number of exposed newborns was small because five AL cases and three controls resided at birth within 50 m of a HVOL (mainly VHV-HVOL) (Draper *et al*, 2005), and two AL cases and one control were assumed to be exposed to at least $0.4\,\mu$T (Swanson, 2008). In the present study, we observed no significant trend with decreasing distance to VHV-HVOL.

Recently, in a commentary on the most recent papers by Kroll *et al* (2010) and Kheifets *et al* (2010), Schmiedel and Blettner (2010) drew attention to the current limitations of epidemiology with regard to affording new insights in the field and answering questions in the absence of satisfactory biological models. Geocap was designed for quantitative modelling and the study of coexposures, and may thus be considered an appropriate tool for contributing to knowledge in the field.

CONCLUSION

In conclusion, the present study has generated additional findings, based on a recent nationwide unselected population-based study, that support the hypothesis that living <50 m from a 225 or 400 kV HVOL may be associated with an increased incidence of childhood AL. No increase in risk was observed further from those lines and no increase in childhood AL risk was detected within 50 m of the 63–150 kV HVOL. Model-based estimates of ELF-MF exposures will be used to investigate for potential involvement of ELF-MF in the observed association.

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DISCLAIMER

A written contract between RTE and Inserm U1018 team 6 has been concluded and states that team 6 has complete control over the conduct, interpretation and publication of the study. This paper has not been approved by any RTE personnel member other than François Deschamps, who approved it in his capacity as author. The paper does not necessarily represent RTE's views.

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Guest Editor:

Electromagnetic fields act *via* activation of voltage-gated calcium channels to produce beneficial or adverse effects

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- Introduction
- Possible modes of action following voltage-gated calcium channel stimulation
- Therapeutic bone-growth stimulation *via* Ca^{2+}/nitric oxide/cGMP/protein kinase G
- Ca^{2+}/nitric oxide/peroxynitrite and pathophysiological responses to EMF exposures: the example of single-strand DNA breaks
- Discussion and conclusions

Abstract

The direct targets of extremely low and microwave frequency range electromagnetic fields (EMFs) in producing non-thermal effects have not been clearly established. However, studies in the literature, reviewed here, provide substantial support for such direct targets. Twenty-three studies have shown that voltage-gated calcium channels (VGCCs) produce these and other EMF effects, such that the L-type or other VGCC blockers block or greatly lower diverse EMF effects. Furthermore, the voltage-gated properties of these channels may provide biophysically plausible mechanisms for EMF biological effects. Downstream responses of such EMF exposures may be mediated through Ca^{2+}/calmodulin stimulation of nitric oxide synthesis. Potentially, physiological/therapeutic responses may be largely as a result of nitric oxide-cGMP-protein kinase G pathway stimulation. A well-studied example of such an apparent therapeutic response, EMF stimulation of bone growth, appears to work along this pathway. However, pathophysiological responses to EMFs may be as a result of nitric oxide-peroxynitrite-oxidative stress pathway of action. A single such well-documented example, EMF induction of DNA single-strand breaks in cells, as measured by alkaline comet assays, is reviewed here. Such single-strand breaks are known to be produced through the action of this pathway. Data on the mechanism of EMF induction of such breaks are limited; what data are available support this proposed mechanism. Other Ca^{2+}-mediated regulatory changes, independent of nitric oxide, may also have roles. This article reviews, then, a substantially supported set of targets, VGCCs, whose stimulation produces non-thermal EMF responses by humans/higher animals with downstream effects involving Ca^{2+}/calmodulin-dependent nitric oxide increases, which may explain therapeutic and pathophysiological effects.

Keywords: intracellular Ca^{2+} • voltage-gated calcium channels • low frequency electromagnetic field exposure • nitric oxide • oxidative stress • calcium channel blockers

Introduction

An understanding of the complex biology of the effects of electromagnetic fields (EMFs) on human/higher animal biology inevitably must be derived from an understanding of the target or targets of such fields in the impacted cells and tissues. Despite this, no understanding has been forthcoming on what those targets are and how they may lead to the complex biological responses to EMFs composed of low-energy photons. The great puzzle, here, is that these EMFs are comprised of low-energy photons, those with insufficient energy to individually influence the chemistry of the cell, raising the question of how non-thermal effects of such EMFs can possibly occur. The author

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has found that there is a substantial literature possibly pointing to the direct targets of such EMFs and it is the goal of this study to review that evidence as well as review how those targets may lead to the complex biology of EMF exposure.

The role of increased intracellular Ca^{2+} following EMF exposure was already well documented more than 20 years ago, when Wallenczek [1] reviewed the role of changes in calcium signalling that were produced in response EMF exposures. Other, more recent studies have confirmed the role of increased intracellular Ca^{2+} following EMF exposure, a few of which are discussed below. His review [1] included two studies [2, 3] that showed that the L-type voltage-gated channel blocker, verapamil could lower or block changes in response to EMFs. The properties of voltage-gated calcium channels (VGCCs) have been reviewed elsewhere [4]. Subsequently, extensive evidence has been published clearly showing that the EMF exposure can act to produce excessive activity of the VGCCs in many cell types [5–26] suggesting that these may be direct targets of EMF exposure. Many of these studies implicate specifically the L-type VGCCs such that various L-type calcium channel blockers can block responses to EMF exposure (Table 1). However, other studies have shown lowered responses produced by other types of calcium channel blockers including N-type, P/Q-type, and T-type blockers (Table 1), showing that other VGCCs may have important roles. Diverse responses to EMFs are reported to be blocked by such calcium channel blockers (Table 1), suggesting that most if not all EMF-mediated responses may be produced through VGCC stimulation. Voltage-gated calcium channels are essential to the responses produced by extremely low frequency (including 50/60 Hz) EMFs and also to microwave frequency range EMFs, nanosecond EMF pulses, and static electrical and magnetic fields (Table 1).

In a recent study, Pilla [27] showed that an increase in intracellular Ca^{2+} must have occurred almost immediately after EMF exposure, producing a Ca^{2+}/calmodulin-dependent increase in nitric oxide occurring in less than 5 sec. Although Pilla [27] did not test whether VGCC stimulation was involved in his study, there are few alternatives that can produce such a rapid Ca^{2+} response, none of which has been implicated in EMF responses. Other studies, each involving VGCCs, summarized in Table 1, also showed rapid Ca^{2+} increases following EMF exposure [8, 16, 17, 19, 21]. The rapidity of these responses rule out many types of regulatory interactions as being involved in producing the increased VGCC activity following EMF exposure and suggests, therefore, that VGCC stimulation in the plasma membrane is directly produced by EMF exposure.

Possible modes of action following VGCC stimulation

The increased intracellular Ca^{2+} produced by such VGCC activation may lead to multiple regulatory responses, including the increased nitric oxide levels produced through the action of the two Ca^{2+}/calmodulin-dependent nitric oxide synthases, nNOS and eNOS. Increased nitric oxide levels typically act in a physiological context through increased synthesis of cGMP and subsequent activation of protein kinase G [28, 29]. In contrast, in most pathophysiological contexts, nitric oxide reacts with superoxide to form peroxynitrite, a potent non-radical oxidant [30, 31], which can produce radical products, including hydroxyl radical and NO_2 radical [32].

Therapeutic bone-growth stimulation *via* Ca^{2+}/nitric oxide/cGMP/protein kinase G

An example of a therapeutic effect for bone repair of EMF exposure in various medical situations includes increasing osteoblast differentiation and maturation and has been reviewed repeatedly [33–44]. The effects of EMF exposure on bone cannot be challenged, although there is still considerable question about the best ways to apply this clinically [33–44]. Our focus, here, is to consider possible mechanisms of action. Multiple studies have implicated increased Ca^{2+} and nitric oxide in the EMF stimulation of bone growth [44–49]; three have also implicated increased cGMP and protein kinase G activity [46, 48, 49]. In addition, studies on other regulatory stimuli leading to increased bone growth have also implicated increased cGMP levels and protein kinase G in this response [50–56]. In summary, then, it can be seen from the above that there is a very well-documented action of EMFs in stimulating osteoblasts and bone growth. The available data, although limited, support the action of the main pathway involved in physiological responses to Ca^{2+} and nitric oxide, namely Ca^{2+}/nitric oxide/cGMP/protein kinase G in producing such stimulation.

Ca^{2+}/nitric oxide/peroxynitrite and pathophysiological responses to EMF exposures: the example of single-strand DNA breaks

As was noted above, most of the pathophysiological effects of nitric oxide are mediated through peroxynitrite elevation and consequent oxidative stress. There are many reviews and other studies, implicating oxidative stress in generating pathophysiological effects of EMF exposure [see for example 57–64]. In some of these studies, the rise in oxidative stress markers parallels the rise in nitric oxide, suggesting a peroxynitrite-mediated mechanism [64–67].

Peroxynitrite elevation is usually measured through a marker of peroxynitrite-mediated protein nitration, 3-nitrotyrosine (3-NT). There are four studies where 3-NT levels were measured before and after EMF exposure [66, 68–70]. Each of these studies provides some evidence supporting the view that EMF exposure increases levels of peroxynitrite and therefore 3-NT levels [66, 68–70]. Although these cannot be taken as definitive, when considered along with the evidence on oxidative stress and elevated nitric oxide production in response to EMF exposure, they strongly suggest a peroxynitrite-mediated mechanism of oxidative stress in response to EMFs.

Table 1 EMF responses blocked or lowered by calcium channel blockers

Ref. no.	EMF type	Calcium channel	Cell type or organism	Response measured
2	Pulsed magnetic fields	L-type	Human lymphocytes	Cell proliferation; cytokine production
3	Static magnetic field (0.1 T)	L-type	Human polymorphonuclear leucocytes	Cell migration; degranulation
5	ELF	L-type	Rat chromaffin cells	Differentiation; catecholamine release
6	Electric field	L-type	Rat and mouse bone cells	Increased Ca^{2+}, phospholipase A2, PGE2
7	50 Hz	L-type	Mytilus (mussel) immunocytes	Reduced shape change, cytotoxicity
8	50 Hz	L-type	AtT20 D16V, mouse pituitary corticotrope-derived	Ca^{2+} increase; cell morphology, premature differentiation
9	50 Hz	L-type	Neural stem/progenitor cells	*In vitro* differentiation, neurogenesis
10	Static magnetic field	L-type	Rat	Reduction in oedema formation
11	NMR	L-type	Tumour cells	Synergistic effect of EMF on anti-tumour drug toxicity
12	Static magnetic field	L-type	Myelomonocytic U937 cells	Ca^{2+} influx into cells and anti-apoptotic effects
13	60 Hz	L-type	Mouse	Hyperalgesic response to exposure
14	Single nanosecond electric pulse	L-type	Bovine chromaffin cells	Very rapid increase in intracellular Ca^{2+}
15	Biphasic electric current	L-type	Human mesenchymal stromal cells	Osteoblast differentiation and cytokine production
16	DC & AC magnetic fields	L-type	β-cells of pancreas, patch clamped	Ca^{2+} flux into cells
17	50 Hz	L-type	Rat pituitary cells	Ca^{2+} flux into cells
18	50 Hz	L-type, N-type	Human neuroblastoma IMR32 and rat pituitary GH3 cells	Anti-apoptotic activity
19	Nanosecond pulse	L-type, N-type, P/Q-type	Bovine chromaffin cells	Ca^{2+} dynamics of cells
20	50 Hz	Not determined	Rat dorsal root ganglion cells	Firing frequency of cells
21	700–1100 MHz	N-type	Stem cell–derived neuronal cells	Ca^{2+} dynamics of cells
22	Very weak electrical fields	T-type	Sharks	Detection of very weak magnetic fields in the ocean
23	Short electric pulses	L-type	Human eye	Effect on electro-oculogram
24	Weak static magnetic field	L-type	Rabbit	Baroreflex sensitivity
25	Weak electric fields	T-type	Neutrophils	Electrical and ion dynamics
26	Static electric fields, 'capacitive'	L-type	Bovine articular chondrocytes	Agrican & type II collagen expression; calcineurin and other Ca^{2+}/calmodulin responses

EMF: electromagnetic field; ELF: extremely low frequency.

Such a peroxynitrite-mediated mechanism may explain the many studies showing the single-stranded breaks in DNA, as shown by alkaline comet assays or the similar microgel electrophoresis assay, following EMF exposures in most such studies [71–89], but not in all [90–97]. Some of the factors that are reported to influence whether such DNA single-strand breaks are detected after EMF exposure include the type of cell studied [79, 86], dosage of EMF exposure [78] and the type of EMF exposure studied [73, 77]. Oxidative stress and free radicals have roles, both because there is a concomitant increase in oxidative stress and because antioxidants have been shown to greatly lower the generation of DNA single-strand breaks following EMF exposure [72, 75, 81, 82] as has also been shown for peroxynitrite-mediated DNA breaks produced under other conditions. It has also been shown that one can block the generation of DNA single-strand breaks with a nitric oxide synthase inhibitors [82].

Peroxynitrite has been shown to produce single-strand DNA breaks [98–100], a process that is inhibited by many but not all antioxidants [99, 100]. It can be seen from this that the data on generation of single-strand DNA breaks, although quite limited, support a mechanism involving nitric oxide/peroxynitrite/free radical (oxidative stress). Although the data on the possible role of peroxynitrite in EMF-induced DNA single-strand breaks are limited, what data are available supports such a peroxynitrite role.

Discussion and conclusions

How do EMFs composed of low-energy photons produce non-thermal biological changes, both pathophysiological and, in some cases, potentially therapeutic, in humans and higher animals? It may be surprising that the answer to this question has been hiding in plain sight in the scientific literature. However, in this era of highly focused and highly specialized science, few of us have the time to read the relevant literature, let alone organize the information found within it in useful and critical ways.

This study shows that:

1 Twenty-three different studies have found that such EMF exposures act *via* activation of VGCCs, such that VGCC channel blockers can prevent responses to such exposures (Table 1). Most of the studies implicate L-type VGCCs in these responses, but there are also other studies implicating three other classes of VGCCs.

2 Both extremely low frequency fields, including 50/60 cycle exposures, and microwave EMF range exposures act *via* activation of VGCCs. So do static electric fields, static magnetic fields and nanosecond pulses.

3 Voltage-gated calcium channel stimulation leads to increased intracellular Ca^{2+}, which can act in turn to stimulate the two calcium/calmodulin-dependent nitric oxide synthases and increase nitric oxide. It is suggested here that nitric oxide may act in therapeutic/potentially therapeutic EMF responses *via* its main physiological pathway, stimulating cGMP and protein kinase G. It is also suggested that nitric oxide may act in pathophysiological responses to EMF exposure, by acting as a precursor of peroxynitrite, producing both oxidative stress and free radical breakdown products.

4 The interpretation in three above is supported by two specific well-documented examples of EMF effects. Electromagnetic fields stimulation of bone growth, modulated through EMF stimulation of osteoblasts, appears to involve an elevation/nitric oxide/protein kinase G pathway. In contrast to that, it seems likely that the EMF induction of single-stranded DNA breaks involves a Ca^{2+}/elevation/nitric oxide/peroxynitrite/free radical (oxidative stress) pathway.

It may be asked why we have evidence for involvement of VGCCs in response to EMF exposure, but no similar evidence for involvement of voltage-gated sodium channels? Perhaps, the reason is that there are many important biological effects produced in increased intracellular Ca^{2+}, including but not limited to nitric oxide elevation, but much fewer are produced by elevated Na^{+}.

The possible role of peroxynitrite as opposed to protein kinase G in producing pathophysiological responses to EMF exposure raises the question of whether there are practical approaches to avoiding such responses? Typically peroxynitrite levels can be highly elevated when both of its precursors, nitric oxide and superoxide, are high. Consequently, agents that lower nitric oxide synthase activity and agents that raise superoxide dismutases (SODs, the enzymes that degrade superoxide) such as phenolics and other Nrf2 activators that induce SOD activity [101], as well as calcium channel blockers may be useful. Having said that, this is a complex area, where other approaches should be considered, as well.

Although the various EMF exposures as well as static electrical field exposures can act to change the electrical voltage-gradient across the plasma membrane and may, therefore, be expected to stimulate VGCCs through their voltage-gated properties, it may be surprising that static magnetic fields also act to activate VGCCs because static magnetic fields do not induce electrical changes on static objects. However, cells are far from static. Such phenomena as cell ruffling [102,103] may be relevant, where thin cytoplasmic sheets bounded on both sides by plasma membrane move rapidly. Such rapid movement of the electrically conducting cytoplasm, may be expected to influence the electrical charge across the plasma membrane, thus potentially stimulating the VGCCs.

Earlier modelling of electrical effects across plasma membranes of EMF exposures suggested that such electrical effects were likely to be too small to explain EMF effects at levels reported to produce biological changes (see, for example [22]). However, more recent and presumably more biologically plausible modelling have suggested that such electrical effects may be much more substantial [104–109] and may, therefore, act to directly stimulate VGCCs.

Direct stimulation of VGCCs by partial depolarization across the plasma membrane is suggested by the following observations discussed in this review:

1 The very rapid, almost instantaneous increase in intracellular Ca^{2+} found in some studies following EMF exposure [8, 16, 17, 19, 21, 27]. The rapidity here means that most, if not all indirect, regulatory effects can be ruled out.

2 The fact that not just L-type, but three additional classes of VGCCs are implicated in generating biological responses to EMF

exposure (Table 1), suggesting that their voltage-gated properties may be a key feature in their ability to respond to EMFs.

3 Most, if not all, EMF effects are blocked by VGCC channel blockers (Table 1).

4 Modelling of EMF effects on living cells suggests that plasma membrane voltage changes may have key roles in such effects [104–109]. Saunders and Jefferys stated [110] that 'It is well established that electric fields ... or exposure to low frequency magnetic fields, will, if of sufficient magnitude, excite nerve tissue through their interactions with ... voltage gated ion channels'. They further state [110] that this is achieved by direct effects on the electric dipole voltage sensor within the ion channel.

One question that is not answered by any of the available data is whether what is known as 'dirty electricity' [111–113], generated by rapid, in many cases, square wave transients in EMF exposure, also acts by stimulating VGCCs. Such dirty electricity is inherent in any digital technology because digital technology is based on the use of such square wave transients and it may, therefore, be of special concern in this digital era, but there have been no tests of such dirty electricity that determine whether VGCCs have roles in response to such fields, to my knowledge. The nanosecond pulses, which are essentially very brief, but high-intensity dirty electricity do act, at least in part, *via* VGCC stimulation (Table 1), suggesting that dirty electricity may do likewise. Clearly, we need direct study of this question.

The only detailed alternative to the mechanism of non-thermal EMF effects discussed here, to my knowledge, is the hypothesis of Friedman *et al.* [114] and supported by Desai *et al.* [115] where the apparent initial response to EMF exposure was proposed to be NADH oxidase activation, leading to oxidative stress and downstream regulatory effects. Although they provide some correlative evidence for a possible role of NADH oxidase [114], the only causal evidence is based on a presumed specific inhibitor of NADH oxidase, diphenyleneiodonium (DPI). However, DPI has been shown to be a non-specific cation channel blocker [116], clearly showing a lack of such specificity and suggesting that it may act, in part, as a VGCC blocker. Consequently, a causal role for NADH oxidase in responses to EMF exposure must be considered to be undocumented.

In summary, the non-thermal actions of EMFs composed of low-energy photons have been a great puzzle, because such photons are insufficiently energetic to directly influence the chemistry of cells. The current review provides support for a pathway of the biological action of ultralow frequency and microwave EMFs, nanosecond pulses and static electrical or magnetic fields: EMF activation of VGCCs leads to rapid elevation of intracellular Ca^{2+}, nitric oxide and in some cases at least, peroxynitrite. Potentially therapeutic effects may be mediated through the Ca^{2+}/nitric oxide/cGMP/protein kinase G pathway. Pathophysiological effects may be mediated through the Ca^{2+}/nitric oxide/peroxynitrite pathway. Other Ca^{2+}-mediated effects may have roles as well, as suggested by Xu *et al.* [26].

Conflicts of interest

The author confirms that there are no conflicts of interest.

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THE INFLUENCE OF STATIC ELECTRIC FIELD GENERATED NEARBY HIGH VOLTAGE DIRECT CURRENT TRANSMISSION LINES ON HORMONAL ACTIVITY OF EXPERIMENTAL ANIMALS

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Abstract – The aim of the study was to estimate the effect of static electric fields with physical parameters generated nearby HVDC transmission lines on hormonal system of experimental animals. 96 male Wistar rats were exposed for 56 consecutive days (8 hours daily) to static electric field with intensity of 16, 25 and 35 kV/m, while 32 control rats were shame-exposed. Exposure to static electric fields evoked transient stimulation of insulin and thyroid hormones secretion as well as decrease in corticosterone level. As observed effects appeared mostly for intensity above 16 kV/m in prepared recommendations potential harmful effect of electric fields with such intensities should be regarded.

Introduction

The results of experimental studies suggest that different forms of electric field affect significantly hormonal activity of hypophysis, adrenal cortex, thyroid gland and testes of experimental animals, probably as a result of stimulation by this physical factor - acting as a non-specific stressor – the activity of hypothalamus-hypophysis-peripheral glands system or direct effect on synthesis and secretion of particular hormones. The divergence of obtained results is related mainly to different physical parameters of electric field and experimental models used by particular authors. Nowadays transport of electric power using air High Voltage Direct Current (HVDC) transmission lines becomes very popular. Regarding the lack of reports dealing with the influence of strong static electric fields on activity of endocrine glands in available literature, the aim of the study was to estimate the effect of static electric fields with physical parameters generated nearby HVDC transmission lines on hormonal system of experimental animals.

Material and Methods

Experimental material consisted of 128 male Wistar albino rats aged 6 weeks, weighting about 150 g. During the whole experiment all animals were placed in identical environmental conditions (constant temperature 22 ± 1°C and humidity of air) under a 12 h light-dark cycle) and fed with standard laboratory pellet food Labofed B (15g per day) and free access to tap water. All animals were randomly divided into 4 equal groups (32 animals each) with no significant differences in body weight. Two weeks before the beginning of exposure cycle rats from all groups were adapted to new environmental conditions in room, in which subsequently whole experiment was performed. This adaptation process and optimal environmental

conditions in a specially designed room enabled to exclude the influence of other factors than electric field action on hormonal activity of experimental animals.
The animals from 3 experimental groups were exposed for 56 consecutive days (8 hours daily, alternately between $7^{00} \div 15^{00}$, $15^{00} \div 23^{00}$ and $23^{00} \div 7^{00}$, similarly as in case of electric current transmission lines staff working in shifts) to static electric field with different electric field intensity values in a specially designed experimental system consisting of autotransformer, high voltage transformer 220V/60000V, cascade rectifier, water rheostat, 2 electrodes with round shape and specially profiled edges placed in a distance of 50 cm from each other, typical plastic cage placed between both electrodes containing 8 animals at a same time and magnetostatic kilo-voltmeter C196 type. Rats from first experimental group were exposed to static electric field with intensity of 16 kV/m, rats from second experimental group were exposed to static electric field with intensity of 25 kV/m and rats from third experimental group were exposed to static electric field with intensity of 35 kV/m. The control animals were subjected to sham-exposure in the same experimental system, during which no electric field was generated between electrodes. Taking into account the lack of regulations limiting the parameters of exposure to static electric field generated nearby High Voltage Direct Current transmission lines, in selection of analyzed electric field intensity values actual obligatory norms for occupational exposure to variable electric fields with frequency above 1 Hz as well as results of measurements of electric field intensity in the corridor of actually existing HVDC transmission lines were included. The lowest value of chosen electric field intensity – 16 kV/m is contained within the range of permissible norm for variable electric fields in conditions of occupational exposure, intermediary value of 25 kV/m corresponds with typical values of static electric field intensity observed in „corridor" of actually existing HVDC transmission lines and highest value of 35 kV/m conforms to top level of electric field intensity, which occur sometimes in close proximity of electric field transmission lines in especially unfavourable weather conditions.
At 14^{th}, 28^{th} and 56^{th} day of exposure cycle and then at 28^{th} day after the end of exposure cycle a part of animals from all groups (8 rats at a same time) was exsanguinated in Morbital narcosis (50 mg/kg of body weight i.p.) between 8^{00} and 10^{00} a.m. regarding daily profile of concentration of some hormones with highest excretion level in the morning. Then the collected blood (6-8 ml) was decanted and centrifuged and in obtained serum the concentrations of some hormones as insulin, glucagon, adrenocorticotropin, corticosterone, triiodothyronine, thyroxine and testosterone were estimated. Concentration of particular hormones were determined by means of radioimmunologic method using respectively: Rat Insulin RIA Kit RI-13K (LINCO Research St. Charles, MI, USA), Glucagon Radioimmunoassay (RIA) Kit RK-028-02 (Phoenix Peptide, Belmont, CA, USA), DSL-2300 ACTH Radioimmunoassay (RIA) Kit, DSL-80100 Rat Corticosterone Radioimmunoassay (RIA) Kit, DSL-3100 ACTIVE Triiodothyronine (T3) Coated-Tube Radioimmunoassay (RIA) Kit, DSL-3200 ACTIVE Thyroxine Coated-Tube Radioimmunoassay (RIA) Kit and DSL-4000 ACTIVE Testosterone Coated-Tube Radioimmunoassay (RIA) Kit (all Diagnostic Systems Laboratories, Inc., Oxon, Great Britain).
The results of measurements presented as mean values ± SEM for particular groups were subjected to statistical analysis by means of analysis of variance (Kruskal-Wallis ANOVA test) with subsequent detailed analysis of differences between particular groups by means of post-hoc U-Mann-Whitney test.

Results

Mean serum concentration of insulin at 14^{th} day of exposure cycle in group 16 kV/m was significantly higher comparing to control group (by 110,3% (p=0,012)). In other groups of animals exposed to electric field mean serum concentration of this hormone did not differ significantly in comparison with control group. At 28^{th} day of exposure cycle mean serum concentration of insulin in group 16 kV/m did not differ significantly comparing to control group, while in groups 25 kV/m and 35 kV/m it was significantly higher in comparison with control group (by 38,8% (p=0,046) and 67,0% (p=0,046), respectively). At 56^{th} day of exposure cycle mean serum concentration of insulin in groups 16 kV/m i 25 kV/m was significantly higher in comparison with control group (by 59,1% (p=0,012) and 90,2% (p=0,006), respectively), while in group 35 kV/m it did not differ significantly comparing to control group. At 28^{th} day after the end of exposure cycle mean serum concentration of insulin in groups of rats exposed to electric field did not differ significantly in comparison to control group. Mean serum concentration of glucagon at 14^{th} day of exposure cycle in groups 16 kV/m and 25kV/m did not differ significantly in comparison with control group, while in group 35 kV/m it was significantly higher comparing to control group (by 65% (p=0,016)). At 28^{th} day of exposure cycle mean serum concentration of glucagons in group 16 kV/m did not differ significantly in comparison with control

group, while in groups 25 kV/m and 35 kV/m it was significantly higher comparing to control group (by 48,6% (p=0,046) and 44,3% (p=0,046), respectively). At 56th day of exposure cycle mean serum concentration of glucagons in groups 16 kV/m and 25 kV/m did not differ significantly in comparison with control group, while in group 35 kV/m it was significantly lower comparing to control group (by 48,9% (p=0,027)). At 28th day after the end of exposure cycle mean serum concentration of glucagon in groups of rats exposed to electric field did not differ significantly in comparison to control group. Mean serum concentration of adrenocorticotropin at 14th day of exposure cycle in groups 16 kV/m and 25 kV/m did not differ significantly in comparison with control group while in group 35 kV/m it was significantly lower comparing to control group (by 31,2% (p=0,009). At 28th and 56th day of exposure cycle and at 28th day after the end of this cycle mean serum concentration of adrenocorticotropin in groups of rats exposed to electric field did not differ significantly in comparison with control group. Mean serum concentration of corticosterone at 14thday of exposure cycle in all groups of animals exposed to electric field (16 kV/m, 25kV/m i 35kV/m) was significantly lower in comparison to control group (by 34,3% (p=0,046), 36,8% (p=0,046) and 50,7% (p=0,006), respectively). At 28th day of exposure cycle mean serum concentration of corticosterone in group 16 kV/m did not differ significantly comparing to control group, while in groups 25 kV/m and 35 kV/m it was significantly lower in comparison with control group (by 41,5% (p=0,036) and 78,1% (p=0,002), respectively). At 56th day of exposure cycle and at 28th day after the end of this cycle mean serum concentration of corticosterone in groups of rats exposed to electric field did not differ significantly in comparison with control group. Mean serum concentration of triiodothyronine at 14th day of exposure cycle in all experimental groups did not differ significantly comparing to control group. At 28th day of exposure cycle mean serum concentration of triiodothyronine in group 16 kV/m did not differ significantly comparing to control group, while in groups 25 kV/m and 35 kV/m it was significantly higher in comparison with control group (by 16,1% (p=0,021) and 24,9% (p=0,002), respectively). Also at 56th day of exposure cycle mean serum concentration of this hormone in group 16 kV/m did not differ significantly comparing to control group, while in groups 25 kV/m and 35 kV/m it was significantly higher in comparison with control group (by 23,0% (p=0,046) and 28,8% (p=0,036), respectively). At 28th day after the end of exposure cycle serum concentration of triiodothyronine in group 16 kV/m did not differ significantly comparing to control group, while in groups 25 kV/m and 35 kV/m it was significantly higher in comparison with control group (by 25,6% (p=0,006) and 32,2% (p=0,003), respectively). Mean serum concentration of thyroxine at 14th day of exposure cycle in all groups of animals exposed to electric field (16 kV/m, 25 kV/m i 35 kV/m) was significantly higher in comparison with control group (by 31,3% (p=0,016), 33,4% (p=0,012) and 57,8% (p=0,002), respectively). Similarly at 28th day of exposure cycle mean serum concentration of thyroxine in all groups of animals exposed to electric field (16 kV/m, 25 kV/m and 35 kV/m) was significantly higher in comparison with control group (by 28,6% (p=0,006), 23,6% (p=0,046) and 50,9% (p=0,001), respectively). At 56th day of exposure cycle mean serum concentration of thyroxine in group 16 kV/m was significantly higher comparing to control group (by 30,7% (p=0,009)), while in other experimental groups concentration of this hormone did not differ in comparison with control group. At 28th day after the end of exposure cycle mean serum concentration of thyroxine in groups of rats exposed to electric field did not differ significantly in comparison with control group. Mean serum concentration of testosterone at 14th day of exposure cycle in all groups of animals exposed to electric field (16 kV/m, 25 kV/m i 35 kV/m) was significantly higher in comparison with control group (by 666,5% (p=0,006), 657,7% (p=0,021) and 692,0% (p=0,005), respectively). At 28th and 56th day of exposure cycle and at 28th day after the end of this cycle mean serum concentration of testosterone in experimental groups did not differ significantly in comparison with control group.

Discussion

The observed effect of exposure of experimental animals to static electric field resulting in transient significant increase in insulin, thyroxine, triiodothyronine and testosterone activities during exposure cycle, as well as significant decrease in corticosterone activity in early phase of exposure cycle with subsequent normalization of this activities after the end of exposure approximate typical two-phase stress reaction to external stimulus as e.g. immobilization [1]. Unfortunately, lack of data dealing with the influence of static electric field on activity of hormonal axis hypothalamus-pituitary gland-peripheral glands in attainable literature does not allow to confirm univocally the hypothesis on stress origin of obtained effects. It seems that results of experimental studies on hormonal effects of variable electric fields with similar values of electric field intensities could support this hypothesis. Exposure of male mice to electric field (frequency 50

Hz, intensity 10 kV/m) [2] and (frequency 60 Hz, intensity 25, 50 kV/m) [3] led to increase in morning corticosterone level with subsequent normalization during further exposure. On the other hand exposure of rats to electric field (frequency 60 Hz, intensity 15 kV/m) [4] and (frequency 60 Hz, intensity 64 kV/m) [5] evoked significant decrease in corticosterone level and both in corticosterone and testoterone level, respectively. Finally exposure of rats to electric field (frequency 50 Hz intensity 50 Hz) [6] caused a slight decrease in triiodothyronine concentration without any significant changes in corticosterone and thyroxine level, while exposure of young rabbits to electric field with the same parameters resulted only in decrease in corticosterone level [7]. Presented results indicate that electric fields could influence hormonal activity of adrenal gland, thyroid gland and testicles in experimental animals both by activation of physiological hormonal axis or by direct stimulation of synthesis and secretion of hormones in particular glands. The divergence of time dependence and direction of obtained changes in hormone concentrations are due to different physical parameters of electric field and experimental models used.

Conclusions

1. Long-term exposure of rats to strong static electric fields with intensity generated nearby High Voltage Direct Current transmission lines evokes transient stimulation of excretion of insulin and thyroid hormones as well as decrease in corticosterone level probably in the course of long-lasting stress reaction caused by electric field action.
2. The observed hormonal effects of electric field action were intensity-related and they appeared mostly for intensity values above 16 kV/m.
3. In prepared recommendations potential harmful effect of electric fields with such physical parameters should be taken into account, and intensity values of static electric field nearby planned High Voltage Direct Current transmission lines must not exceed level of 16 kV/m.

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Original Contribution

Residence Near Power Lines and Mortality From Neurodegenerative Diseases: Longitudinal Study of the Swiss Population

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The relation between residential magnetic field exposure from power lines and mortality from neurodegenerative conditions was analyzed among 4.7 million persons of the Swiss National Cohort (linking mortality and census data), covering the period 2000–2005. Cox proportional hazard models were used to analyze the relation of living in the proximity of 220–380 kV power lines and the risk of death from neurodegenerative diseases, with adjustment for a range of potential confounders. Overall, the adjusted hazard ratio for Alzheimer's disease in persons living within 50 m of a 220–380 kV power line was 1.24 (95% confidence interval (CI): 0.80, 1.92) compared with persons who lived at a distance of 600 m or more. There was a dose-response relation with respect to years of residence in the immediate vicinity of power lines and Alzheimer's disease: Persons living at least 5 years within 50 m had an adjusted hazard ratio of 1.51 (95% CI: 0.91, 2.51), increasing to 1.78 (95% CI: 1.07, 2.96) with at least 10 years and to 2.00 (95% CI: 1.21, 3.33) with at least 15 years. The pattern was similar for senile dementia. There was little evidence for an increased risk of amyotrophic lateral sclerosis, Parkinson's disease, or multiple sclerosis.

dementia; neurodegenerative diseases; radiation, nonionizing

Abbreviations: ALS, amyotrophic lateral sclerosis; CI, confidence interval; ELF-MF, extremely low frequency magnetic field(s); ICD-10, *International Classification of Diseases, Injuries, and Causes of Death*, Tenth Revision.

Research on the long-term effects of extremely low frequency magnetic fields (ELF-MF) has focused on cancer since Wertheimer and Leeper (1) published their results on childhood cancer and wiring configurations in 1979. In 2001, the International Agency for Research on Cancer classified exposure to residential magnetic fields above 0.4 μT as a "possible" cause of childhood leukemia (2). For noncancer endpoints, an initial report by Sobel et al. (3) on occupational ELF-MF exposure and Alzheimer's disease suggested that the risk could be substantial. Studies published subsequently have produced inconsistent results, but a recent meta-analysis (4) reported elevated risks in cohort, as well as case-control, studies. A recent review of the evidence for an association between ELF-MF and Alzheimer's disease by the World Health Organization (5) concluded that the available data were inadequate, and the topic was identified as a key research priority.

To our knowledge, no study has so far examined whether residential exposure from power lines is associated with an elevated risk of neurodegenerative diseases. Even a small association could be of high public health relevance, since a considerable number of persons are exposed to these fields. For example, 9.2% of the Swiss population live within 600 m of a 220 or 380 kV power line. We used the Swiss National Cohort, a longitudinal study of the Swiss population (6), to investigate whether living in the vicinity of power lines was associated with mortality from neurodegenerative diseases such as Alzheimer's disease, senile dementia, amyotrophic lateral sclerosis (ALS), multiple sclerosis, and Parkinson's disease.

MATERIALS AND METHODS

Study population

The present analysis was based on the 2000 national census. Mortality data were available for the period 2000–2005,

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Table 1. Number of Deaths by Cause, Recorded in Swiss Mortality Data Between December 4, 2000, and December 31, 2005

	ICD-10 Codes	Total No. of Cases[a]	No. of Included Cases[b]	% of Total Cases	Mean Age at Death (Interquartile Range), years	Female Cases, %
All causes		294,833	282,378	96	78.2 (71.6–88.5)	51
Alzheimer's disease	G30	9,758	9,228	95	85.3 (80.0–90.5)	68
Senile dementia	G30, F00, F03	29,975	28,288	94	86.9 (82.7–91.7)	68
Amyotrophic lateral sclerosis	G12.2	759	744	98	70.3 (63.5–79.0)	46
Parkinson's disease	G20–21	6,994	6,683	96	83.7 (79.6–88.8)	48
Multiple sclerosis	G35	838	773	92	67.0 (57.9–77.4)	67
Cancer of the trachea, bronchus, or lung	C33–C34	14,384	14,281	99	70.0 (62.4–78.1)	26
Cancer of the esophagus	C15	2,119	2,101	99	70.5 (61.5–79.9)	24
Alcoholic liver disease	K70	3,356	3,303	98	63.4 (55.4–71.5)	28

Abbreviation: ICD-10, *International Classification of Diseases, Injuries, and Causes of Death*, Tenth Revision.
[a] Deaths that could be linked to the census (refer to the text).
[b] Excluded were persons with unknown building coordinates or who were under 30 years of age at the start of follow-up or death.

with causes of death coded according to the *International Classification of Diseases, Injuries, and Causes of Death*, Tenth Revision (ICD-10). Enumeration in the 2000 census is nearly complete: Coverage was estimated at 98.6% (7). Deterministic and probabilistic record linkages were used to link census records to a death record or an emigration record (6). Of death records of persons older than 30 years, 95.1% could be successfully linked to a 2000 census record. At present, the database includes follow-up data until December 31, 2005.

We excluded persons aged 29 years or less at the census, as well as persons with incomplete information on building coordinates. The database contains information on age, sex, marital status, education, and occupation, as well as additional variables describing, for example, the degree of urbanization of the area or building characteristics such as the number of apartments per building. The geo-coded place of residence of the participants (i.e., Swiss-grid coordinates extracted from the Swiss building registry) is also included in the census data. In general, these coordinates pinpoint a location within a few meters of the building's midpoint. Data from the 1990 census were used to identify the place of residence at that time. The 1990 and 2000 censuses additionally include information on whether individuals had lived at the same place 5 years before the census, that is, in 1985 or in 1995. We were thus able to identify persons who had lived at their place of residence for at least 5, 10, or 15 years.

Outcomes

We considered deaths from the following neurodegenerative diseases: Alzheimer's disease, senile dementia, ALS, Parkinson's disease, and multiple sclerosis. These diseases had to be listed on the death certificate as the primary or a concomitant cause of death. The recording of neurodegenerative diseases on death certificates might be related to socioeconomic position. We therefore included outcomes that are known to be related to socioeconomic position: cancer of the trachea, bronchus, or lung; alcoholic liver disease; and all-cause mortality. The ICD-10 codes used are listed in Table 1.

Exposure

Exposure assessment was based on the distance of the place of residence to the nearest power line. We included all 220–380 kV power lines in Switzerland, over 5,100 km in total. We obtained geodata of the power lines from the Federal Inspectorate for Heavy Current Installations. Figure 1 illustrates localization of the power lines and buildings in Switzerland. We determined the shortest distance to any of the transmission lines and derived the number of persons living within the corridors around the power lines. We defined corridors of 0–<50 m, 50–<200 m, 200–<600 m, and 600 m or beyond. We determined exposure at the time of the 2000 census.

Information about the use of a building as a clinic or nursing home was available from a separate building record, which was completed by the owner of the building, and this information was then matched to the personal records of individuals. Some persons might live in a nursing home or clinic because of a neurodegenerative disease. Therefore, in order to obtain more appropriate exposure data for individuals living in such an institution in 2000, we used the exposure for the place of residence at the time of the 1990 census instead. Persons who lived in a nursing home or clinic in 1990 were excluded from the analysis.

Statistical analyses

We analyzed data using Cox proportional hazard models. We compared the risk of dying from neurodegenerative diseases across corridors and according to the duration of residence in exposed corridors (at least 5, 10, and 15 years). Person-years of observation were defined as the interval between December 4, 2000 (the date of the census), and death, emigration, or December 31, 2005.

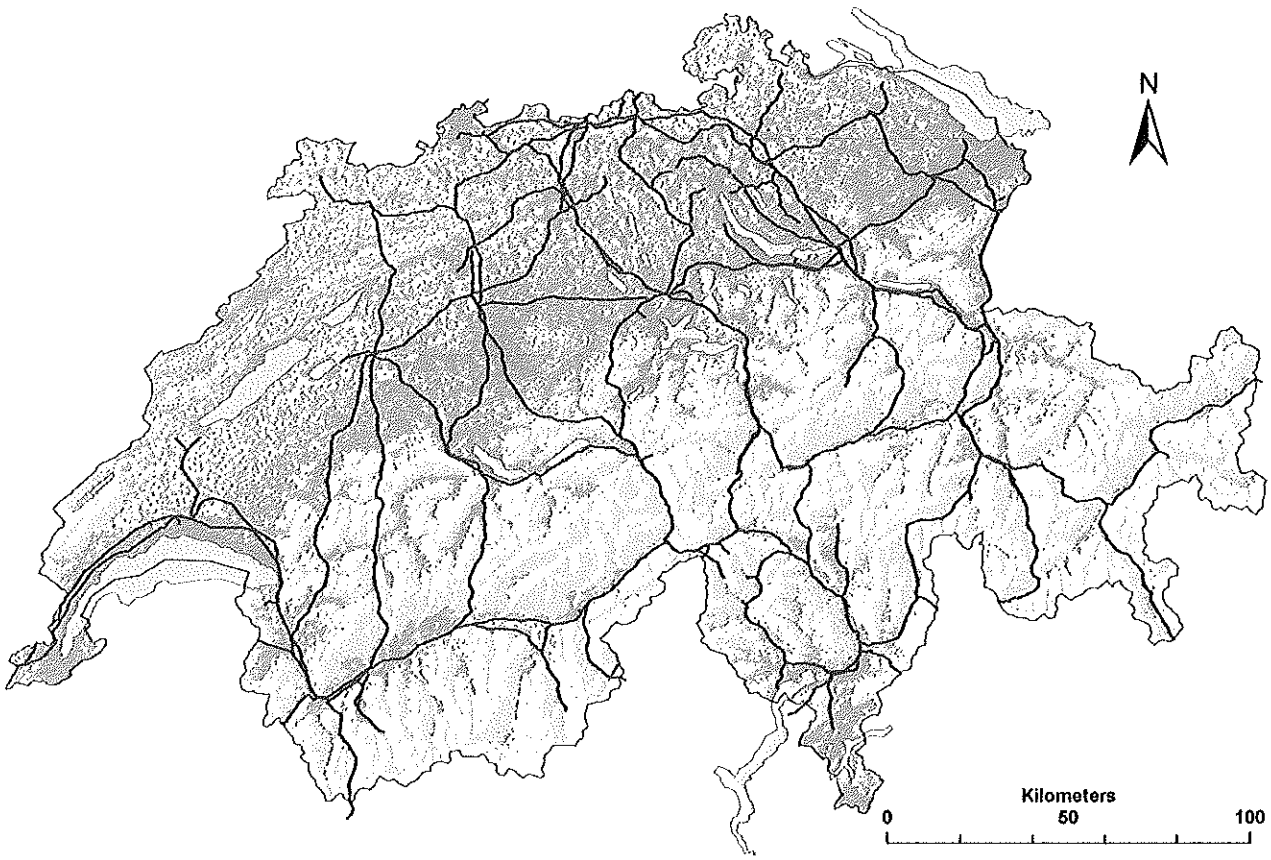

Figure 1. Power lines and buildings in Switzerland. Data sources: Federal Inspectorate for Heavy Current Installations, Fehraltdorf (power lines); Register of Buildings and Dwellings, Federal Statistical Office, Neuchâtel (building coordinates); and Federal Office of Topography swisstopo, Wabern (background map of Switzerland).

We used age as the underlying timescale in our models. All models were adjusted for sex; educational level (compulsory education, secondary level, and tertiary level); highest reported occupational attainment by code (4 levels extracted from the International Standard Classification of Occupations of 1988—1) legislators, senior officials, managers, and professionals, 2) technicians and associate professionals, clerks, service workers, and shop and market sales workers, 3) skilled agricultural and fishery workers, craft and related trades workers, plant, machine operators, and assemblers, and elementary occupations, and 4) no occupation reported); civil status (single, married, divorced, widowed); urbanization category (city, agglomeration, rural municipality); and language region (German, French, Italian). We also included the number of apartments per building into the model, a potential risk factor for magnetic field exposure due to indoor wiring (8).

Finally, because Alzheimer's disease might be associated with benzene exposure, we adjusted models for living within 50 m of a major road. We extracted proximity of the buildings to the "major road network" using data from the Swiss TeleAtlas database for this purpose. The major roads network includes motorways and motorway exits, as well as "major roads of high importance": nearly 8,700 km with 7% of the population exposed to major roads in the 50-m corridor. In sensitivity analyses, we repeated analyses for persons aged less than 85 years, by sex, and examined whether results differed between deaths where Alzheimer's disease or senile dementia had been coded as the primary or concomitant cause of death.

We tested our models successfully for the proportionality assumption using Nelson-Aalen survivor functions and statistical tests based on Schoenfeld residuals. Data were analyzed by using Stata 9 (StataCorp LP, College Station, Texas) software. Results are presented as hazard ratios with 95% confidence intervals.

The Swiss National Cohort was approved by the cantonal ethics committees of Bern and Zurich.

RESULTS

Of the 7.29 million persons recorded in the 2000 census, 2.59 million were excluded because they were under the age of 30 years at the census. Furthermore, 39,871 persons with unknown building coordinates were excluded. The cohort

Table 2. Number of Deaths, Person-Years of Follow-up, and Hazard Ratios for Alzheimer's Disease and Senile Dementia Mortality According to Distance to Power Lines, Entire Study Population and Individuals With at Least 15 Years at the Identical Place of Residence, Switzerland, 2000–2005[a]

Cause of Death	Distance to 220–380 kV Power Line, m	No. of Cases	No. of Person-Years	Crude		Adjusted	
				Hazard Ratio	95% Confidence Interval	Hazard Ratio	95% Confidence Interval
Entire study population							
Alzheimer's disease	0–<50	20	58,423	1.18	0.76, 1.83	1.24	0.80, 1.92
	50–<200	130	363,460	1.12	0.94, 1.33	1.13	0.95, 1.34
	200–<600	572	1,688,323	0.99	0.91, 1.08	1.02	0.94, 1.11
	≥600	8,506	20,711,618	1	Referent	1	Referent
Senile dementia	0–<50	60	58,423	1.19	0.92, 1.53	1.23	0.96, 1.59
	50–<200	371	363,460	1.06	0.96, 1.18	1.08	0.97, 1.19
	200–<600	1,702	1,688,323	0.98	0.93, 1.02	0.99	0.94, 1.04
	≥600	26,155	20,711,618	1	Referent	1	Referent
Individuals living at least 15 years at the identical place of residence							
Alzheimer's disease	0–<50	15	22,320	1.90	1.14, 3.15	2.00	1.21, 3.33
	50–<200	63	145,148	1.12	0.88, 1.44	1.15	0.89, 1.47
	200–<600	259	641,017	0.96	0.85, 1.09	1.00	0.88, 1.13
	≥600	3,861	7,698,419	1	Referent	1	Referent
Senile dementia	0–<50	33	22,320	1.40	0.99, 1.97	1.41	1.00, 1.98
	50–<200	169	145,148	1.00	0.86, 1.16	1.01	0.86, 1.17
	200–<600	819	641,017	1.00	0.93, 1.07	1.01	0.94, 1.09
	≥600	11,930	7,698,419	1	Referent	1	Referent

[a] Cox proportional hazard models were based on either 4.65 million (entire study population) or 1.75 million (individuals with at least 15 years at the identical place of residence) people, with age as the underlying timescale, crude and adjusted for sex, educational level, occupational attainment, urban-rural area, civil status, language region, number of apartments per building, and living within 50 m of a major road.

thus consisted of 4.65 million persons. During the study period, 282,378 eligible and linked deaths from all causes were recorded, including 9,228 deaths from Alzheimer's disease, 28,288 deaths from senile dementia, 773 deaths from multiple sclerosis, and 6,683 deaths from Parkinson's disease (Table 1). The total number of person-years of follow-up was 22.82 million for the whole study population and 8.51 million for persons who reported living for at least 15 years at the identical place of residence (Tables 2 and 3).

The adjusted hazard ratio of Alzheimer's disease for persons living within 50 m of a 220–380 kV power line compared with that for persons who lived at a distance of 600 m or more was 1.24 (95% confidence interval (CI): 0.80, 1.92). There was little evidence of an increased risk beyond 50 m. Analysis by exposure duration revealed a dose-response relation with respect to years of residence in the vicinity of power lines: Persons living at least 5 years within 50 m had an adjusted hazard ratio of 1.51 (95% CI: 0.91, 2.51), which increased to 1.78 (95% CI: 1.07, 2.96) for persons with at least 10 years and to 2.00 (95% CI: 1.21, 3.33) for persons with at least 15 years (Figure 2; Table 2). These adjusted hazard ratios of 2.04 (95% CI: 1.06, 3.93) and 1.96 (95% CI: 0.88, 4.38) were similar for women and men, respectively, and for persons under 85 years of age (adjusted hazard ratio = 1.94, 95% CI: 0.97, 3.89).

For senile dementia, we observed the same pattern as with Alzheimer's disease, although associations tended to be weaker. For increasing exposure time in the vicinity of power lines, the adjusted hazard ratio increased from 1.23 (95% CI: 0.96, 1.59) for any exposure duration to 1.34 (95% CI: 0.98, 1.82) for persons with at least 5 years, to 1.36 (95% CI: 0.98, 1.89) with at least 10 years, and to 1.41 (95% CI: 1.00, 1.98) with at least 15 years of residence near the power line (Table 2). For both Alzheimer's disease and senile dementia, there was little evidence for a difference in effects between deaths coded as primary and deaths coded as concomitant cause ($P_{\text{interaction}} > 0.2$).

Parkinson's disease and ALS were not associated with residence in the proximity of power lines. The adjusted hazard ratio for any duration of exposure in the 50-m corridor was 0.83 (95% CI: 0.46, 1.49) for Parkinson's disease and could not be estimated (no case occurred in the 50-m corridor) for ALS. The adjusted hazard ratio for multiple sclerosis was 1.20 (95% CI: 0.30, 4.80). Similar results were obtained when restricting analyses to persons with at least 15 years at the same place of residence (Table 3).

No increased risk in the proximity of a power line was found for all-cause mortality, cancer of the lung, bronchus, or trachea, cancer of the esophagus, or alcoholic liver disease, for any duration of residence (data not shown) or when

Table 3. Number of Deaths, Person-Years of Follow-up, and Hazard Ratios for Amyotrophic Lateral Sclerosis, Parkinson's Disease, and Multiple Sclerosis Mortality According to Distance to Power Lines, Entire Study Population and Individuals With at Least 15 Years at the Identical Place of Residence, Switzerland, 2000–2005[a]

Cause of Death	Distance to 220–380 kV Power Line, m	No. of Cases	No. of Person-Years	Crude		Adjusted	
				Hazard Ratio	95% Confidence Interval	Hazard Ratio	95% Confidence Interval
	Entire study population						
Amyotrophic lateral sclerosis	0–<50	0	58,423				
	50–<200	10	363,460	0.88	0.47, 1.64	0.85	0.46, 1.59
	200–<600	39	1,688,323	0.74	0.54, 1.02	0.72	0.52, 1.00
	≥600	695	20,711,618	1	Referent	1	Referent
Parkinson's disease	0–<50	12	58,423	0.95	0.54, 1.67	0.87	0.50, 1.56
	50–<200	99	363,460	1.15	0.94, 1.40	1.06	0.87, 1.29
	200–<600	416	1,688,323	0.98	0.90, 1.09	0.92	0.84, 1.02
	≥600	6,156	20,711,618	1	Referent	1	Referent
Multiple sclerosis	0–<50	2	58,423	1.11	0.28, 4.43	1.19	0.30, 4.79
	50–<200	16	363,460	1.38	0.84, 2.26	1.45	0.88, 2.39
	200–<600	60	1,688,323	1.12	0.86, 1.45	1.16	0.89, 1.51
	≥600	695	20,711,618	1	Referent	1	Referent
	Individuals living at least 15 years at the identical place of residence						
Amyotrophic lateral sclerosis	0–<50	0	22,320				
	50 –<200	7	145,148	1.05	0.50, 2.21	1.00	0.47, 2.11
	200–<600	29	641,017	0.97	0.66, 1.41	0.93	0.63, 1.35
	≥600	389	7,698,419	1	Referent	1	Referent
Parkinson's disease	0–<50	8	22,320	1.25	0.63, 2.51	1.15	0.57, 2.30
	50–<200	56	145,148	1.25	0.96, 1.63	1.14	0.87, 1.49
	200–<600	210	641,017	0.99	0.86, 1.14	0.93	0.81, 1.08
	≥600	3,006	7,698,419	1	Referent	1	Referent
Multiple sclerosis	0–<50	1	22,320	1.26	0.18, 8.98	1.35	0.19, 9.62
	50–<200	11	145,148	2.09	1.15, 3.82	2.19	1.19, 4.01
	200–<600	26	641,017	1.10	0.74, 1.65	1.14	0.76, 1.71
	≥600	299	7,698,419	1	Referent	1	Referent

[a] Cox proportional hazard model based on 4.65 million and 1.75 million people, with age as the underlying timescale, crude and adjusted for sex, educational level, occupational attainment, urban-rural area, civil status, language region, number of apartments per building, and living within 50 m of a major road.

restricting analyses to persons with at least 15 years at the same place of residence (Table 4).

DISCUSSION

This large study of the entire Swiss population found that persons who lived within 50 m of a 220–380 kV power line were at increased risk of death from Alzheimer's disease, compared with persons who lived farther away from power lines. The risk increased with increasing duration of residence in the 50-m corridor. Notably, the risk declined rapidly with increasing distance, with only weak evidence for an increased risk beyond 50 m. A similar pattern was observed for senile dementia. In contrast, we found no consistent association for ALS, Parkinson's disease, or multiple sclerosis. Our study thus indicates a possible association between ELF-MF exposure and risks of Alzheimer's disease and senile dementia.

Comparison with previous studies

Established risk factors for Alzheimer's disease include age and genetic factors (9). Controversy remains regarding environmental risk factors, including ELF-MF (10). The association between Alzheimer's disease and ELF-MF has generally been studied with respect to occupational exposures. Occupational exposures are typically about 0.5 μT for electricians, some machine operators, or train drivers, above 1 μT for some machine operators, and around 3 μT for electrical power installers and repairers (11). In occupational settings, increased risks of Alzheimer's disease have been reported with magnetic field exposures at levels around 0.5 μT (4). To our knowledge, an analysis of the potential

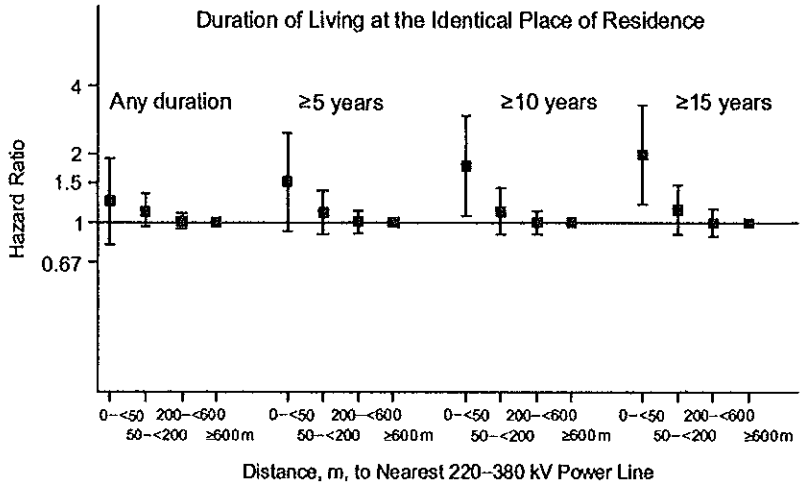

Figure 2. Mortality from Alzheimer's disease in relation to proximity to 220–380 kV power lines, Switzerland, 2000–2005. Cox proportional hazard models for persons in Switzerland who reported living at the place of residence at the time of the 2000 census or at the identical place of residence for at least 5, 10, or 15 years, using age as the underlying timescale, adjusted for sex, educational level, occupational attainment, urban-rural area, civil status, language region, number of apartments per building, and living within 50 m of a major road.

association of neurodegenerative diseases and residential exposure has not been reported in the scientific literature, even though ELF-MF exposure from power lines can be of the same magnitude as in occupational settings. In the United Kingdom, propagation of magnetic fields at levels of about 0.5 μT at a distance of 50 m to a 275 kV line was reported (12). At maximum load, these levels could, however, be considerably higher. In Switzerland, the Federal

Table 4. Number of Cases and Hazard Ratios for Comparison Outcomes of Total Mortality, Alcoholic Liver Disease, Cancer of the Esophagus, and Lung Cancer According to Persons Who Reported Living at Least 15 Years at the Identical Place of Residence, Switzerland, 2000–2005[a]

Cause of Death	Distance to 220–380 kV Power Line, m	No. of Cases	Crude		Adjusted	
			Hazard Ratio	95% Confidence Interval	Hazard Ratio	95% Confidence Interval
Total mortality	0–<50	341	1.11	1.00, 1.24	1.07	0.96, 1.19
	50–<200	2,144	1.01	0.97, 1.06	0.97	0.93, 1.01
	200–<600	10,104	1.02	1.00, 1.04	1.00	0.98, 1.02
	≥600	135,851	1	Referent	1	Referent
Alcoholic liver disease	0–<50	4	1.01	0.38, 2.70	1.11	0.41, 2.96
	50–<200	32	1.23	0.87, 1.75	1.31	0.92, 1.86
	200–<600	94	0.82	0.66, 1.01	0.87	0.70, 1.07
	≥600	1,409	1	Referent	1	Referent
Cancer of the esophagus	0–<50	1	0.37	0.05, 2.62	0.36	0.05, 2.55
	50–<200	16	0.88	0.54, 1.45	0.84	0.51, 1.38
	200–<600	77	0.94	0.75, 1.19	0.92	0.73, 1.16
	≥600	1,055	1	Referent	1	Referent
Lung cancer	0–<50	19	1.02	0.65, 1.59	1.00	0.64, 1.57
	50–<200	119	0.95	0.79, 1.14	0.94	0.78, 1.12
	200–<600	551	0.98	0.90, 1.07	0.99	0.90, 1.08
	≥600	7,248	1	Referent	1	Referent

[a] Cox proportional hazard models, using age as the underlying timescale, crude and adjusted for sex, educational level, occupational attainment, urban-rural area, civil status, language region, number of apartments per building, and living within 50 m of a major road. The study population is the same as that for Table 3.

Office for the Environment estimated that, at full load, 1 μT would not be exceeded at a distance of 60–80 m from a 380 kV line and at 40–55 m from a 220 kV line (13).

For ALS, an association between the risk of ALS and employment in electrical occupations, which is related to both magnetic field exposure and the risk of experiencing electric shock, has been reported (14). The electric shock hypothesis would be consistent with our results, as we did not observe an association with residential magnetic field exposure. In the absence of a known biologic mechanism, the World Health Organization recently concluded that the available evidence on a possible association between ELF-MF and Alzheimer's disease, as well as ALS, was inadequate (5).

Of the few studies so far that evaluated magnetic field exposure and multiple sclerosis, none reported statistically significant increased risks, which is in line with the inconsistent results observed here (15–17). Also in line with previous studies, our results for Parkinson's disease provide little evidence for an association (18).

Strengths and limitations

This study combined the mortality register data with nearly complete population data from the 2000 census, complemented with information on duration of residence from the 1990 census. With the exception of persons emigrating from Switzerland, particularly older immigrants who tend to return to their countries after retirement, mortality data are also virtually complete. Record linkage failed in some instances, but this is unlikely to be associated with residence in the vicinity of power lines. Linkage success is very high in the age group above 30 years and highest in the age group between 65 and 85 years. Because mortality from neurodegenerative diseases is negligible in younger people, we restricted our analyses to persons aged 30 years or over. In sensitivity analyses, we excluded people aged 85 years or older and obtained virtually identical results.

The development of neurodegenerative disease, as well as its recording on death certificates, may be associated with socioeconomic position. The availability of data on education and occupation and other potential confounders on an individual level is an important strength of our study. This allowed us to adjust for several indicators of socioeconomic position, but this adjustment had only very small effects on our estimates. In addition, causes of death known to be associated with socioeconomic position were included for comparison but did not show an increased risk in the 50-m corridor.

There is no registry for neurodegenerative diseases in Switzerland, and we had to rely on information given on death certificates, where neurodegenerative diseases are known to be underreported (19–21). The degree of underreporting varies by disease. Death certification of cases of ALS and multiple sclerosis has been found to be reasonably accurate (22, 23). Underreporting of Alzheimer's disease, as well as senile dementia, is more common and increases with the age of the deceased (19, 21, 24–27). Mortality rates for Alzheimer's disease have been increasing since 1995, when a specific code was introduced in the ICD-10 system, indicating that reporting of Alzheimer's disease on death certificates has become more complete in recent years. However, it is unlikely that the completeness of reporting is associated with living in the proximity of power lines.

The magnetic fields produced by power lines depend on a variety of factors, including the load characteristics, distance between conductors, and the placement of phases. Unfortunately, information on these characteristics was not available in our study. We acknowledge that the use of exposure corridors, without measurements or taking the load of the line and other factors into account, may have introduced Berkson-type error into the exposure assessment (28), and this could have reduced the power of our study. On the other hand, it is possible that our surrogate is not predictive for true exposures at all because other sources may be more important, for instance, at work or when travelling. This would imply that the observed association is due to another factor that could not be controlled for in the analysis. However, we believe that we allowed for the most important factors in the analysis, and we are not aware of other exposures that could plausibly explain the observed associations.

There is no consensus as to which exposures from overhead power lines are biologically relevant and should be measured (2). For example, ionized particles or contact currents may also be relevant (29–31). However, all of these exposures are associated with distance to a power line. We extended the corridors around power lines up to a distance of 600 m to make our results comparable with those of the study by Draper et al. (32). In contrast to their study, we found little evidence for an increased risk beyond 50 m. With respect to a potential mechanism, we can only speculate whether one of the mechanisms that have been proposed in the literature (5) might be of importance in the context of magnetic field exposure and neurodegenerative diseases. For example, induced electric fields in neural networks (electric fields induced in tissue by exposure to extremely low frequency electric and magnetic fields) have been reported to affect synaptic transmission in neural networks, as well as the radical pair mechanism (5). Increased free radical concentrations can cause oxidative damage to cellular components, which could play a role in the etiology of Alzheimer's disease.

Finally, underground cables that replace overhead power lines in some urban areas may represent an additional source of residential magnetic field exposure, but these were not considered in our study. In Switzerland, underground cables of 220–380 kV represent only around 0.8% of the grid, and we decided to omit cables from our analyses.

Public health implication

Assuming that the associations observed in this study are causal, what are the public health implications? Considering the relatively small number of cases of Alzheimer's disease and senile dementia diagnosed in the 50-m corridor (Alzheimer's disease: 20 of 9,164 (0.22%); senile dementia: 59 of 28,045 (0.21%)), it is clear that the public health impact appears limited. The true public health impact, however, is difficult to determine. Rates of Alzheimer's disease were reported to be from 2- to 8-fold higher if diagnoses were

based on clinical examination instead of death certificates (20, 24). In addition, Alzheimer's disease might go undiagnosed in another group of persons. Finally, although we found only weak evidence for an increased risk beyond 50 m, it is unlikely that there is an abrupt change in risk at 50 m. Nevertheless, our results do provide reassurance for the population living at distances of 50–600 m from a power line.

Conclusions

The results of our study support the hypothesis that magnetic field exposure plays a role in the etiology of Alzheimer's disease and senile dementia but not of ALS or other neurodegenerative diseases. Despite the large sample size covering the whole Swiss population, these findings must be interpreted with caution, because of the lack of known biologic mechanisms.

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Review

The Effects of Low-Frequency Environmental-Strength Electromagnetic Fields on Brain Electrical Activity: A Critical Review of the Literature

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Reports dealing with the stimulus-response relationship between low-level, low-frequency electromagnetic fields (EMFs) and changes in brain electrical activity permit assessment of the hypothesis that EMFs are detected by the body via the process of sensory transduction. These reports, as well as those involving effects on brain activity observed after a fixed time of exposure, are critically reviewed here. A consistent stimulus-response relationship between EMFs and changes in brain activity has been demonstrated in animal and human subjects. The effects, which consisted of onset and offset evoked potentials, were observed under conditions permitting the inference that the fields were transduced like ordinary stimuli such as light and sound. However, unlike the changes in brain activity induced by these stimuli, the changes induced by EMFs were governed by nonlinear laws. The studies involving attempts to determine whether a period of EMF exposure caused a metabolic effect reflected in pre-exposure/post-exposure differences in brain activity were generally inconclusive.

Keywords Electromagnetic field; Brain electrical activity; Nonlinear analysis; Electroencephalogram; Evoked potentials; Recurrence analysis.

Introduction

Concern regarding the impact of environmental-strength electromagnetic fields (EMFs) on the nervous system arose independently from two strikingly different research initiatives. Referring to research he had done from 1965–69 to help explicate the Soviet microwave irradiation of the American embassy in Moscow and the results in several published reports (Gavalas et al., 1970; Bawin et al., 1973), Ross Adey said:

> My colleagues and I have observed the effects of weak electric and electromagnetic fields on the behavior of man and animals, and we have correlated these observations with neurophysiological effects and brain

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> chemistry. The most striking conclusion drawn from these observations is that mammalian central nervous functions can be modified by electrical gradients in cerebral tissue substantially less than those known to occur in postsynaptic excitation, and also substantially smaller than those presumed to occur with inward membrane currents at synaptic terminals in release of transmitter substances. (Adey, 1976)

During the same time period, Robert Becker sought to understand the role of endogenous electrical signals in the control of tissue regeneration; in 1972, after summarizing his work he said:

> I also feel concern for a much broader problem, which is the continuous exposure of the entire North American population to an electromagnetic environment in which is present the possibility of inducing currents or voltages comparable with those now known to exist in biological control systems. (Becker, 1972)

The idea they had in common was that man-made EMFs might interfere with the electrical signals that governed the body's regulatory systems, like sand in the gears of a machine, thereby promoting human disease.

In 1980, Becker and Marino presented a general theory of the link between EMFs and disease, based on a putative electrogenic protein in excitable cells whose functional state was altered by the presence of weak pericellular EMFs (Fig. 1)

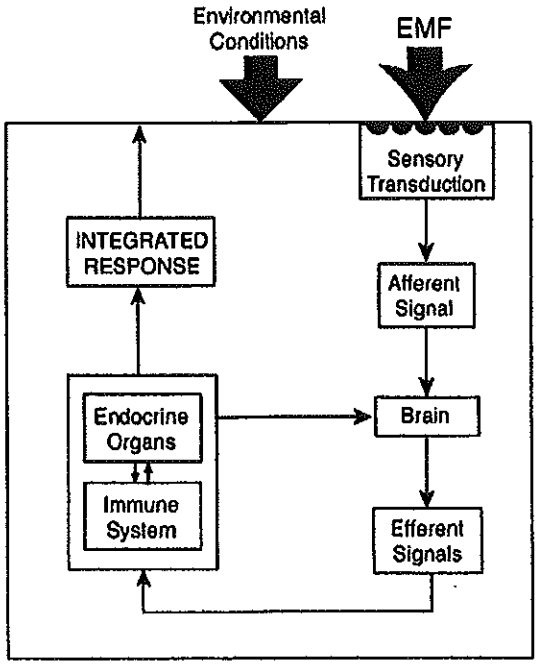

Figure 1. The proposed control system that mediates EMF-induced biological effects. The field is transduced and the resulting signal is cognitively processed thereby permitting the brain to initiate and regulate the appropriate adaptive physiological responses. A key observable in the theory is the stimulus-response relationship formed by onset of the EMF and subsequent deterministic changes in brain electrical activity.

(Becker and Marino, 1982). As theorized, a resulting subthreshold change in membrane potential led to an afferent signal, cognitive processing, and efferent signals to the body's effector systems. In this view, the reported links between EMFs and effects in body tissues (and ultimately human disease) were indirect and stemmed from overtaxing the body's sensory and compensatory mechanisms (excess biological stress).

The theory predicted that the onset of an EMF almost immediately triggered alterations in brain electrical activity. Consequently, evidence of a stimulus-response relationship between presentation of an EMF and changes in brain electrical activity would support the validity of the initial stages of our theory (Fig. 1). Our purpose here is to describe and evaluate the literature pertinent to the existence of such a relationship. Only studies dealing with the effects of low-frequency EMFs on brain electrical activity will be discussed; effects due to high-frequency EMFs (mobile phones) were reviewed elsewhere (Carrubba and Marino, In press).

Methods

We searched electronic databases (PubMed, Science Citation Index) using various combinations of an electrical term (field, electromagnetic, electric, magnetic, ELF, nonionizing, DC, AC), a device (high-voltage powerlines, electrical appliances), and an outcome (electroencephalogram, evoked potentials, brain electrical activity) to identify English-language studies that involved the effects of low-frequency, non thermal EMFs on the brain electrical activity of humans or animals. The inclusion criteria were: (1) a reasonable description of the experimental conditions; (2) use of a control group; and (3) statistical evaluation of the data. The exclusion criteria were: (1) the use of thermal EMFs; and (2) application of electrical energy by means of surface electrodes rather than fields. All other factors including blinding of study participants, counter-balancing of experimental conditions, performance of sham studies, and corrections for multiple comparisons were considered with regard to the weight given to the study rather than to its admissibility as evidence of the ability of EMFs to affect brain activity.

Linear Studies

Animal Studies

Bell et al. (1992b) statistically compared brain electrical activity from rabbits in the presence and absence of fields, using spectral analysis. The EMFs studied were: (1) 1 G, 5 Hz (a prominent frequency in the rabbit brain); (2) 0.64 G, 25 Hz (the ion-resonance conditions for K^+); (3) 1 G, 25 Hz (a field whose suspected physiological significance was that it was a nospecific stressor). Each rabbit was exposed to the three fields, a light stimulus (positive control), and a sham stimulus (negative control) in one experimental session, and each test session was repeated ($\geq$1 day between replications). The fields were uniform throughout the animal's body, thereby permitting an accurate characterization of its strength at the location of the electrogenic protein, wherever it occurred.

We avoided the use of ANOVAs to obviate the possibility that averaging the results across the subjects might obscure a real effect if the subjects reacted differently

from one another. Instead, we acquired multiple independent trials of brain activity, each containing a stimulus (or sham stimulus) and control epoch, and the effect of the stimulus was evaluated in each animal. The stimulus was applied for 2-s epochs, with a variable inter-stimulus period (5–11-s, varied randomly). The first 30 ms of each field-exposure epoch was removed to eliminate the field-onset spike in the electroencephalogram (EEG) and the remaining signal was filtered at 0.3–35 Hz; these precautions were taken in all subsequent studies involving the effects of fields on brain electrical activity (Bell et al., 1991, 1992a, 1994a,b, 1996; Marino et al., 1996, 2002, 2003, 2004; Carrubba et al., 2006, 2007a,b, 2008). Fourier transforms were performed on all 2-s stimulus epochs and their corresponding control epochs (the 2-s period immediately preceding the stimulus) (N = 200). The Fourier analysis of each epoch yielded 39 dependent variables consisting of the power at 1–20 Hz (units of μV^2) in increments of 0.5 Hz, each of which was compared between the stimulus and control epochs under conditions such that the family-wise error rate for the decision that a rabbit detected the field was $p < 0.05$.

Sixty-seven percent of the rabbits detected the light stimulus and none detected the sham stimulus. All of the rabbits tested detected the 1-G, 5-Hz magnetic field, but not the other two fields. The rapidity and circumstances of the effect (observed during 2 s of stimulus presentation in the context of multiple independent trials on the same animal) suggested that the effects were a result of sensory transduction (because other known forms of signal detection would have been too slow). When the EEG measurements were repeated after the rabbits had been killed, the results showed that the 5-Hz effect could not be attributed to an induction artifact.

A major shortcoming of the study was the assumption that any real effect in any specific animal was necessarily consistent. The assumption was made tacitly when we chose to use the *t* test to compare the average spectral power between groups. Mathematically, the assumption was that any change in the Fourier coefficient at a particular frequency would be more or less identical from trial to trial. The problem generated by this assumption was ultimately appreciated and eliminated (see the Nonlinear Studies section below).

Normal Human Subjects

Our initial human studies were performed to determine whether frequency-specific responses also occurred in the human brain during EMF exposure (Bell et al., 1992a). We measured the electroencephalogram (EEG) from C3, C4, P3, P4, O1, and O2 (International 10–20 System, referenced to linked ears) in 19 subjects; this electrode configuration was used in all subsequent human studies (Bell et al., 1991, 1994a,b; Marino et al., 1996, 2004; Carrubba et al., 2007a,b, 2008). As with the rabbits, each subject served as his own control, the spike artifact in the EEG due to field onset was eliminated, and the results were protected against family-wise error. Using 0.2 and 0.4 G at 1.5 and 10 Hz, we found altered brain activity at the stimulation frequency during exposure in each subject. The effect was more likely at 10 Hz compared with 1.5 Hz, and more likely at 0.4 G compared with 0.2 G (Bell et al., 1992a).

To study the effect of a field whose frequency was not significantly present in the EEG, we exposed subjects to 250–500 mG, 35–40 Hz for 2-s epochs (inter-stimulus period 5–11 s), and compared the spectral power measured during exposure with that measured during the inter-stimulus period in 50 independent trials for each subject (Bell et al., 1991). The control for each field epoch was the immediately preceding 2-s

period. The criterion for concluding that a subject had detected the field was that it produced at least 2 bilateral successes (statistically significant difference between exposed and control epochs) in at least one pair of electrodes, provided that those changes were in the same direction (family-wise error $p < 0.02$). We found that 7 of 14 subjects responded to the EMF, as evidenced by statistically reliable changes in the spectral power at specific frequencies. No false-positive results were seen when the entire procedure was repeated using sham exposure.

The 50% detection rate for a field that had no physiological significance generally supported our theory (Fig. 1), but raised the question of why half the subjects had apparently not responded to the field. We therefore performed replicate studies but using 60 Hz, which we reasoned might yield a higher detection rate because the population has been preconditioned to fields at this frequency since the development of commercial power systems (Bell et al., 1994a). We employed 0.78 G, 60 Hz, in the presence and absence of 0.78 G, DC. Each of 20 subjects underwent a block of trials involving exposure to the DC field (B_{DC}), the 60-Hz field (B_{AC}), combined fields (B_{DC+AC}), and a sham field. A trial consisted in the presentation of the field for 2 s, followed by a 5-s field-off interval; the control epoch for each field epoch was the immediately preceding 2-s interval.

The Fourier coefficients at 1–18 Hz were analyzed; the criterion for accepting an effect due to the presentation of the field was that it resulted in at least 2 bilateral successes in at least one pair of electrodes (family-wise error rate, $p = 0.04$). B_{DC}, B_{AC}, and B_{DC+AC} were detected by 7, 15, and 13 subjects, respectively. Overall, 19 of the 20 subjects tested responded to at least one of the fields studied. Both increases and decreases in field-induced activity were observed, depending on the Fourier frequency. No effects occurred with the sham field.

A major question raised by the two previous studies (Bell et al., 1991, 1994a) involved the interpretation of the negative results that occurred in 35% ([7+5]/[14+20]) of the subjects studied. One possibility was that the non responders were inherently insensitive to the field (true negatives), thereby suggesting that sensitivity to EMFs was not a general human trait. In our next study, therefore, we measured the false-negative rate of our method for detecting stimulus-induced effects in the EEG, using the reaction to light as the gold standard (Marino et al., 1996).

Each subject underwent a block of trials that included stimulus (either light or magnetic fields) and control epochs. A trial consisted of the presentation of a stimulus (or a sham) for 2 s, followed by a 5-s stimulus-free interval. Only 11 of 28 subjects detected the light ($p < 0.05$ for each subject), whereas all the subjects reported that they had seen the light, which necessarily implied that brain electrical activity had been altered. Thus, the results indicated that the false-negative rate of the method when used to detect light-induced changes in the EEG was 61% (Marino et al., 1996). In 19 other subjects, 11 detected 0.8 G (either 1.5 or 10 Hz) corresponding to a non response rate of 42%. Overall, these results indicated that the true detection rate for low-frequency EMFs was probably higher than the 50–75% that we had observed in our studies.

Several additional reports involved the sensory response of the human brain to EMFs (Heusser et al., 1997; Lyskov et al., 2001; Stevens, 2007). A composite EMF stimulus (17 mG, 8–12 Hz, and 25 mG DC) decreased the global field power (a measure roughly equivalent to the spatial standard deviation of the EEG from 12 scalp locations) during field exposure in a study group of 20 subjects ($P = 0.06$, Wilcoxon signed rank test) (Stevens, 2007).

In a second study, the relative spectral power measured in 62 subjects during exposure to 350 mG (rms), 3 Hz, was compared with pre-exposure levels (Heusser et al., 1997). The induction artifact associated with application of the field was minimized by slowly ramping the field, which was applied for 20 min. Comparisons were made between the pre-exposure levels, each of four 5-min successive intervals during exposure, and the 5-min period following cessation of exposure. Of the 30 planned comparisons (5 E-C conditions × 2 electrode locations (left and right side of the head) × 3 frequency bands (theta, alpha, beta)), 4 were statistically significant. The probability of 4 successes due to chance (pair-wise significance $p < 0.05$) in 30 tests is $p = 0.06$. Consequently, as the authors recognized, the results may or may not indicate the true occurrence of a field-induced change in the EEG. Moreover, since most of the significant tests were associated with ≥20 minutes' exposure, they were probably not relevant to sensory (as opposed to general metabolic) changes in the EEG.

The study (Heusser et al., 1997) illustrated the quandary faced by an investigator who does not have a hypothesis regarding the nature of the effects of EMFs on the EEG. In such cases the experimental plan invariably calls for the performance of numerous statistical tests involving multiple dependent parameters that characterize brain activity. Usually, some tests are pair-wise significant but their meaning is dubious because of a lack of protection against family-wise error (the alternative explanation that the pair-wise significant effects were all due to chance). Even worse, if one regards the family-wise error rate as sufficient for indicating the occurrence of an effect, it is not possible to identify specific effects. In the present study, for example, the significances occurred in theta on the left side after 5-min exposure, in beta on the right and left side after 20-min exposure, and in beta on the right side following exposure. Even if one could validly conclude that brain electrical activity was affected, there would be no way to decide exactly what was affected or when.

In a third study, the relative spectral power in the resting EEG was unaltered during exposure to 100 mG, 60 Hz in normal subjects and in self-selected electrically hypersensitive subjects (Lyskov et al., 2001); the results were also negative when the exposures were repeated while the subjects performed an arithmetic task. The small applied field, non stationarity of the EEG, inter-subject variations, and the use of a 3-way ANOVA, individually and in combination are reasonable explanations for the consistent negative results.

As part of the power industry's assessment of potential health risks due to the electric and magnetic fields of high-voltage powerlines, investigators studied the effect of these fields on evoked potentials in subjects who were simultaneously exposed to visual or auditory stimuli (Graham et al., 1987; Cook et al., 1992; Graham et al., 1994). In one study, 9 kV/m and 200 mG were applied together while the subjects were presented with visual or auditory stimuli in the context of target-detection tasks (the oddball paradigm) (Cook et al., 1992). The visual stimulus was light from a red/green light-emitting diode, and the auditory stimulus consisted of high- and low-pitched tones; the stimuli (50 ms in duration) were presented 140 times, and the EEG from C_Z (10–20 System) was averaged to characterize the auditory (AEP) and visual (VEP) evoked potentials. The infrequent target stimuli (20% high tones or red lights) were randomly interspersed among the non target stimuli (80% low tones or green lights), and the amplitude and latency of the P300 wave of the evoked potential were computed for each sensory modality for target and non target stimuli, before, during, and after both field exposure and sham exposure. The field altered the non target AEP amplitude during and after exposure, but had no effect on latency. There was no

effect on VEP amplitude either during or after field exposure, but there was a reduction in latency during field exposure (Cook et al., 1992).

In another study, three groups of subjects (18 per group) were exposed to 6 kV/m and 100 mG, 9 kV/m and 200 mG, 12 kV/m and 300 mG, respectively (Graham et al., 1994). Significant alterations in the latency and amplitude of the AEP were found in the low- and medium-strength fields, but not in the high-strength field. However, the effects occurred at N200-P300 in the evoked potential, not at P300 as in the earlier study (Cook et al., 1992).

Counting their initial unpublished results (Graham et al., 1987), the investigators reported some kind of field-induced effect on brain potentials evoked by light or sound in three studies. However, several factors undercut the reliability of their observations. First, the data was embedded in a highly complex set of screening studies involving numerous neurophysiological parameters, and it is difficult to have confidence that their post-hoc data-mining approach yielded anything other than chance associations. On the other hand, roughly parallel changes were observed in three separate experiments, and the work was performed under contract to industry-related groups (which would be predisposed in favor of negative data). Consequently, the experiments probably furnish modest support for the proposition that field exposure affected cognitive brain processing as reflected in changes in brain potentials evoked by other stimuli.

Patients with Epilepsy

If brain electrical activity is altered in the presence of an EMF, it is reasonable to suspect that the effect would occur in subjects with epilepsy because their brain electrical activity is labile and vulnerable to changes caused by imperceptibly subtle internal and external factors. This possibility was investigated in a series of studies involving exposure of subjects with mesial temporal lobe epilepsy (MTLE) who were stimulated with 1–40 G (Fuller et al., 1995, 2003; Dobson et al., 2000a,b). The fields were applied for a fixed interval in multiple independent trials, and the distributions of the anomalous spikes characteristic of epilepsy that occurred during the 10-s intervals before and after the exposure interval were compared (Fig. 2a). In the first study, 6 of 7 subjects showed significantly higher levels of epileptiform activity following field exposure (Fig. 2b) (Fuller et al., 1995). Similar results were claimed in a second study, but the experimental protocols were complex (many combinations of field strengths, durations of field exposure, and times between independent trials), and only 3 subjects were studied (Dobson et al., 2000a). In a third study, 5 of 10 subjects suffering from MTLE exhibited a significant ($p < 0.05$) response to the field (Dobson et al., 2000b). When these results were averaged over all the subjects, no field effect was found. In a fourth study, an increase in epileptic activity following field exposure was observed in 1 of 3 subjects, and a progressive increase in epileptic activity may have occurred during what had previously been assumed to be independent trials (Fuller et al., 2003).

The investigators concluded that they had demonstrated field-induced changes in the EEG from MTLE patients, and that may indeed have been the case. However, they did not discuss the limitations of their conclusion. First, although they used scalp electrodes, it appears their most quantitatively reliable data was obtained from implanted electrodes that monitored the hippocampus. The possibility that the observed effects arose from current induced in the electrodes and delivered deep in the

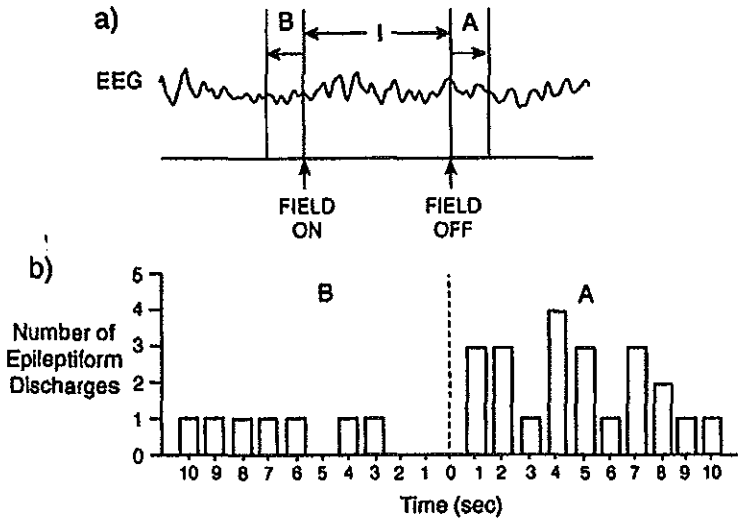

Figure 2. Exposure of a subject with mesial temporal lobe epilepsy to DC magnetic fields. (a) Experimental design. The subject was exposed to the field for a predetermined interval (I) and the epileptiform activity that occurred during the 10-s intervals before (B) and after (A) exposure were compared in multiple independent trials in each subject. (b) Typical result, showing the number of epileptiform discharges in A and B in subject WB (Fuller et al., 1995); control activity is shown for the 10-s interval prior to field application (cumulative results for 27 trials).

brain was not discussed. The authors manually switched on and off the magnetic field for the express purpose of minimizing consequences of Faraday induction but they neither evaluated the effectiveness of this precaution nor applied it in all experiments.

The investigators used terms "increased" and "decreased" to refer to statistical decisions ($p < 0.05$) and also to quantitative data that had not been evaluated statistically, which sometimes makes it difficult to ascertain which inferences were justified statistically. Also, they employed complex exposure protocols involving different field strengths but did not explain why they thought that the results could be combined for analysis.

The authors favored the view that the effect on epileptiform activity arose not from the presence of the field but from the fact that it was switched on and off. However, given their experimental design (Fig. 2a), it is equally possible that the effect could have been due (wholly or partly) to the presence of the field. In the study in which both individual and group analyses were performed (Dobson et al., 2000b), they found that the individual effects were averaged away when the subjects were analyzed as a group. This result is consistent with an inference that the effects were nonlinear, but it could also be explained by assuming that the effects were linear but weak, and hence were not averaged away but simply diluted by the 50% of the subjects who did not show statistically significant results.

Nonlinear Studies

Initial Reports

The principal shortcoming in the studies described above was the assumption by the investigator, almost always made tacitly, that any real effect associated with

presentation of an EMF stimulus would be consistent from trial to trial. When we recognized that this assumption was unwarranted and probably incorrect, we began analyzing the effects of EMFs on brain electrical activity using mathematical tools that had been developed for studying nonlinear systems. These methods, phase-space embedding followed by calculation and quantitation of the corresponding recurrence plot, permitted us to capture the deterministic activity in the EEG caused by the stimulus (regardless of whether it was an increase or a decrease) prior to comparing means in a statistical analysis. The basic mathematical techniques and the tailoring necessary to apply them to the analysis of the EEG are described in detail elsewhere (Carrubba et al., 2006).

Rabbits were exposed to 2.5 G, 60 Hz, using a set of coils that ensured the field was uniform throughout the animal's environment (Marino et al., 2002). The field was applied for 2 s (E epoch) followed by a field-free period of 5 s (minimum of 60 trials). The procedure was repeated using light as the stimulus (positive control). The signal from the last 2 s of each trial was used as the control (C) epoch for the corresponding E epoch. The signal from the 2 s preceding the C epoch was defined as the sham (S) epoch and was analyzed statistically relative to C to evaluate the possibility that any positive results might be attributable solely to our analytical method.

The induction artifacts (approximately 30 ms at onset and offset of the field) and trials containing movement artifacts were removed from the recorded voltage. The remaining trials were embedded in a 5-dimensional space with a time delay of 1 point. Recurrence plots were then produced for the E, S, and C epochs in each trial, and the plots were quantitated using percent recurrence (%R) and percent determinism (%D), which, respectively, represent the number of recurrence points in the plot and the percentage of the recurrent points that fell along diagonal lines (Webber and Zbilut, 1994).

We first evaluated the data from one rabbit, using a discriminant procedure to optimize our ability to detect an effect. Corresponding segments of the stimulus and control epochs of the EEG (E and C, respectively) were systematically compared using the Wilcoxon signed rank test to identify the portion of the signal that was most responsive to the field (window). In this manner we localized the effect of the field to a 250-ms segment centered at 250 ms after commencement of the field. In a similar manner, we determined that the response to the light stimulus occurred within a 266-ms interval centered at 175 ms after the light was applied.

The windows in the E epoch thus identified were studied prospectively in nine additional rabbits to analyze the effect of application of each of the stimuli. In each case the nonlinear quantifiers (%R and %D) were significantly greater (family-wise $p < 0.05$) in the E epoch segment, and there were no cases of false-positive results (assessed by comparing the sham and control segments) (Marino et al., 2002). The entire experiment was repeated three times for each rabbit and the results were identical.

To study the effect of the level of consciousness on the ability of the stimuli to affect brain electrical activity, we repeated the experiments following induction of anesthesia. The previously observed effect of the field on the EEG was absent in all rabbits; in contrast, anesthesia had no effect on the EEG changes caused by light. After the animals were killed the field experiments were repeated. The input signals to the EEG amplifier were analyzed as previously, and we found that %R and %D were essentially zero, independent of the presence of the field.

The reproducibility and consistency of the results far exceeded those of any previously reported study involving the biological effects of electromagnetic fields.

We attributed this consistency to the use of nonlinear analysis because we found that linear analytical methods were not capable of evidencing field-induced effects in the EEG.

The coil arrangement used in the study (Marino et al., 2002) produced fields that varied by less than 5% throughout the region occupied by the rabbit; we therefore knew that the field at the location of the electrogenic protein was 2.5 G, ± 5%, even though we did not know its anatomical location. One possibility was that electroreception occurred throughout the body as, for example, in somatosensory transduction. Alternatively, electroreception might have been localized, such as for the special senses. To help choose between the two possibilities we modified the coil arrangement so that the average magnetic fields in the cranial and caudal half of the rabbit were maximally different (Marino et al., 2003). Exposure of the cranial half of the animal resulted in effects on %R and %D in each case as previously (with one exception), with no false-positive results. When the experiment was repeated with the cranial half in the low-field region and the caudal half in the high-field region, no effect on the EEG was observed. When the field was localized to the head, the effects on determinism in the EEG described above were again seen. When the field was further localized to the eye, the effects did not occur. Taken together, the results can be interpreted to indicate that EMF transduction occurred somewhere in the head, probably the brain.

Employing conditions of analysis similar to those described in connection with the rabbit studies (Marino et al., 2002), we measured the response rate of normal human subjects to a low-strength, low-frequency magnetic field (Marino et al., 2004). Eight subjects were exposed to a series of trials consisting of the application of 1 G, 60 Hz, for 2 s, followed by a field-free period of 5 s, and the EEG was analyzed statistically using phase-space methods to assess whether the subject detected the field. As we had done with the rabbits, we used a discriminant procedure in the first subject to locate the epoch-segment windows that maximized the effect of the stimulus, and then applied those windows prospectively to compare E vs. C and S vs. C in the remaining subjects. The criterion for accepting the conclusion that a stimulus-related change in brain activity actually occurred was that the field resulted in at least 2 significant differences from among the 6 EEG derivations (family-wise error $p < 0.05$). As in all our previous studies, we removed the 30-ms portion of each trial after field onset and offset, and deleted trials that contained movement artifacts (<5% of all trials).

We found that a 190-ms window centered at 215 ms after commencement of the field yielded the lowest p value for E vs. C (C segment centered at 5.215 s, width of 190 ms) when p was not significant for S (3.215 s, width of 190 ms) vs. C. When the 190-ms window was shifted 30 ms earlier or later, the E vs. C comparison was not significant, indicating that the subject's response started at about 100 ms. The window width and location thus determined were then applied prospectively to 7 additional subjects in 7 independent experiments to ascertain the effect of exposure, and significant ($p < 0.05$) differences in %R and %D were found in each experiment (Marino et al., 2004). Light was also detected by all the subjects (190 and 175 ms for width and center location, respectively). No false-positive comparisons were found when the same mathematical procedures were used to compare sham-exposed and control segments.

The 100% response rate to EMFs manifested by the human subjects (Marino et al., 2004) was similar to the results found with the rabbits (Bell et al., 1992b),

suggesting that the ability to detect low-strength EMFs is a common property of the mammalian nervous system.

Recent Reports

Although the nonlinear method successfully showed that essentially all rabbit and human subjects exhibited altered brain activity when an EMF was presented (Marino et al., 2002, 2004), the way we implemented the nonlinear approach superimposed on each study subject a specific latency and duration of response that could be observed. We therefore modified the method so that the latency or duration of the response were not fixed in advance of the application of the field, but rather were determined for each subject with the requisite degree of statistical reliability; the details are given elsewhere (Carrubba et al., 2006).

Employing the improved procedure, we found that evoked potentials caused by onset or offset of the field (2 G, 60 Hz) occurred 109–454 ms after the stimulus application, depending on the subject; the evoked potentials were detected in the occipital electrodes in 16 of 17 subjects (family-wise error rate, <0.05 in each case) (Carrubba et al., 2007a). The potentials, which consisted of statistically significant increases or decreases in the nonlinear quantifiers, could not be detected when the EEG was analyzed by time averaging, indicating that occurrence of the potentials was nonlinearly related to presentation and removal of the field.

Several considerations led to the conclusion that the observed effects were true post-transduction changes in brain electrical activity triggered by the magnetic stimulus, that is, magnetosensory evoked potentials (MEPs): (1) The alternative explanation (that the effects resulted from interaction between the field and the scalp electrodes) was ruled out because the observed MEPs occurred several hundred ms after the stimulus (typical latency for evoked potentials); (2) sensory evoked potentials are typically produced by both onset and offset of a stimulus, and both responses were observed with EMFs; and (3) inter-subject variation in latency (within a well-defined range) was seen, as is the case with all known types of evoked potentials. It followed for all these reasons that the observed changes in brain electrical activity were true MEPs.

Nonlinear systems do not follow the law of superposition, and therefore their reaction to change in external conditions cannot be precisely predicted. If the MEPs (Carrubba et al., 2007a) were nonlinear, the brain electrical response exhibited by human subjects would be expected to differ even when the experimental conditions were replicated. We tested this hypothesis by comparing a subject's response to a weak magnetic stimulus at two times, separated by at least one week (Carrubba et al., 2007b). Eight clinically normal subjects were exposed to 1 G, 60 Hz applied for 2 s, with a 5-s inter-stimulus period, and EEGs were recorded from O1 and O2 (International 10–20 System) and analyzed as described previously (Carrubba et al., 2007a) to detect the onset MEP. Using nonlinear analysis, MEPs were detected in all subjects in the initial series of studies, and in all but one subject in the replicate studies (Fig. 3) (Carrubba et al., 2007b); no MEPs were detected using linear analysis. With one exception (Fig. 3, S6), the MEPs observed in the initial studies were also observed in the replicates. However, the relation of the determinism in the replicate (the law-governed dynamical activity reflected in the recurrence plot and characterized by the quantifier %R) to that in the original MEP differed significantly from subject to subject. The replicate MEP was manifested as a consistent increase in %R in S1 and

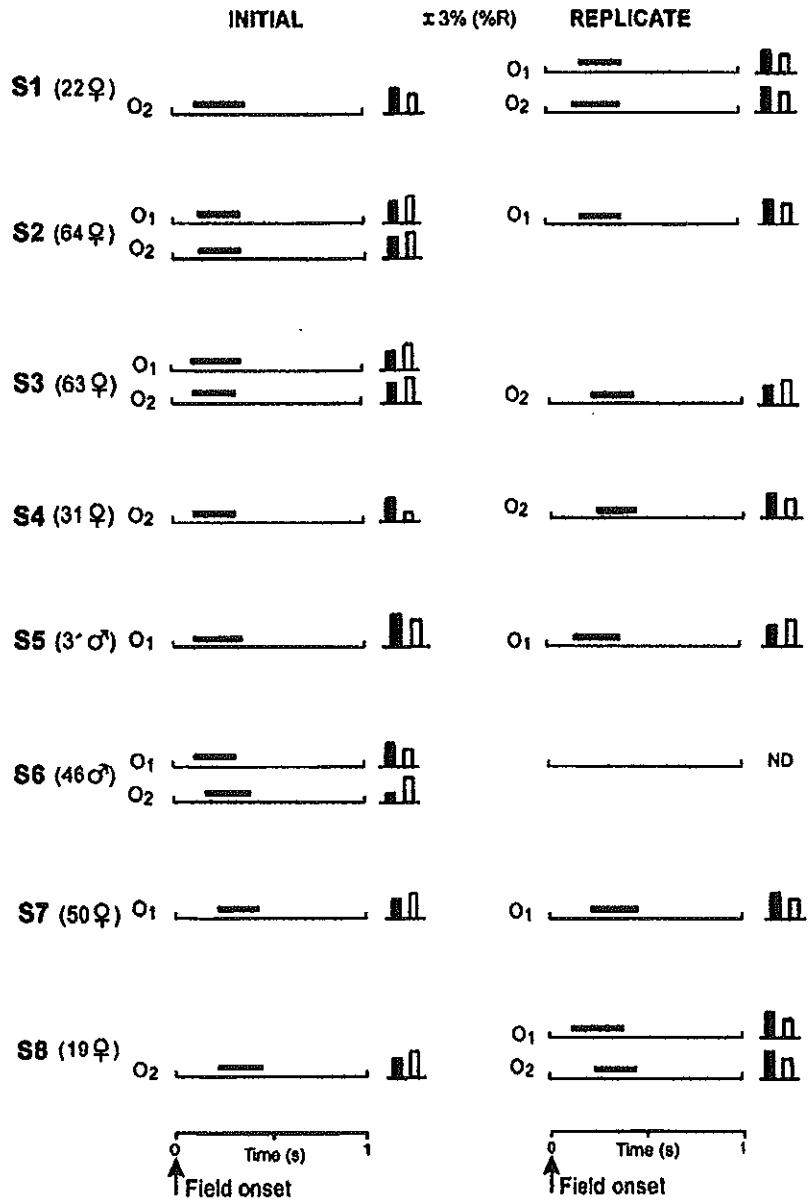

Figure 3. Detection of magnetosensory evoked potentials (MEP) in initial and replicate studies, using recurrence analysis. Latency and duration in each subject are indicated on the time axis. Bar graphs indicate the mean of the MEP (average of the significant points in the %R time series); black and white bars correspond to onset and control epochs, respectively (SD not resolved at scale presented). S1–8, subjects 1–8. ND, not detected (Carrubba et al., 2007b).

S4, a consistent decrease in S3, and as inconsistent differences in the other subjects which included 3 subjects who first exhibited a decrease and then an increase (S2, S7, S8) and one subject who responded oppositely (S5). Thus, the MEPs detected in this study were inconsistent, as predicted. Only a system governed by nonlinear laws can exhibit such a pattern of response.

Given that the effects of EMFs on brain electrical activity were nonlinear in origin (Carrubba et al., 2007a,b), it became necessary to reevaluate how the scientific requirement of reproducibility should be formulated because, in distinction to linear systems, consistency in the magnitude and direction of a stimulus-response relationship are not general properties of nonlinear systems. We therefore developed a procedure for demonstrating the consistent occurrence of changes in magnetosensory evoked potentials (MEPs) in individual subjects exposed to a magnetic field (Carrubba et al., 2008). In these studies, the magnetic field was applied for only 50 ms, and the MEPs were recorded during the interstimulus period. After all conditions that affected the analysis of the EEG in association with the presentation of a stimulus were specified in advance, we detected MEPs in all 15 subjects ($p < 0.05$ in each experiment) (Carrubba et al., 2008). The MEPs occurred within the predicted latency interval, were independent of the frequency and direction of the field, and were not detected using the traditional linear method of analysis, time averaging. When the results obtained within subjects were averaged across subjects, the evoked potentials could not be detected, indicating how nonlinear phenomena can be averaged away when incorrect analytical procedures are used.

Metabolic Studies

The studies discussed above were designed to test the hypothesis that EMFs were transduced by the sensory system (Fig. 4a) or were at least pertinent to that hypothesis (Fig. 4b). Another group of studies involved an attempt to determine whether field exposure resulted in a generalized metabolic effect that was reflected in brain electrical activity (Fig. 4c). For example, we compared the 10-Hz power in the occipital EEG one minute after 10 min exposure to 1 G, 10 Hz, with the pre-exposure 10-Hz power (Bell et al., 1994b) and found that the power was significantly reduced. Thus, after 10 min exposure, brain electrical activity was reduced immediately following the exposure—for whatever that means.

When the average relative spectral power in 20 subjects before and after exposure for 1 h to 12.6 G, 45 Hz was compared, changes in various frequency bands were seen, depending on the electrode derivation (Lyskov et al., 1993); the effects occurred when the field was applied intermittently (1 s on and 1 s off), but not when it was applied continuously. This result was consistent with the idea that the body recognized the onset and/or offset of the field (as opposed to its presence); however, the data was not protected against the possibility of family-wise error.

Investigators exposed subjects to complex, therapeutically motivated pulses whose salient features were an amplitude of 1.4 G (rms), a width of 853 ms, and a variable inter-stimulus period (110–1200 ms) (Cook et al., 2004, 2005). Occipital alpha power was increased after 15 min exposure (Cook et al., 2004). The investigators were unable to replicate their observation, but did report a decrease in alpha power in the context of a complicated exposure procedure (Cook et al., 2005).

The major limitation of these studies (Cook et al., 2004, 2005) was the absence of consideration of the family-wise error in the statistical analysis. In each experiment, several hundred complex ANOVAs were performed; consequently, the several statistically significant results found could reasonably be attributed to chance. On the other hand, it seems statistically improbable for chance results to occur in two independent experiments in the same electrodes (occipital) at the same Fourier frequencies (alpha).

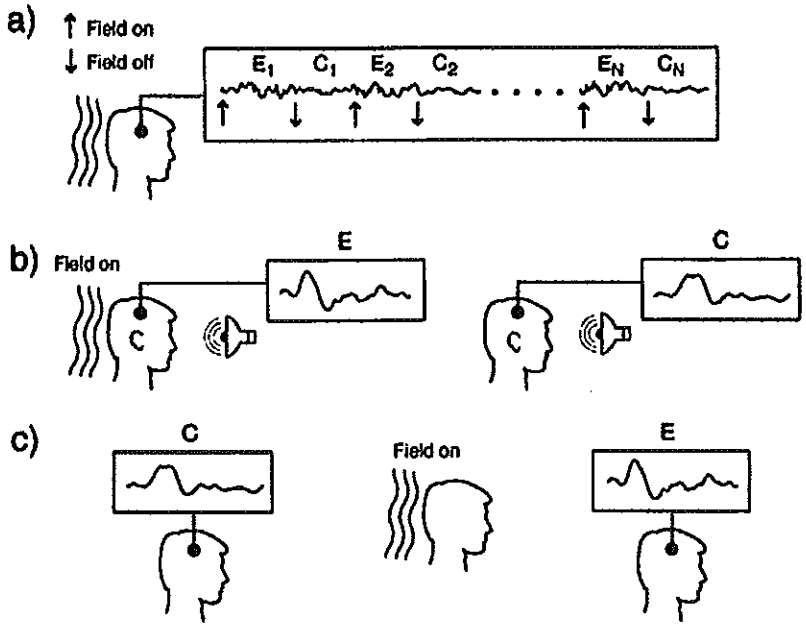

Figure 4. Distinction between sensory and metabolic studies. (a) A comparison between exposed (E) and control (C) epochs permits statistical evaluation of the hypothesis that the onset (or offset) of the field causes evoked potentials. (b) Comparison of auditory (or visual or somatosensory) evoked potentials in the presence and absence of a field permits statistical evaluation of the hypothesis that fields alter ongoing sensory processing. (c) Comparison of brain activity before and after a period of EMF treatment can establish that the field causes an effect on body metabolism but is not directly probative with regard to the responsible biological processes.

When subjects were exposed for 90 min to 50 Hz, 280 and 560 mG (rms), alpha activity from O_Z was significantly increased (176%, $p < 0.05$) at the higher field in 15 subjects but was unaffected in 10 subjects exposed to the lower field (Ghione et al., 2005). The difference in absolute alpha might have been real, but several pertinent considerations suggested otherwise. First, the authors did not present the results for relative alpha power; although it was not a planned comparison, it could have helped in the interpretation of the results. Second, the results were inconsistent with other dependent variables measured by the investigators (for example, an effect on hyperanalgesia was observed at the lower field strength but not at the higher field strength).

Several studies involved the effect of EMF exposure on brain activity during sleep. Sleep is divided into stages defined principally by the frequency content and pattern of the EEG. The deepest sleep levels (stages 3 and 4) are characterized by the presence of prominent delta waves (slow-wave sleep). Exposure of 18 subjects to 50 Hz, 10 mG, significantly reduced the duration of slow-wave sleep (fraction of the sleep period during which the subjects were in stages 3 and 4) (Akerstedt et al., 1999). In another study, however, exposure to 60 Hz, 283 mG had no effect on slow-wave sleep (Graham and Cook, 1999). Not surprisingly, there were numerous differences between the two studies that could have accounted for the differing results.

The metabolic effects of EMF treatment on the response to visual and auditory stimuli has been evaluated for several different purposes. In studies undertaken as part of a health assessment of power-frequency magnetic fields, investigators assayed

many electrophysiological variables in subjects exposed to 1 G, 50 Hz (Crasson et al., 1999; Crasson and Legros, 2005). In the first study (Crasson et al., 1999), the investigators reported that the amplitude of the N1 wave in a specialized AEP paradigm (dichotic listening task) and the P300 latency in a visual discrimination task were altered after magnetic-field exposure. However a large number of 2-way ANOVAs were performed, only a few of which were statistically significant. The second study (Crasson and Legros, 2005) was conducted specifically to test the hypothesis that the original observations were real, however none of the expected effects were found.

The possible explanations for the generally negative results of the first were listed (Crasson, 2003): (1) differences in the functional state of the nervous system; (2) differences in individual sensitivity; (3) the possibility that the effect was simply small and was lost in the noise. However, the most reasonable explanation was that the relationship between the applied field and the neurophysiological response was nonlinear, and consequently was unlikely to be detected using linear analysis.

In another biohazard study (Lyskov et al., 2001), exposure to 100 mG, 60 Hz, for 10 min did not alter the fundamental frequency in the Fourier representation of the visual evoked potential (flickering video display, refresh frequency, 60 Hz), on average, in either normal subjects (8.1 ± 4.5 Hz and 7.9 ± 4.1 Hz before and after exposure, respectively) or in 20 self-selected electrically hypersensitive subjects (9.4 ± 8.1 Hz and 9.1 ± 6.9 Hz) (Lyskov et al., 2001). The experimental design was based on a 3-way ANOVA, which may have been insufficiently sensitive for detecting changes in the VEP.

Pain-related somatosensory evoked potentials obtained before and after 2-h exposure to 0.7 G, 0.03–0.07 Hz were compared (Sartucci et al., 1997); the field-generating apparatus had been designed to study the effect of earth-strength magnetic fields on the homing ability of pigeons. The amplitudes of the P150 and P250 waves were reduced after exposure, but the waveform latencies were unaffected. The difficulty with the results involved the statistical analysis. For example, the reported amplitudes ($\pm$ SEM) of the P150 waves (in μV) were 6.3 ± 1.2 and 4.8 ± 0.8 before and after exposure, respectively. The investigators claimed that these means differed at $p < 0.05$; however, the two-tailed p value for this data is $p = 0.31$. A similar problem occurred for all of the reported evoked-potential data.

Event-related potentials (visual oddball task, 9 EEG channels) were measured before and after 20-min exposure to 20 G, either 5 Hz or 20 Hz (Wei et al., 1997). A reduction in P300 latency was reported after 5-Hz but not 20-Hz stimulation, in some of the electrodes. However, the results were not protected against family-wise error.

Discussion

The seminal question regarding the effects of low-frequency electromagnetic fields is whether their presence is detected by the body. If so, then the diverse biological effects attributed to EMFs might all be deterministically explainable within the broad biological theory of stress. If not, EMF-induced bioeffects are not logically possible. We theorized that the detection process was sensory transduction. Whenever stimulus-induced changes in brain activity are observed, cognitive processing of stimulus-related information, hence transduction of the stimulus, can reliably be inferred. It was with an intent to argue in this manner that we performed a series of studies on animal and human subjects regarding the effects of EMFs on brain

electrical activity (Bell et al., 1991, 1992a,b, 1994a,b; Marino et al., 1996, 2002, 2003, 2004; Carrubba et al., 2006, 2007a,b, 2008). Other investigators conducted similar studies for their own purposes, and those studies were included in this review.

From a dynamical perspective the changes in brain activity triggered by EMFs could have been linear or nonlinear; but like poor Oedipus who did not know who he was, we did not know which model was correct. In our initial studies we assumed a linear model and found a stimulus-response relation between EMFs and brain electrical activity; but we could demonstrate this relation in only some subjects (Bell et al., 1991, 1992a,b, 1994a,b; Marino et al., 1996). Other investigators who also assumed a linear model found results that were generally in accord with ours, namely some subjects responded, some did not, and at least some of the non-responders could probably be explained by a lack of sensitivity of the analytical method (Fuller et al., 1995, 2003; Dobson et al., 2000a,b). Although a linear model was incorrectly assumed in both groups of experiments, the further error of averaging the data over all subjects was avoided. In six other studies where the data was averaged across the subjects, a recognizable pattern regarding the meaning of the results did not emerge (Graham et al., 1987, 1992, 1994; Cook et al., 1992; Heusser et al., 1997; Lyskov et al., 2001; Stevens, 2007); such inconsistency is normal in all areas of EMF biology whenever the data is averaged in that manner.

When the effects of EMFs on brain electrical activity were analyzed using mathematical tools that had been developed for studying nonlinear systems, it became possible to capture the deterministic activity in the EEG caused by the stimulus (regardless of whether it was an increase or a decrease) prior to comparing means in a statistical analysis. Capturing the effect of the stimulus prior rather than subsequent to averaging the data was the key step that enabled us to overcome the problem that we identified, and allowed us to show that EMFs were consistently transduced by essentially all the animal and human subjects (Marino et al., 2002; Carrubba et al., 2007a). We showed that a fundamental effect of an EMF stimulus is the triggering of onset and offset evoked potentials in the brain (Carrubba et al., 2007a), and we described a procedure by which their presence can be demonstrated consistently, in every subject, with the requisite statistical reliability (Carrubba et al., 2008).

The various meanings of "nonlinear" are discussed elsewhere (Marino and Frilot, 2003). As used here, the term refers to the nature of the law that governs brain electrical activity when the brain is cognitively processing EMF-stimulus-related information. If a process is "nonlinear," some counter-intuitive (at least to some investigators) phenomena can properly fall within the realm of science (law-governed activity), for example phenomena that are "inconsistent" with regard to various pertinent characteristics (Fig. 3). It is crucial to recognize that the scientific requirement of reproducibility applies with full force to nonlinear EMF phenomena. Properly applied, "reproducibility" simply means that the EMF stimulus affected brain activity—there is no further condition regarding, as examples, magnitude, or direction of the change.

After the first concerns that man-made electromagnetic fields in the environment might be a hazard to public health were raised almost 40 years ago (Becker, 1972; Adey, 1976), the main counter-argument was that the reported EMF-induced bioeffects were inconsistent, thereby indicating only the existence of inconspicuous experimental errors, not real biological processes. There never was any reliable evidence that the argument was true. Now, there is clear evidence the argument is false; magnetosensory evoked potentials elicited by EMFs can be detected in essentially every subject examined when the proper form of analysis is used (Carrubba et al., 2008).

The results of the metabolic EMF studies do not materially advance our understanding of EMF biology. Perhaps EMFs can alter spectral power (Lyskov et al., 1993; Bell et al., 1994b; Cook et al., 2004, 2005; Ghione et al., 2005), sensory evoked potentials (Sartucci et al., 1997; Wei et al., 1997; Lyskov et al., 2001), or brain activity during sleep (Akerstedt et al., 1999; Graham and Cook, 1999). Focused, hypothesis-driven studies having appropriate statistical designs are needed to verify and establish the validity of these ideas.

In closing, we think it appropriate to speculate on how and why human subjects respond nonlinearly to EMFs. Electric and magnetic receptors that facilitate finding food, avoiding predators, and navigating in the environment occur in lower life forms (Wachtel and Szamier, 1969; Manger and Pettigrew, 1996; Walker et al., 1997). We previously described a biophysical process that could explain how EMF transduction occurs in these species (Kolomytkin et al., 2007); vestiges of this detection system might still exist in human beings. Evolutionary considerations also suggest a reason that the MEPs were nonlinear. The processes responsible for the linear correspondence between stimuli such as sound or light and the cognitive responses they induce resulted from evolution by natural selection, leading progressively to physiological linear sensory systems because consistency conferred a selective advantage. Conversely, in the absence of natural selection there is no process by which the phenomenon of consistency in response to a stimulus can come about. Compared with their present-day levels, EMFs were negligible throughout the period of evolution of life on earth, and consequently, a physical mechanism capable of producing a linear response did not develop. In this view, the existence of a nonlinear human magnetic sense could be a vulnerability in the molecular machinery chosen by evolution to mediate other sensory modalities because any physical realization of a sensory system for one kind of stimulus is unlikely to be completely immune to all other kinds of inputs (Nesse and Williams, 1998).

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