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Issue(s): Public Interest, Health Effects
Witness: Dr. Dennis Smith, D.O.
Sponsoring Party: Neighbors United Against Ameren's Power Line
Type of Exhibit: Rebuttal Testimony
Case No.: EA-2015-0146
Date Testimony Prepared: October 21, 2015

MISSOURI PUBLIC SERVICE COMMISSION

CASE NO. EA-2015-0146

REBUTTAL TESTIMONY

OF

DR. DENNIS SMITH, D.O.

ON BEHALF OF

NEIGHBORS UNITED AGAINST AMEREN'S POWER LINE

October 21, 2015

Q. Please state your name and where you reside.

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

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

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

Q. What is your educational background?

A. I received a degree of Doctor of Osteopathic Medicine from Des Moines University in 1994. I completed a residency in Emergency Medicine at Darnall Army Hospital, Ft. Hood, Texas, in 1997 and I am Board Certified in Emergency Medicine by the American Board of Emergency Medicine. As a military emergency physician, I had extensive training in chemical, biological, radiation and non-ionizing radiation warfare and casualties. A copy of my CV is attached as **Schedule DS-01** to my testimony.

Q. What is the purpose of your testimony?

A. I have been asked to address the unacceptable health risks to the people in the path of the proposed Ameren Transmission Company of Illinois (ATXI) 345kV AC transmission line in North East Missouri. While industry and its supporters downplay the risk of EMF to health, there are recent peer reviewed studies that support prior studies showing adverse health effects. Since people in the path of High Votage Overhead Lines live their lives near the lines on a daily basis and in some cases 24 hours per day, the burden of proof that they will not be harmed should be overwhelmingly on the agency that wants to construct a line that will expose them to health dangers on their own property against their will.

Q. Have you testified in other proceedings involving EMF?

A. Yes. On September 15, 2014, I submitted testimony to the Missouri Public Service Commission regarding a proposed high voltage DC line, Grain Belt Express, Case No. EA-2014-0207.

Q. Do you have evidence to refute the claim that the World Health Organization (WHO) does not confirm the existence of any health consequences from exposure to low level EMFs?

A. First of all the above statement is double speak. Ameren states in literature available on their internet site that the World Health Organization (WHO) does not confirm the existence of any health consequences from exposure to low level EMFs. **Schedule DS-02**. While that statement is taken from the WHO literature, it fails to show that ongoing concerns about adverse health effects have triggered the WHO to call for research in multiple health areas. The 2007 WHO Research Agenda for Extremely Low Frequency Fields calls for additional research in multiple areas of health and places High Priority on several of those areas, which include childhood brain tumor studies, childhood leukemia, and amyotrophic lateral sclerosis. **Schedule DS-03**. Quotes from the call for additional research include the following:

- "Several studies have observed an increased risk of amyotrophic lateral sclerosis in 'electric occupations'."
- "There is some evidence that the risk of miscarriage may be affected by ELF magnetic fields exposure."
- "For Alzheimer's disease, it remains a question whether ELF magnetic fields constitute a risk factor. "

The statements in the WHO's own call for research certainly is enough to make a reasonable person want to avoid exposure to EMFs.

Q. Are there other agencies publishing concerns about exposure to EMFs?

A. There is enough evidence linking EMF exposure from High Voltage Overhead Lines (HVOL) to childhood leukemia and other health problems such as breast cancer to cause the International Agency for Research on Cancer (IARC) to list EMF as a Group 2B carcinogen risk. **Schedule DS-04**.

Q. Is there any recent research that demonstrates damage at a cellular level done by EMF?

A. One of the arguments against EMFs causing cancer has been that there has been no plausible explanation for the causation of cancer. Since cancer is generally believed to be caused by DNA damage, any EMF induced effect on DNA provides the plausible explanation that has been reported missing by the WHO. Low levels of environmental EMF penetrate the nucleus of a cell inducing a DNA stress response. This is the same stress response generated when the body is exposed to toxins or extreme heat. See generally, Blank & Goodman, Electromagnetic fields stress living cells, Pathophysiology 16 (2009) 71-78. The study by Blank & Goodman demonstrated that cells can be affected at energy levels as low as 0.5 μT to 1 μT (5-10mG). ATXI reports, "Ameren levels at the edge of Right-of Way for 345kV transmission lines (75ft) are typically at or below 90 mG." The exposure quoted by ATXI is 9-18 times greater than the level of energy found to interact with the DNA of cells.

Q. Is there any new evidence linking EMF to childhood leukemia?

A. In 1979 Nancy Wertheimer and ED Leeper were the first authors to link childhood cancer and high voltage AC lines. Industry has often faulted the research in this area as showing bias or having study sizes too small to be valid A 2013 British Journal of Cancer study of 2,779 cases of childhood acute leukemia and 30,000 controls generated additional findings and support to previous studies linking the cancer to EMF exposure. This study had both numbers and efforts to eliminate any previous bias. **Schedule DS-06**.

Q. Is there any evidence of long term health effects other than cancer?

A. In 2013, an article in the Journal of Cellular and Molecular Medicine

reported both therapeutic and harmful effects of exposure to EMF. Bone growth stimulation and DNA breaks through stimulation of Voltage Gated Calcium Channels (VGCCs) were demonstrated. Bone growth can be a long term health benefit; however, DNA breaks are generally felt to be related to cancer formation. **Schedule DS-07.**

Q. Is the information you present enough to dispute the safety of the 345,000-volt transmission line proposed by ATXI?

A. ATXI's website documents quote only three (3) sources to cite the safety of the proposed line. One of the sources is the WHO. The WHO double speaks the safety issue as reported previously in my testimony. While the WHO is a very important organization in world health matters, it is not an infallible organization as demonstrated in 2014 by its utter failure to identify the dangers of the EBOLA outbreak. One only has to do a quick search of world news organizations on that topic to see the failure to identify the risk. Another citation by ATXI is the Environmental Protection Agency. We have seen that agencies failure to identify the risk of its activities in the 2015 Colorado mine clean up activity. This too is a organization that does great work, yet it can make mistakes. My summary of information disputing the safety of the proposed line is short and there are many more studies available on EMFs. As a busy physician, I am only pointing out that there is evidence to raise concern for the health of people in the path of the proposed line.

Q. What is your conclusion?

A. People in the path of the proposed project have legitimate fears about the possible adverse health effects. Eminent domain is necessary in some cases to provide needed services to a population. In the case of ATXI's line, the industry is proposing to put a group of people at risk on their own properties, in their own homes, and in some cases children in their schools.

ATXI attempts to minimize the risk using statements from the WHO or Environmental Protection Agency; however there is evidence that there are real health risks. People should not be forced to expose themselves to that risk just because they live, attend school, or work in the path of a line. Eminent domain use would give the people no choice about exposure that is not providing electricity for their comfort or commerce. The WHO comments in some of its literature that even if risk is proven, it is minimal. No one would consider the risk insignificant if his/her child or grandchild is the one affected by a disease such as childhood leukemia. No one should be forced against their will to expose their family to any entity they fear on the property they have toiled to purchase and maintain.

Q. Does this conclude your testimony?

A. Yes it does. Thank you.

BEFORE THE PUBLIC SERVICE COMMISSION
OF THE STATE OF MISSOURI

In the Matter of the Application of Ameren Transmission Company of Illinois for Other Relief or, in the Alternative, a Certificate of Public Convenience and Necessity Authorizing it to Construct, Install, Own, Operate, Maintain and Otherwise Control and Manage a 345,000-volt Electric Transmission Line from Palmyra, Missouri, to the Iowa Border and Associated Substation near Kirksville, Missouri.	)))))))	**File No. EA-2015-0146**

AFFIDAVIT OF DR. DENNIS SMITH, D.O.

STATE OF MISSOURI)
) **ss**
COUNTY OF Randolph)

Dr. Dennis Smith, D.O., being first duly sworn on his oath states:

1. My name is Dr. Dennis Smith, D.O., and I am employed as a physician and Medical Director of the Emergency Department at the Moberly Regional Medical Center, Moberly, Missouri.

2. Attached hereto and made a part hereof for all purposes is my rebuttal testimony on behalf of Neighbors United Against Ameren's Power Line consisting of 7 pages and Schedules DS-01 through DS-07, and prepared in written form for introduction into evidence in the above-referenced docket.

3. I hereby swear that my answers to the questions contained in the attached rebuttal testimony are true and correct to the best of my knowledge, information and belief.

Dr. Dennis Smith, D.O.

Subscribed and sworn to before me this 20th day of October, 2015

Luann R Nanneman
Notary Public

LUANN R. NANNEMAN
Notary Public - Notary Seal
State of Missouri
Commissioned for Randolph County
My Commission Expires: July 27, 2019
Commission Number: 15219378

Dennis Smith, DO, FACEP,FAAEM
3705 Highway NN
Moberly, MO 65270

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.

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
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

Mark Twain Transmission Project

About the Project
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161 kV Connector

Know the Facts about the Mark Twain Transmission Project

Ameren Transmission Company of Illinois (ATXI) is planning to build a 345,000-volt transmission line in northeast Missouri along with a new substation near Kirksville. Known as the **Mark Twain Transmission Project**, it consists of two line segments, from Palmyra to Kirksville, and Kirksville to the Iowa border. The total length of these segments is approximately 100 miles. The Mark Twain Transmission Project also includes construction of a 161,000-volt connector transmission line from the existing Adair Substation to the Zachary Substation. This connection will be approximately 2.2 miles in length.

- **A need for delivering renewable energy** – Missouri law requires utilities to provide greater amounts of renewable energy. To help meet this need for renewable energy, the Midwest region's transmission system operator developed an electricity grid improvement plan, including the Mark Twain Transmission Project, to provide the transmission capacity needed to promote the development and delivery of renewable energy.

- **Greater reliability** – From communications and transportation to manufacturing, virtually every aspect of our society depends not just on electricity, but a reliable supply of electricity. The Mark Twain Transmission Project will improve reliability by strengthening the Midwestern transmission grid.

- **Job creation and economic benefits** – It is anticipated that construction of the Mark Twain Transmission Project will create 200 good, well-paying jobs. A study released on Sept. 30, 2014, by the Mid-Continent Independent System Operator (MISO) also found the economic benefit of the regional transmission plan to Missouri will be 2.3 to 3.3 times the transmission investment. Missouri electric customers all along the route will benefit from the availability of electricity transported on the Mark Twain Transmission Project line.

- **A source of tax revenue** – The Mark Twain Transmission Project will lead to additional local tax revenue to support schools, roads, police and fire protection districts.

- **No one source of power** – The power carried by the Mark Twain Transmission Project line will not come from any one source, but from any and all electric generation sources connected to the Midwest grid.

- **A cleaner environment** – In its Sept. 30, 2014 study, the regional transmission operator finds its plan will reduce carbon emissions from electric generating units by 9 to 15 million tons annually.

- **Compatible with farming** – The Mark Twain Transmission Project will utilize single-shaft, steel poles that do not require guy wires. Farmers can continue to use land under the transmission line for crops and pasture. Large equipment can be used around and under the transmission lines, with some restrictions and recommendations regarding proximity to the pole structures and clearances under the line. The line will be designed to meet or exceed minimum NESC code design clearances (25 feet for 345,000 volts). Our goal is to minimize the impact on agriculture.

- **Acquiring easements** – The Mark Twain Transmission Line Project will primarily be built on permanent easements ranging in width from 100 feet to 150 feet depending on the voltage of the line. ATXI will need to acquire these easements, and additional land rights, from landowners. Project representatives will be contacting landowners for the purpose of conducting good-faith negotiations with a goal of reaching agreements with each landowner. Fair market value paid for the easements is discussed in more detail below. ATXI cannot rule out the possibility that eminent domain authority would be exercised if our good-faith efforts to negotiate the required easements prove unsuccessful.

- **Fair compensation for transmission line impact** – Landowners are fully compensated for the impact of the transmission line. ATXI's offer of compensation for easements is intended to "make the landowners whole" by fully compensating them for any effect on the market value of their property caused by the imposition of the easement. Upon completion of construction, ATXI's representatives assess, and, if necessary, repair or compensate landowners for damages that may result from construction of the transmission line. This includes damages to crops, soil, fences and other property or improvements.

- **No tax money** – No federal, state or local tax monies will be used to build, operate or maintain this transmission line. This transmission line will be built, operated and maintained by ATXI, a wholly-owned subsidiary of St. Louis-based Ameren Corporation.

- **Explaining electromagnetic fields** – Electromagnetic fields (EMFs) are generated by anything that uses or conducts electricity. Some typical in-home sources of EMFs include refrigerators, microwave ovens, vacuum cleaners, hair dryers, video display monitors and fluorescent lamps to name just a few. Distribution and transmission lines also can contribute to magnetic fields in homes, but the electric field from these outside sources contributes little to indoor levels because it is effectively shielded by building materials.

  Based on a recent in-depth review of the scientific literature, the World Health Organization (WHO) concluded that current evidence does not confirm the existence of any health consequences from exposure to low level EMFs. Furthermore, it is clear that the exposure to EMFs of people living in the vicinity of high voltage power lines differs very little from the typical range of exposure of the entire population. Studies have also found no adverse effect of EMFs from power lines on crops or farm animals, including cattle that graze below power lines.

- **Compatible with hunting** – The Mark Twain Transmission Project will not interfere with hunting. According to the University of Michigan, "White-tailed deer prefer forest edges that are close to farmlands, old fields, and brushland." Thus, deer populations tend to do well where transmission lines border wooded areas. Ameren has also fostered a relationship with the National Wild Turkey Federation to improve turkey habitats in the right of way.

FOR THREE DECADES, RESEARCHERS HAVE STUDIED ELECTRIC AND MAGNETIC FIELDS (ELECTROMAGNETIC FIELDS - EMF) — THOSE FIELDS GENERATED BY EVERYTHING ELECTRICAL FROM POWER LINES AND HOUSE WIRING TO PERSONAL COMPUTERS AND HOUSEHOLD APPLIANCES.

Ameren appreciates your interest in this scientific topic and hopes you find this brochure useful. We have included information from respected scientific sources to many of the questions previously asked by Ameren customers regarding EMF concerns. These sources include The National Institute of Environmental Health Sciences (NIEHS), The World Health Organization (WHO), United States Environmental Protection Agency (EPA), The International Commission on Non-Ionizing Radiation Protection (ICNIRP) and the American Conference of Governmental Industrial Hygienists (ACGIH).

If you need additional information on EMF, please visit the information sources websites, addresses provided, or call our EMF information line at **314.554.2402**.

WHAT IS EMF?

Electromagnetic fields are generated by anything that uses or conducts electricity — not just power lines.

EMF consists of two components:

- Electric fields are created by the voltage of electricity in a wire (similar to water "pressure" in a hose) — the higher that voltage, the stronger the electric field. Electric fields are produced on any energized conductor regardless of whether current is flowing.
- Magnetic fields exist only when current is flowing (similar to water moving through a hose) — the greater the current, the stronger the magnetic field.

HOW ARE MAGNETIC FIELDS MEASURED?

The intensity of magnetic fields is measured with an instrument called a gauss meter. Field intensity is typically recorded in milligauss (one-thousandth of a gauss). Electromagnetic fields decline substantially with distance from the source. Lines that are many feet away from a person offer less exposure than appliances that are much closer. Measurements are merely a snapshot of values at a given time and are valid only for that moment. Values can change dramatically depending upon the amount of electricity flowing through power lines or appliances at any given time.

Magnetic fields close to electrical appliances are often much stronger than those from other sources, including magnetic fields directly under power lines. Appliance fields decrease in strength with distance more quickly than do power line fields.[1] See table in this publication of typical field levels compiled by the National Institute of Environmental Health Sciences.

EMF EXPOSURE STANDARDS

Are there exposure standards for 60-Hz EMF? In the United States, there are no federal standard limiting occupational or residential exposure to power line EMF.[1] Two states have set standards for magnetic fields — Florida and New York.[1]

STATE TRANSMISSION LINE STANDARDS AND GUIDELINES

State	Magnetic Field On R.O.W.	Edge R.O.W.
Florida	—	150 mG* (max. load)
		200 mG* (max. load)
		250 mG* (max. load)
New York	—	200 mG (max. load)

**R.O.W. = right-of-way (in the Florida standard, contain additional areas adjoining the right-of-way); also lines of 69-230 kV differ 500 kV lines. †For 500 kV lines on certain existing R.O.W.*

Ameren levels at the edge of Right-Of-Way for 345 kV transmission lines (75 ft) are typically at or below 90 mG.

TYPICAL MAGNETIC FIELD LEVELS FROM HOUSEHOLD SOURCES* (in milligauss, mG)

Distance from Source	6 in.	1 ft.	2 ft.	4 ft.
Blenders				
**Lowest	50	9	1	—
Median	200	40	5	—
Highest	1,000	300	40	4
Power Saws				
Lowest	500	40	3	—
Median	600	150	20	2
Highest	1,500	300	30	4
Vacuum Cleaners				
Lowest	100	20	4	—
Median	300	60	10	1
Highest	700	200	50	10
Microwave Ovens				
Lowest	100	1	1	—
Median	200	40	10	2
Highest	300	200	30	20

Distance from Source	6 in.	1 ft.	2 ft.	4 ft.
Hair Dryers				
**Lowest	1	—	—	—
Median	300	1	—	—
Highest	700	70	10	1
Video Display Terminals (PCs with color monitors)				
Lowest	7	2	1	—
Median	14	5	2	—
Highest	20	6	3	—
Refrigerators				
Lowest	—	—	—	—
Median	2	2	1	—
Highest	40	20	10	10
Fluorescent Lights				
Lowest	20	—	—	—
Median	40	6	2	—
Highest	100	30	8	4

The dash (—) in the above table means that the magnetic field measurement at this distance from the operating appliance could not be distinguished from the background measurements taken before the appliance had been turned on.

** From EMF in Electric and Magnetic Fields Associated with the Use of Electric Power, National Institute of Environmental Health Sciences (June 2002).*

*** Refers to the lowest, median and highest readings of all appliances measured in each category.*

TYPICAL MAGNETIC FIELDS PRODUCED BY AMEREN TRANSMISSION LINES[1] (in milligauss, mG)

Type of Transmission Life	Maximum on Right-of-Way	Distance from the Center of the Right-of-Way 50 ft	75 ft	100 ft.	200 ft.	300 ft.	400 ft.
138/161 Kilovolts (kV)							
Single power line[2] on two wooden poles	45-160	15-55	5-30	5-15	1-5	0-2	0-1
Single power line[2] on one steel pole	25-105	10-35	5-20	3-11	1-3	0-2	0-1
Two power lines[2] on steel towers or steel poles	10-85	5-55	3-35	2-23	0-7	0-3	0-2
345 Kilovolts (kV)							
Single power line[3] on two wooden poles	72-240	40-130	25-75	15-50	4-13	2-6	1-4
Single power line[3] on one steel pole	60-160	30-90	20-55	12-35	3-10	2-5	1-3
Two power lines[3] on steel towers or steel poles	55-155	45-120	30-80	20-55	5-16	2-7	1-4
Combination 345kV and 138kV [4]	35-180	10-145	10-90	8-55	3-13	1-6	1-3

[1] The values shown in this table are typical for normal system peak operating conditions and do not reflect abnormal circumstances that rarely occur for a short period of time.

[2] A single 138/161 kV transmission line consists of three large wires and one or two small wires to protect the line from lightning damage.

[3] A single 345 kV transmission line consists of three sets of two large wires and one or two small wires to protect the line from lightning damage.

[4] Values in this table should not be added or subtracted to calculate different combinations of line configurations because the field from each wire affects the fields from other wires and are not necessarily cumulative.

Two organizations have developed voluntary occupational expo guidelines for EMF exposure — ICNIRP and ACGIH.[1]

ICNIRP GUIDELINES FOR EMF EXPOSURE

Exposure (60 Hz)	Magnetic field
Occupational	4.2 G (4,200 mG)
General Public	0.833 G (833 mG)

International Commission on Non-Ionizing Radiation Protection (ICNIRP) is an organization of 15,000 scientists from 40 nations who specialize in radiation protection. Source: ICNIRP, 1998.

ACGIH OCCUPATIONAL THRESHOLD LIMIT VALUES FOR 60-HZ EMF

	Magnetic field
Occupational exposure should not exceed	10 G (10,000 m
Exposure of workers with cardiac pacemakers should not exceed	1 G (1,000 mG

American Conference of Governmental Industrial Hygienists (ACGIH) is a professional organization that facilitates the exchange of technical, informati about worker health protection. It is not a government regulatory agency. Source ACGIH, 2001.

The above levels are not exceeded near Ameren transmission li

An important point to make is that a guideline limit is not a pr delineation between safety and hazard.[2]

VHY DOESN'T THE UTILITY COMPANY BURY LINES IF IELDS DROP OFF RAPIDLY?

urying lines does not eliminate exposure. While electric fields re easily shielded, magnetic fields are not. At street level, agnetic field strength from underground power lines depends n the number of cables, the spacing of the cables, the amount f current flowing through the lines and the distance you are om them.

eak magnetic field levels as high as 70 mG have been measured irectly below overhead distribution lines and as high as 40 mG bove underground lines. [1]

IEALTH EFFECTS

re people living near high voltage power at greater risk?

ven the exposure of people living in the vicinity of high voltage ower lines differs very little from the average exposure in he population. [2]

fave clusters of cancer or other adverse health effects een linked to EMF exposure?

here have been no proven instances of cancer clusters linked vith EMF exposure. [1]

What are the health effects on general health?

lased on a recent in-depth review of the scientific literature, he WHO concluded that current evidence does not confirm the xistence of any health consequences from exposure to low level lectromagnetic fields. [2]

s there an increase risk of cancer?

t is clear that if electromagnetic fields do have an effect n cancer, then any increase in risk will be extremely small. he results to date may contain inconsistencies, but no large ncreases in risk have been found for any cancer in children r adults. [1]

How do you interpret epidemiological studies?

Epidemiological studies alone typically cannot establish a clear cause and effect relationship, mainly because they detect only statistical associations between exposure and disease, which may or may not be caused by the exposure. The case for a cause-and-effect link is strengthened if there is a consistent and strong association between exposure and effect, a clear dose-response relationship, a credible biological explanation, support provided by relevant animal studies, and above all consistency between studies. These factors have generally been absent in studies involving electromagnetic fields and cancer. This is one of the strongest reasons why scientists have generally been reluctant to conclude that weak electromagnetic fields have health effects. [2]

Is there a link between EMF exposure and childhood leukemia?

Despite more than two decades of research to determine whether elevated EMF exposure, principally to magnetic fields, is related to an increase risk of childhood leukemia, there is still no definitive answer. [1]

Extremely low frequency (ELF) magnetic fields were classified as possibly carcinogenic to humans based on epidemiological studies of childhood leukemia. An example of a well-known agent classified in the same category is coffee, which may increase risk of kidney cancer, while at the same time be protective against bowel cancer. "Possibly carcinogenic to humans" is a classification used to denote an agent for which there is limited evidence of carcinogenicity in humans and less than sufficient evidence for carcinogenicity in experimental animals . . . While the classification of ELF magnetic fields as possibly carcinogenic to humans has been made by the International Agency for Research on Cancer, it remains possible that there are other explanations for the observed association between exposure to ELF magnetic fields and childhood leukemia. [2]

Does EMF affect people with pacemakers or other medical devices?

The occupational exposure guidelines developed by ACGIH state that workers with cardiac pacemakers should not be exposed to a 60-Hz magnetic field greater than 1,000 mG. If you are concerned about EMF exposure effects on pacemakers, implantable defibrillators or other implanted electronic medical devices you should consult your doctor. [1]

OTHER POSSIBLE EFFECTS

What are the effects of EMF on farm animals?

Studies performed to date have found little evidence of EMF effects on fauna at levels below ICNIRP's guideline levels. In particular, there were no adverse effects found on cattle grazing below power lines. [4]

What are the effects on crops and other plants?

Field studies of 50-60 Hz exposure to plants and crops have shown no effects at the levels normally found in the environment, nor even at field levels directly under power lines up to 765 kV. [4]

How does EMF affect GPS for farm equipment?

Right up close to a pylon, there might be some degradation in GPS performance, just as there can be some degradation close to buildings and trees. Other than that, there is no evidence of power lines interfering with GPS.

USEFUL ADDRESSES AND PHONE NUMBERS

Ameren's EMF Information Line
314.554.2402

U.S. Environmental Protection Agency Office of Radiation and Indoor Air Radiation Protection Division (MC 6608J)
1200 Pennsylvania Avenue, NW
Washington, D.C. 20460-0001
202.343.9677

National Institute of Environmental Health Sciences Office of Communications & Public Liaison
P.O. Box 12233, MD NH-10
Research Triangle Park, NC 27709-2233
919.541.3345

Regional Office for the Americas of the World Health Organization
525 Twenty-third Street, N.W.
Washington, D.C. 20037
202.974.3000

REFERENCES

[1] The National Institute of Environmental Health Sciences (NIEHS) — EMF Electric and Magnetic Fields Associated with the Use of Electric Power June 2002.
niehs.nih.gov/health/topics/agents/emf/.

[2,3,4] The World Health Organization (WHO) - What is EMF; Establishing a Dialogue on Risks from Electromagnetic Fields — 2002; Electromagnetic Fields and Public Health Effects of EMF on the Environment — February 2005.
who.int/peh-emf/about/WhatisEMF/en.

[1] U.S. Environmental Protection Agency — Electric and Magnetic Field (EMF) Radiation from Power Lines — April 2006
epa.gov/radtown/power-lines.html#resources

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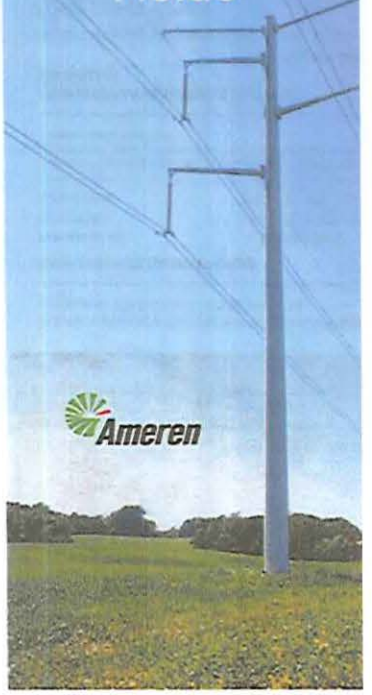
ANSWERING YOUR QUESTIONS ABOUT

Electromagneti Fields



Schedule DS-02

World Health Organization

2007 WHO Research Agenda for Extremely Low Frequency Fields

Introduction

In 1997, the WHO International EMF Project developed a Research Agenda in order to facilitate and coordinate research worldwide on the possible adverse health effects of electromagnetic fields (EMF). In subsequent years, this agenda has undergone periodic review and refinement.

In October 2005, WHO carried out a health risk assessment of extremely low frequency (ELF) electromagnetic fields up to 100 kHz, which is published as a WHO Environmental Health Criteria monograph[1]. Gaps in knowledge about possible health effects of ELF field exposure are identified in this monograph, and form the basis for research recommendations given in this Research Agenda.

Following a standard health risk assessment process, it was concluded that there were no substantive health issues related to ELF *electric* fields at levels generally encountered by members of the public. Thus this Research Agenda addresses further research concerning the possible acute and long term effects of exposure to ELF *magnetic* fields.

In general, acute effects are known to result from exposure to ELF magnetic field which induces electric fields and currents in the body. These can, at high experimentally induced field strengths (well above 100 μT), cause nerve and muscle stimulation and changes in nerve cell excitability in the central nervous system. Various research recommendations are made which address uncertainty in the threshold levels of these acute effects. With regard to long term effects, epidemiological studies have presented data indicating an association between ELF exposure above approximately 0.3-0.4 μT and an increased risk of childhood leukaemia. Despite several decades of work, however, compelling evidence from experimental studies to support a causal relationship is lacking. In addition, there is no widely accepted mechanism by which ELF fields at normal environmental and occupational exposure levels might affect the incidence of cancer or any other disease in the human population. Therefore, there is a need to support the epidemiological evidence by establishing an in vitro cell response or animal model response to ELF fields that is widely transferable between laboratories, if indeed such responses occur.

Most studies carried out have concerned the possible effects of exposure to power frequency fields. Further research on intermediate frequencies, usually taken as frequencies between 300 Hz and 100 kHz, is required given the present lack of data in this area. For these frequencies very little of the required knowledge base for a health risk assessment has been gathered and most existing studies have contributed inconsistent results, which need to be further substantiated. General requirements for constituting a sufficient intermediate frequencies

[1] World Health Organization (2007). Extremely Low Frequency Fields. Environmental Health Criteria 238. Geneva, World Health Organization (see: www.who.int/emf).

database for health risk assessment include exposure assessment, epidemiological and human laboratory studies, and animal and cellular (in vitro) studies.

Researchers are encouraged to use the present Research Agenda as a guide to studies that have high value for future health risk assessments. To maximize the effectiveness of large research programs, government and industry funding agencies are encouraged to address the WHO Research Agenda in a coordinated fashion. Such coordination will minimize unnecessary duplication of effort and will ensure the timeliest completion of the studies identified as being of high priority for health risk assessment.

This Research Agenda is ordered in successive sections according to the weight each research activity carries in human health risk assessment: epidemiology, laboratory studies in humans, animals, cellular systems, and mechanisms. It should be recognized that, while epidemiological and human laboratory studies directly address endpoints related to human health, cellular and animal studies are of value in assessing causality and biological plausibility.

Research topics relating to social sciences are included in this Research Agenda because of the need to better understand the perception of risk from the general public and to better communicate with the public on issues relating to ELF field exposure and health.

Each research activity is given a priority as follows:

- **High priority research needs:** Studies to fill important gaps in knowledge that are needed to significantly reduce the uncertainty in the current scientific information relevant to health risk assessment.
- **Other research needs:** Studies to better assist the understanding of the impacts of ELF field exposure on health and that would contribute useful information to health risk assessment.

Epidemiology

Epidemiological studies are of primary importance in health risk assessment. When planning epidemiological studies, investigators should consider international coordination and collaboration to maximize statistical power to estimate small risks and to evaluate the role of exposure patterns in different countries. Studies should focus not only on cancer but also on non-cancer endpoints (e.g. chronic diseases such as neurodegenerative diseases, sleep disturbances). Particular attention should be paid to the use of adequate estimates of exposure from all relevant sources.

High priority research needs:

- **Pooled analyses of existing childhood brain tumour studies**

  Rationale: Brain cancer studies have shown inconsistent results. This was also the case for childhood leukaemia studies and here, pooled analyses have been very informative. Therefore a pooled analysis of childhood brain cancer studies is recommended. Such pooled analysis can inexpensively provide greater and improved insight into existing data, including the possibility of a selection bias, and, if studies are sufficiently homogeneous, provide the best estimate of risk.

- **Update of existing pooled analyses of childhood leukaemia with new information**

  Rationale: Since the pooled analyses have been performed, several new epidemiological studies have been published. The pooled analyses should be updated with the results from these recent studies.

- **Further study of the risk of amyotrophic lateral sclerosis in 'electric' occupations**

Rationale: Several studies have observed an increased risk of amyotrophic lateral sclerosis in 'electric occupations'. It is considered important to investigate this association further in order to find whether ELF magnetic fields are involved in the causation of this rare neurodegenerative disease. This research requires studies in which sufficient information is collected on ELF magnetic field exposure, electric shock exposure as well as exposure to other potential confounders.

Other research needs:

- **Update of existing pooled and meta-analyses of adult leukaemia and brain tumour studies and cohorts of occupationally exposed individuals**

  Rationale: For adult leukaemia and brain cancer, it is recommended that existing large cohorts of occupationally exposed individuals be updated. Occupational studies and pooled and meta-analyses for leukemia and brain cancer have been inconsistent and inconclusive. However, new data have subsequently been published and should be used to update these analyses.

- **Further study of the possible link between miscarriage and ELF magnetic field exposure**

  Rationale: There is some evidence that the risk of miscarriage may be affected by ELF magnetic fields exposure. Taking into account the potentially high public health impact of such an association, further epidemiological research into this hypothesis is recommended.

- **Further study of the risk of Alzheimer's disease in relation to ELF magnetic field exposure**

  Rationale: For Alzheimer's disease, it remains a question whether ELF magnetic fields constitute a risk factor. The data currently available are not sufficient and this association should be further investigated. Of particular importance is the use of morbidity rather than mortality data.

Human volunteer studies

Human laboratory studies allow ELF field effects to be studied on humans with control of experimental parameters, but are confined to investigations of acute, transient effects. For all volunteer studies, it is mandatory that research on human subjects is conducted in full accord with ethical principles, including the provisions of the Helsinki Declaration[2].

High priority research needs:

None.

Other research needs:

- **Cognitive, sleep and EEG studies in volunteers, including children and occupationally exposed subjects, using a wide range of ELF frequencies at high field strengths**

  Rationale: Studies of adult volunteers and animals suggest that acute cognitive effects may occur with short-term exposures to intense fields. The characterization of such effects is very important for the development of exposure guidance, but there is a lack of specific data concerning field-dependent effects, particularly in children. It is recommended that

[2] World Medical Association (2004). Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. (http://www.wma.net/e/ethicsunit/helsinki.htm, accessed 12-2-2007).

laboratory-based studies of cognition and changes in electroencephalograms (EEG) in people exposed to ELF magnetic fields be performed, including children and occupationally exposed adults.

Animal studies

Animal studies are used when it is unethical or impractical to perform studies on humans and have the advantage that experimental conditions can be rigorously controlled, even for chronic exposures.

High priority research needs:

- **Development of transgenic mouse models of childhood leukaemia for use in EMF studies**

  Rationale: Resolving the conflict between epidemiological results and experimental and mechanistic results for childhood leukaemia is the highest priority. It is recommended that epidemiologists and experimental scientists collaborate on this. To this end, the development of transgenic mouse models for childhood leukaemia should be undertaken in order to provide appropriate experimental animal models relevant to the epidemiological data showing an association of EMF exposure with childhood leukaemia.

- **Evaluation of co-carcinogenic effects of ELF fields**

  Rationale: For animal studies the weight of evidence is that there are no significant carcinogenic effects of ELF magnetic fields alone. Therefore high priority should be given to studies in which ELF fields are rigorously evaluated as a co-carcinogen.

Other research needs:

- **Studies of pre- and post-natal EMF exposure up to 100 kHz on subsequent cognitive function in animals**

  Rationale: Behavioural studies with immature animals provide a useful indicator of possible cognitive effects in children. Possible effects of pre- and post-natal exposure on the development of the nervous system and cognitive function should be studied. These studies could be usefully supplemented by investigations on the effects of exposure to ELF magnetic fields and induced electric fields on nerve cell growth using brain slices or cultured neurons.

- **Further investigation of opioid and cholinergic responses in animals**

  Rationale: There is a need to further investigate potential health consequences suggested by a considerable body of experimental data showing opioid and cholinergic responses in animals. Studies examining the modulation of opioid and cholinergic responses in animals should be extended and the exposure parameters and the mechanistic biological basis for these behavioural responses should be defined.

- **Studies of ELF magnetic field exposure on immune and haemopoietic systems development in juvenile animals**

  Rationale: While changes observed in immune and haematological parameters observed in adults exposed to ELF showed inconsistency, there are essentially no research data available for children. Therefore, the recommendation is to conduct studies on the effects of ELF magnetic exposure on the development of the immune and haemopoietic systems in juvenile animals.

Cellular studies

Studies in tissues, living cells and cell-free systems play a supporting role in health risk assessments and are usually used to investigate mechanisms of interaction with EMFs. However, they are not generally taken alone as evidence of effects *in vivo* (in animals or people).

High priority research needs:

- **Evaluation of co-carcinogenic effects using in vitro studies**

  Rationale: The weight of evidence supports the view that there are no significant carcinogenic effects of ELF magnetic fields alone. Therefore high priority should be given to studies in which ELF fields are rigorously evaluated as a co-carcinogen.

Other research needs:

- **Replication of in vitro genotoxic studies**

  Rationale: With regard to other in vitro studies, experiments reporting the genotoxic effects of intermittent ELF magnetic field exposure should be replicated.

Biophysical mechanisms

If ELF electric or magnetic fields, at very low levels, can adversely affect health, then a biophysical interaction must occur through some mechanism whereby biological changes that are detrimental to health are produced in an exposed person. The experimental evidence concerning particular biological effects would be strengthened by the identification of plausible interaction mechanisms that can lead to such effects.

There are three main areas where there are obvious limits to current understanding of mechanisms: signal-to-noise ratios in multi-cell systems such as neuronal networks, magnetic particles in the body and the radical pair mechanism.

High priority research needs:

- **Determination of threshold responses to ELF-induced internal electric fields on multi-cell systems, such as neural networks, using theoretical and in vitro approaches**

  Rationale: The extent to which multi-cell mechanisms operate in the body, especially in the brain, to improve signal-to-noise ratios should be further investigated in order to develop a theoretical framework for quantifying this or for determining any limits on it. In addition, further investigation of the threshold and frequency response of the neuronal networks in the hippocampus and other parts of the brain should be examined using in vitro approaches.

Other research needs:

- **Further study of radical pair mechanisms in immune cells that generate reactive oxygen species as part of their phenotypic function**

  Rationale: The radical pair mechanism is one of the more plausible low-level interaction mechanisms, but it is yet to be shown that it is able to mediate significant effects in cell metabolism. It is particularly important to understand the lower limit of exposure at which it acts, so as to judge whether this could or could not be a relevant mechanism for carcinogenesis. It is recommended that cells of the immune system that generate reactive oxygen species as part of their immune response be used as cellular models for

investigating the potential of the radical pair mechanism, given recent studies in which reactive oxygen species were increased in immune cells exposed to ELF.

- **Further theoretical and experimental study of the possible role of magnetite in ELF magnetic field sensitivity**

  Rationale: Although the presence of magnetic particles (magnetite crystals) in the human brain does not, on present evidence, appear to confer sensitivity to environmental ELF magnetic fields, further theoretical and experimental approaches should explore whether such sensitivity could exist under certain conditions. Moreover, any modification that the presence of magnetite might have on the radical pair mechanism discussed above should be pursued.

Dosimetry

Expert dosimetric support for experimental studies of all types is critical to their proper design and interpretation. Computational dosimetry provides the link between an external magnetic field and the internal electric fields and induced currents in living tissues within the field. Such theoretical techniques allow the fields to be characterized in specific tissues and organs.

High priority research needs:

None.

Other research needs:

- **Further computational dosimetry relating external electric and magnetic fields to internal electric fields, particularly concerning exposure to combined electric and magnetic fields in different orientations**

  Rationale: In the past, most laboratory research was based on induced electric currents in the body as a basic metric and thus dosimetry was focused on this quantity. Only recently work started to explore the relationship between external exposure and induced electric fields. For a better understanding of biological effects and for the development of exposure guidelines, more data on internal electric fields for different exposure conditions are needed. Computation should be made of internal electric fields due to the combined influence of external electric and magnetic fields in different configurations: vectorial addition of out-of phase and spatially varying contributions of electric and magnetic fields is necessary to assess basic restriction compliance issues.

- **Calculation of induced electric fields and currents in pregnant women and in the foetus**

  Rationale: Very little computation has been carried out on advanced models of the pregnant human and the foetus with appropriate anatomical modelling. It is important to assess possible enhanced induction of electric fields during foetal life in relation to the childhood leukaemia issue. Both maternal occupational and residential exposures are relevant here.

- **Further refinement of microdosimetric models taking into account cellular architecture of neural networks and other complex suborgan systems**

  Rationale: There is a need to further refine microdosimetric models to take into account the cellular architecture of neural networks and other complex sub-organ systems identified as being sensitive to induced electric field effects compared to other tissues. This modelling needs to take into account influences in cell membrane electrical potentials and on the release of neurotransmitters.

Sources, Measurements and Exposures

The identification of sources of ELF electric and magnetic fields, the measurement of fields they emit and the exposure of members of the public and workers to such fields is a primary step in the assessment of the possible health consequences of such exposure.

High priority research needs:

- **Identification of gaps in knowledge about occupational ELF exposure, such as in MRI**

  Rationale: It is suspected that in some cases of occupational exposure the present ELF guideline limits are exceeded. More information is needed on exposures (including non-power frequencies) related to work on, for example, live-line maintenance, work within or near the bore of MRI magnets (and hence to gradient switching ELF fields) and work on transportation systems.

Other research needs:

- **Further characterization of homes with high ELF magnetic field exposure in different countries**

  Rationale: Further characterization of homes with high ELF exposure in different countries to identify relative contributions of internal and external sources, the influence of wiring/grounding practices and other characteristics of the home could give insights into identifying a relevant exposure metric for epidemiological assessment. An important component of this is a better understanding of foetal and childhood exposure to EMFs, especially from residential exposure to under-floor electrical heating and from transformers in apartment buildings.

- **Assessment of the ability of residential wiring outside the USA to induce contact currents in children**

  Rationale: Exposure to contact current has been proposed as a possible explanation for the association of magnetic fields with childhood leukaemia. Research is needed in countries other than the USA to assess the capability of residential electrical grounding and plumbing practices to give rise to contact currents in the home. Such studies would have priority in countries with positive associations between ELF magnetic field exposure and childhood leukaemia.

Social Issues

The benefits of the use of electric power, and the possible costs to society of any adverse effects on health that might result from exposure to the electromagnetic fields that electrical equipment generates, are important socio-economic issues. In addition, the development of adequate health protection policies for communities and the communication of appropriate information concerning risk also form an important part of the way in which developing technologies are integrated into society.

High priority research needs:

None.

Other research needs:

- **Further research on risk perception and communication focused on ELF magnetic fields**

  Rationale: Psychological and sociological factors influencing risk perception in general have been widely investigated. However, limited research has been carried out to analyse the relative importance of these factors in the case of ELF magnetic fields, or to identify other factors that are specific to the risk perception of these fields. Recent studies have suggested that precautionary measures, conveying implicit risk messages, can modify risk perception by either increasing or reducing concerns. Deeper investigations in this area are therefore warranted.

- **Development of cost-benefit/effectiveness analysis for mitigation of ELF magnetic fields**

  Rationale: The use of cost-benefit and cost-effectiveness analysis for evaluating whether a policy option is beneficial to society has been researched in many areas of public policy. The development of a framework that will identify which parameters are necessary in order to perform this analysis for ELF magnetic fields is needed. Due to uncertainties in the evaluation, quantifiable and unquantifiable parameters will need to be incorporated.

- **Research on the development and implementation of health protection policies in areas of scientific uncertainty**

  Rationale: When there are uncertainties about the potential health risk an agent imposes on society, precautionary measures may be warranted in order to ensure appropriate protection of the public and workers. Only limited research has been performed on this issue for ELF magnetic fields, and therefore more research would be useful to policy makers.

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

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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

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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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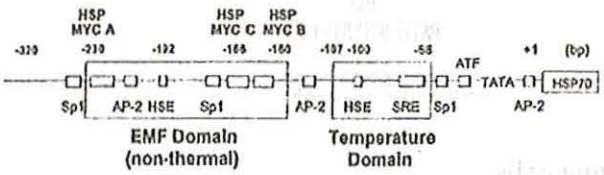

Fig. 1. Diagram of the HSP70 promoter showing the two different DNA sequences that have been identified as activated by EMF (non-thermal) and by thermal stimuli, respectively. The EMF domain contains three nCTCTn consensus sequences (electromagnetic response elements; EMRE), and differs from the consensus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

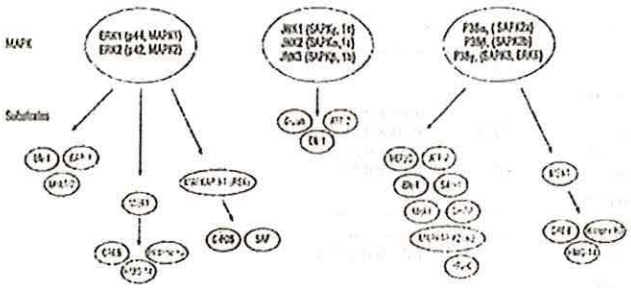

Fig. 2. The four mitogen activated protein kinase (MAPK) signaling cascades identified to date are: extracellular signal regulated kinase 1/2 (ERK), c-Jun-terminal kinase (JNK), p38MAPK and stress activated protein kinase (SAPK). Elements of the three MAPkinase pathways that have been identified as activated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

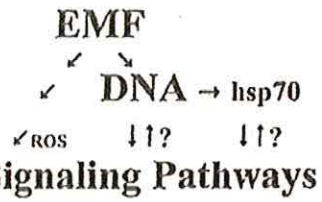

Fig. 3. The signaling pathways and the stress response are activated by EMF. The activation mechanisms discussed in the text are indicated by arrows. In the stress response, DNA activation leads to hsp synthesis and may be due to direct EMF interaction with DNA. The signaling pathways are activated by 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 80 mG 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.

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 = confidance 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

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 (⩾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 ⩾0.4 μT 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 ⩾0.4 μT 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 μT (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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Review Article *J. Cell. Mol. Med. Vol XX, No X, 2013 pp. 1-9*

Guest Editor:

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

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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 Wallec-zek [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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