Health Sciences Practice

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Update of Research on Extremely Low Frequency Electric and Magnetic Fields and Health

August 1, 2012 – July 31, 2014

Greenwich Substation and Line Project

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Submitted to:

Connecticut Siting Council
Ten Franklin Square
New Britain, CT 06051

Prepared by:

Exponent
17000 Science Drive, Suite 200
Bowie, MD 20715

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Acronyms and Abbreviations

AC	Alternating current
ALL	Acute lymphoblastic leukemia
ALS	Amyotrophic lateral sclerosis
AMI	Acute myocardial infarction
AML	Acute myeloid leukemia
BMP	Best Management Practices
CAT	Catalase
CI	Confidence interval
CSC	Connecticut Siting Council
CVD	Cardiovascular disease
ELF	Extremely low frequency
EMF	Electric and magnetic fields (or electromagnetic fields)
EPA	Environmental Protection Agency
G	Gauss
GSH-Px	Glutathione peroxidase
GHz	GigaHertz
HCN	Health Council of the Netherlands
HR	Hazard ratio
HRV	Heart rate variability
Hz	Hertz
IARC	International Agency for Research on Cancer
ICNIRP	International Committee on Non-Ionizing Radiation Protection
IFN-γ	Interferon-γ
IL	Interleukin
ISCO	International Standard Classification of Occupations
JEM	Job exposure matrix
kV	Kilovolt
kV/m	Kilovolts per meter
MDA	Malondialdehyde

mG	Milligauss
MPE	Maximum permissible exposure
NIEHS	National Institute for Environmental and Health Sciences
NO	Nitric Oxide
NRPB	National Radiation Protection Board of Great Britain
OR	Odds ratio
OSI	Oxidative stress index
ROW	Right of way
RR	Relative Risk
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SOD	Superoxide dismutase
TAC	Total anti-oxidant capacity
TOS	Total oxidant status
TWA	Time weighted average
V/m	Volts per meter
WHO	World Health Organization

Limitations

At the request of Northeast Utilities, Exponent prepared this summary report on the status of research related to extremely low-frequency electric- and magnetic-field exposure and health. The findings presented herein are made to a reasonable degree of scientific certainty. Exponent reserves the right to supplement this report and to expand or modify opinions based on review of additional material as it becomes available, through any additional work, or review of additional work performed by others.

The scope of services performed during this investigation may not adequately address the needs of other users of this report, and any re-use of this report or its findings, conclusions, or recommendations presented herein are at the sole risk of the user. The opinions and comments formulated during this assessment are based on observations and information available at the time of the investigation. No guarantee or warranty as to future life or performance of any reviewed condition is expressed or implied.

The following Executive Summary provides only an outline of the material discussed in this report. Exponent's technical evaluations, analyses, conclusions, and recommendations are included in the main body of this report, which at all times is the controlling document.[1]

[1] The report was prepared on September 5, 2014; however, in March 2015, the European Commission's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) released its final "Opinion on Potential health effects of exposure to electromagnetic fields (EMF)," thus, the report has been updated to reference this document.

1 Executive Summary

This report was prepared to address the topic of exposure to extremely low frequency (ELF) electric and magnetic fields (EMF) and health for the Connecticut Siting Council (CSC) at the request of Northeast Utilities as part of its Application for the Greenwich Substation and Line Project.

ELF EMF are invisible fields surrounding all objects that generate, use, or transmit electricity. There are also natural sources of ELF EMF, including the electric fields associated with the normal functioning of our circulatory and nervous systems. People living in developed countries are constantly exposed to ELF EMF in their environments, because electricity is an essential infrastructure of technologically-advanced societies. Sources of man-made ELF EMF include appliances, wiring, and motors, as well as distribution and transmission lines. Section 3 of this report provides information on the nature and sources of ELF EMF, and typical exposure levels.

Research on EMF and health began with the goal of finding therapeutic applications and understanding biological electricity, i.e., the role of electrical potentials across cell membranes and current flows between cells in our bodies. Over the past 30 years, researchers have examined whether EMF from man-made sources can cause short- or long-term health effects in humans using a variety of study designs and techniques. Research on ELF EMF and long-term human health effects was prompted by an epidemiology study conducted in 1979 of children in Denver, Colorado, which reported that children with cancer were more likely to live near distribution and transmission lines that appeared to be capable of producing higher magnetic fields. The results of that study prompted further research on childhood leukemia and other cancers. Childhood leukemia has remained the focus of ELF EMF and health research, although many other diseases have been studied, including other cancers in children and adults, neurodegenerative diseases, reproductive and developmental effects, cardiovascular diseases, and psychological and behavioral effects such as depression or suicide.

Guidance on the possible health risks of all types of exposures comes from health risk assessments, i.e., systematic weight-of-evidence evaluations of the cumulative literature, on a particular topic conducted by expert panels organized by national and international scientific organizations.

The World Health Organization (WHO) published the most recent, comprehensive health risk assessment of EMF in the ELF range in 2007 that critically reviewed the cumulative epidemiologic and laboratory research through 2005, taking into account the strength and quality of the individual research studies. The public and policy makers should look to the conclusions of reviews such as this, because they are conducted by scientists representing the various disciplines required to understand the topic at hand using validated scientific standards and systematic methods. This WHO report was one of the most recent health agency reviews that informed the CSC when it updated its EMF Best Management Practices in 2007. In its revised EMF Best Management Practices, issued on February 20, 2014, the CSC further considered the scientific literature up to 2012 based on systematic reviews provided by two documents submitted with previous applications to CSC.[2,3] In a health risk assessment of any exposure, it is essential to consider the type and strength of research studies available for evaluation. Human health studies vary in methodological rigor and, therefore, in their capacity to extrapolate findings to the population at large. Furthermore, all studies in three areas of research—epidemiologic, *in vivo* (experimental whole animal), and *in vitro* (experimental in cells and tissues)—must be evaluated to understand possible health risks.

Section 4 of this report provides a summary of the methods used to conduct a health risk assessment. Section 5 provides a summary of the WHO's conclusions with regard to various health outcomes (childhood leukemia and brain cancer, adult breast cancer, brain cancer, leukemia/lymphoma; reproductive and developmental effects; neurodegenerative disease; and cardiovascular disease). Finally, this report contains a systematic literature review and a critical evaluation of all epidemiology studies in these areas of research and *in vivo* studies of cancer published between August 1, 2012 and July 31, 2014 (Section 6).[4]

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2 Docket No. 424. "Current Status of Research on Extremely Low Frequency Electric and Magnetic Fields and Health: Interstate Reliability Project, June 10, 2011"

3 Docket No. 435. "Update of Research on Extremely Low Frequency Electric and Magnetic Fields and Health May 1, 2011 – July 31, 2012 Stamford Reliability Cable Project, August 30, 2012"

4 In March 2015, a Scientific Committee commissioned by the European Union updated its previous review on EMF that included reviews of ELF EMF fields. The conclusions of the SCENIHR review are consistent with those of the NIEHS and WHO reviews mentioned above. The SCENIHR review did not conclude that the available scientific evidence confirms a causal link between any adverse health effects (including both cancer and non-cancer health outcomes) and EMF exposure.

2 Introduction

In response to public concern regarding ELF EMF and health, the CSC adopted "EMF Best Management Practices for the Construction of Electric Transmission Lines in Connecticut" (BMP) on December 14, 2007. This BMP was updated in February, 2014. The BMP policy is founded on the recognition of consistent conclusions by "a wide range of public health consensus groups," as well as their own commissioned weight-of-evidence review (CSC BMP, 2014, p. 4). The CSC summarized the current scientific consensus by noting the conclusions of these public health consensus groups, including the most comprehensive review by the WHO in 2007, and earlier reviews published by the National Institute for Environmental and Health Sciences (NIEHS) in 1999, the International Agency for Research on Cancer (IARC) in 2002, the Australian Radiation Protection and Nuclear Safety Agency in 2003, the National Radiological Protection Board of Great Britain (NRPB) in 2004, and the Health Council of the Netherlands (HCN) in 2005.

The WHO report provided the following overall conclusions:

> New human, animal, and in vitro studies published since the 2002 IARC Monograph, 2002 [sic] do not change the overall classification of ELF as a possible human carcinogen WHO, 2007, World Health Organization (WHO) (2007p. 347).
>
> Acute biological effects [i.e., short-term, transient health effects such as a small shock] have been established for exposure to ELF electric and magnetic fields in the frequency range up to 100 kHz that may have adverse consequences on health. Therefore, exposure limits are needed. International guidelines exist that have addressed this issue. Compliance with these guidelines provides adequate protection. Consistent epidemiological evidence suggests that chronic low-intensity ELF magnetic field exposure is associated with an increased risk of childhood leukaemia. However, the evidence for a causal relationship is limited, therefore exposure limits based upon epidemiological evidence are not recommended, but some precautionary measures are warranted (WHO, 2007, p. 355).

The CSC summarized the current scientific consensus as expressed in the above-mentioned reviews as follows: there is limited evidence from epidemiology studies of a statistical association between estimated, average exposures greater than 3-4 milligauss (mG) and childhood leukemia; the cumulative research, however, does not indicate that magnetic fields are a cause of childhood leukemia, since animal and other experimental studies do not suggest that magnetic fields are carcinogenic and the epidemiology studies are of limited quality. The CSC also noted the WHO's recent conclusion with respect to other diseases: "the scientific evidence supporting an association between ELF magnetic field exposure and all of these health effects is much weaker than for childhood leukemia" (CSC BMP, 2014, p. 2).

Based on this scientific consensus, the CSC concluded that proportional precautionary measures for the siting of new transmission lines in the state of Connecticut should include "the use of effective no-cost and low-cost technologies and management techniques on a project-specific basis to reduce MF [magnetic field] exposure to the public while allowing for the development of efficient and cost-effective electrical transmission projects" (CSC BMP, 2014, p. 4).

The BMP also stated that the CSC will "consider and review evidence of any new developments in scientific research addressing MF [magnetic fields] and public health effects or changes in scientific consensus group positions regarding MF" (CSC BMP, 2014, p. 5).

While the initial CSC BMP policies were based largely on the conclusions of the WHO report from 2007, the current BMP, revised in 2014, considers the scientific literature up to 2012 based on systematic reviews provided by two documents submitted as part of previous applications to the CSC.[5,6]

This Exponent report contains a systematic review and a critical evaluation of the literature, including all relevant epidemiology and *in vivo* studies published between August 1, 2012 and July 31, 2014 that were identified in our literature searches. This new report, along with the two previous summaries, provides an analysis of the status of research on ELF EMF inclusive of 2006 through mid-2014.

The studies evaluated in the current and the previous two reports do not provide sufficient evidence to alter the basic conclusion of the WHO: the research does not support the conclusion that ELF EMF at the levels we encounter in our everyday environment are a cause of cancer or any other disease.

There are no national guidelines or standards in the United States to regulate ELF EMF. The WHO recommends adherence to the International Commission on Non-Ionizing Radiation Protection's (ICNIRP) standards or those developed by the IEEE's International Committee for Electromagnetic Safety for the prevention of acute health effects at high exposure levels (ICES, 2002; ICNIRP, 2010). In light of the epidemiologic data on childhood leukemia, these scientific organizations are still in agreement that only no-cost or low-cost interventions to reduce ELF EMF exposure are appropriate.

This policy approach is consistent with the recommendation of CSC for the use of effective no-cost and low-cost technologies to reduce the public's magnetic-field exposure. While the large body of existing research does not indicate any harm associated with ELF EMF, research on this topic will continue to reduce remaining uncertainty.

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5 Docket No. 424. "Current Status of Research on Extremely Low Frequency Electric and Magnetic Fields and Health: Interstate Reliability Project, June 10, 2011"

6 Docket No. 435. "Update of Research on Extremely Low Frequency Electric and Magnetic Fields and Health May 1, 2011 – July 31, 2012 Stamford Reliability Cable Project, August 30, 2012"

3 Extremely Low Frequency Electric and Magnetic Fields: Nature, Sources, Exposure, and Known Effects

Nature of ELF EMF

Electricity is transmitted as current from generating sources to high-voltage transmission lines, substations, distribution lines, and then finally to our homes and workplaces for consumption. The vast majority of electricity is transmitted as alternating current (AC), which changes direction 60 times per second (i.e., a frequency of 60 Hertz [Hz]) in North America. EMF from these AC sources is often referred to as power-frequency or extremely low frequency (ELF) EMF.

Everything that is connected to our electrical system (i.e., power lines, appliances, and wiring) produces ELF EMF (Figure 1). Electric fields and magnetic fields are properties of the space near these electrical sources. Forces are experienced by objects capable of interacting with these fields; electric charges are subject to a force in an electric field, and moving charges experience a force in a magnetic field.

- **Electric fields** are the result of voltages applied to electrical conductors and equipment. The electric field is expressed in measurement units of volts per meter (V/m) or kilovolts per meter (kV/m), where 1 kV/m = 1,000 V/m. Conducting objects including fences, buildings, and our own skin and muscle easily block electric fields. Therefore, certain appliances within homes and workplaces are the major source of electric fields indoors, while power lines are the major source of electric fields outdoors.

- **Magnetic fields** are produced by the flow of electric currents. Unlike electric fields, however, most materials (including the earth) do not readily block magnetic fields. The strength of a magnetic field is expressed as magnetic flux density in units of gauss (G) or mG, where 1 G = 1,000 mG.[7] The strength of the magnetic field at any point depends on characteristics of the source, including (in the case of power lines) the arrangement of conductors, the amount of current flow, and distance from the conductors.

Sources and exposure

The intensity of both electric fields and magnetic fields diminishes with increasing distance from the source. For example, higher EMF levels are measured close to the conductors of distribution and transmission lines and decrease rapidly with increasing distance from the conductors. Transmission line EMF generally decreases with distance from the conductors in proportion to the square of the distance, creating a bell-shaped curve of field strength.

Since electricity is such an integral part of our infrastructure (e.g., transportation systems, homes, and businesses), people living in modern communities literally are surrounded by these fields

[7] Scientists also refer to magnetic flux density at these levels in units of microtesla (µT). Magnetic flux density in mG units can be converted to µT by dividing by 10, i.e., 1 mG = 0.1 µT.

(Figure 1). While EMF levels decrease with distance from the source, any home, school, or office tends to have a "background" EMF level as a result of the combined effect of the numerous EMF sources.

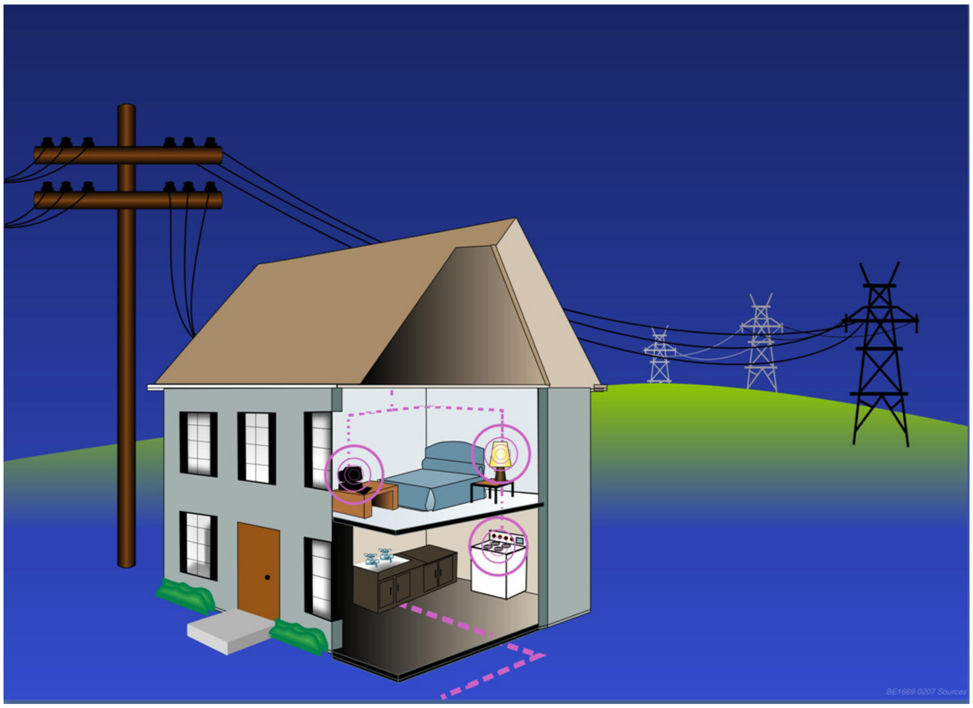


Figure 1. Common sources of ELF EMF in the home (appliances, wiring, currents running on water pipes, and nearby distribution and transmission lines)

Figure 2 outlines typical EMF levels measured in residential settings and occupational environments (all of which contribute to a person's background EMF level) compared to typical EMF levels measured at a typical transmission line's ROW. The fields from underground transmission lines are not included in this figure, as they are a rare source of EMF exposure. The magnetic field over buried conductors can be as high, or even higher, than an overhead line but the magnetic field will diminish more quickly with distance. No electric field will be produced above ground by underground cables. In general, the background magnetic-field level as estimated from the average of measurements throughout a house away from appliances may range up to 5 mG, while levels can be hundreds of mG in close proximity to appliances. Background levels of electric fields range from 10-20 V/m, while appliances produce levels up to several tens of V/m (WHO, 1984).

Experiments have yet to show which aspect of ELF EMF exposure, if any, may be relevant to biological systems. The current standard of EMF exposure for health research is long-term, average personal exposure, which is the average of all exposures to the varied electrical sources encountered in the many places we spend our days and nights. As expected, this exposure is different for every person and is difficult to approximate. Exposure assessment is a source of uncertainty in the epidemiology studies of ELF EMF and health (WHO, 2007). Some basic conclusions drawn from surveys of the general public's exposure to magnetic fields are:

- *Residential sources of magnetic-field exposure:*
  - Residential magnetic-field levels are caused by currents carried by nearby transmission and distribution systems, pipes or other conductive paths, and electrical appliances (Zaffanella, 1993).
  - The highest magnetic-field levels are typically found directly next to appliances (Zaffanella, 1993). NIEHS (2002) identified field levels at various distances from a number of common appliances in the home—the highest reported measured values at 6-inches from selected appliances were as follow: can opener, 1,500 mG; dishwasher; 200 mG; electric range, 200 mG; and washing machine, 100 mG; to name a few.
  - Several parameters affect personal magnetic-field exposures at home: residence type, residence size, type of water line, and proximity to overhead power lines. Persons living in small homes, apartments, homes with metallic piping, and homes close to three-phase electric power distribution and transmission lines tended to have higher at-home magnetic-field levels (Zaffanella and Kalton, 1998).
- *Personal magnetic-field exposure:*
  - A survey of 1,000 randomly selected persons in the United States who wore a magnetic field meter that recorded the magnetic field twice each second reports that the average of all measurements taken over 24-hours, i.e., their time-weighted average (TWA) exposure, is less than 2 mG for the vast majority of persons (Zaffanella and Kalton, 1998).[8]
  - In general, personal magnetic-field exposure is greatest at work and when traveling (Zaffanella and Kalton, 1998).
- *Workplace magnetic-field exposure*
  - Some occupations (e.g., electric utility workers, sewing machine operators, telecommunication workers, industrial welders) have higher exposures due to work near equipment with high ELF EMF levels (NIEHS, 2002).
- *Power-line magnetic-field exposure*
  - The EMF levels associated with power lines vary substantially depending on their configuration and current load, among other factors. At a distance of 300 feet and during average electricity demand, however, the magnetic field levels from many

[8] TWA is the average exposure over a given specified time period (i.e., an 8-hour workday or a 24-hour day) of a person's exposure to a chemical or physical agent. The average is determined by sampling the exposure of interest throughout the time period.

transmission lines are often similar to the background levels found in most homes (Figure 2).

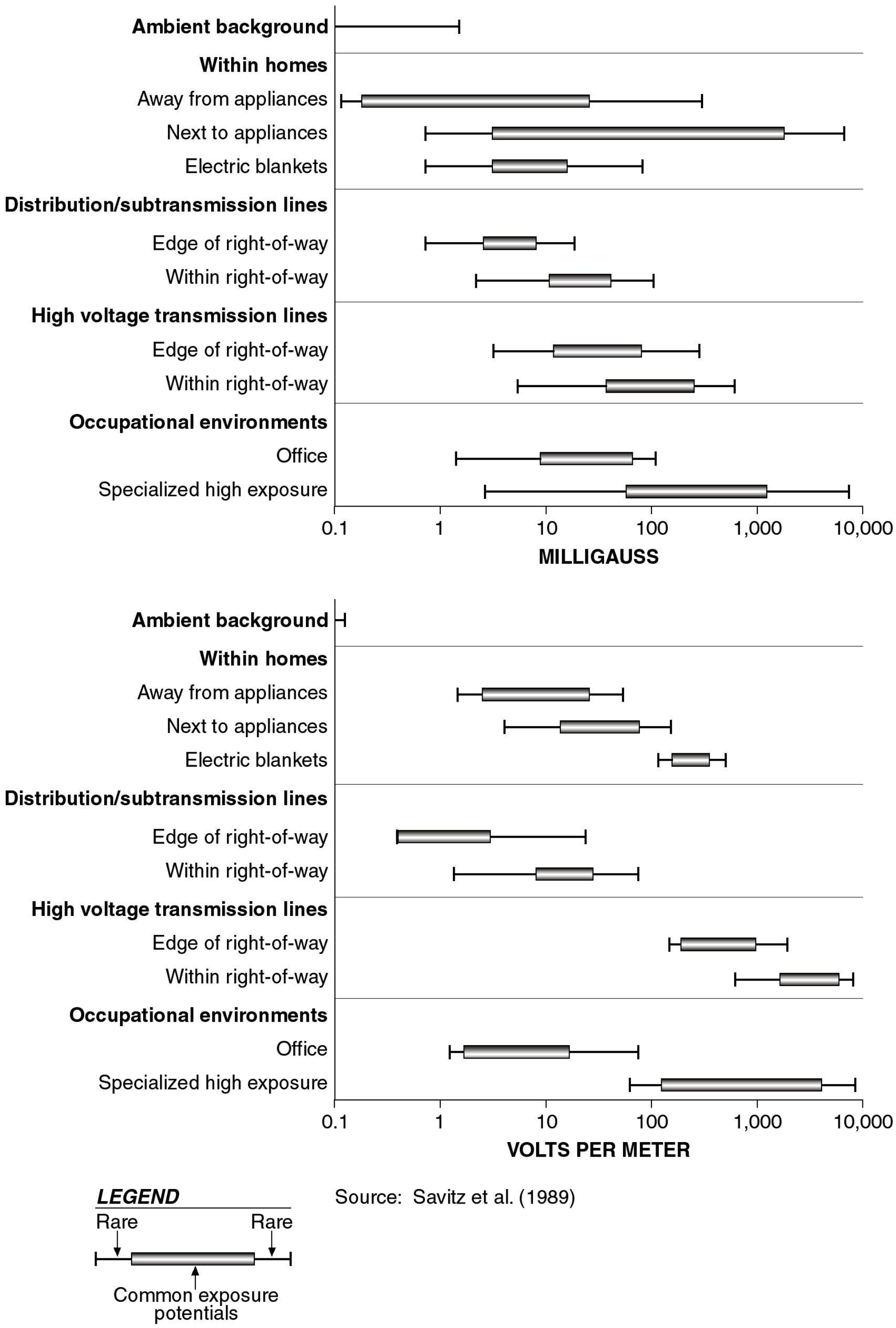


Figure 2. Magnetic and electric field levels in the environment

Known effects

There is a greater opportunity for long-term exposure to magnetic fields since electric fields are effectively blocked by common conductive objects. For this reason, among others, research on long-term health effects has focused on magnetic fields rather than electric fields.

Like virtually any exposure, adverse effects can be expected from exposure to very high levels of ELF EMF. If the current density or electric field induced by an extremely strong magnetic field exceeds a certain threshold, excitation of muscles and nerves is possible. Also, strong electric fields can induce charges on the surface of the body or ungrounded objects that can lead to small shocks (i.e., micro shocks) when discharged. These effects have no long-term damage or health consequences. Limits for the general public and workplace have been set to prevent these effects, but there are no real-life situations where these levels are exceeded on a regular basis.

Two international scientific organizations, ICNIRP and the International Committee on Electromagnetic Safety (ICES), have published guidelines for limiting public exposure to ELF EMF to protect against these acute effects (ICES, 2002; ICNIRP, 1998, 2010). These guidelines were developed following weight-of-evidence reviews of the literature, including epidemiologic and experimental evidence related to both short-term and long-term exposure. Both reviews concluded that the stimulation of nerves and the central nervous system could occur at very high exposure levels immediately upon exposure, but that the research did not suggest any long-term health effects.

The ICNIRP guideline states that exposure to magnetic fields should be below 2,000 mG for the general public and 4,200 mG for workers "[to] provide protection against all established adverse health effects" (ICNIRP, 2010). The ICES recommends a maximum permissible magnetic-field exposure of 9,040 mG for the general public (ICES, 2002). For reference, in a survey by Zaffanella and Kalton (1998), only about 1.6% of the general public experienced exposure to magnetic fields of at least 1,000 mG during a 24-hour period.

The ICNIRP's screening value for exposure to 60-Hz electric fields for the general public is 4.2 kV/m and the ICES screening value is 5 kV/m. Both organizations allow higher exposures if it can be demonstrated that exposures do not produce electric fields within tissues that exceed basic restrictions on internal electric fields.

Table 1. Reference levels for whole body exposure to 60-Hz fields: general public

Organization recommending limit	Magnetic fields	Electric fields
ICNIRP restriction level	2,000 mG	4.2 kV/m
ICES maximum permissible exposure (MPE)	9,040 mG	5 kV/m 10 kV/m[a]

[a] This is an exception within transmission line ROWs because people do not spend a substantial amount of time in ROWs and very specific conditions are needed before a response is likely to occur (i.e., a person must be well insulated from ground and must contact a grounded conductor) (ICES, 2002, p. 27).

The recent literature includes a number of studies of workers with the potential for high field exposures that characterize occupational exposure and evaluate compliance with standards. They include a study of spot measurements of EMF during work tasks at 110-kV switching and transforming stations in Finland to evaluate compliance with ICNIRP reference levels (Korpinen et al., 2011a) and a study of occupational electric field exposure at the same 110-kV switching station that evaluated compliance with the European Union's Directive 2004/40/EC (Korpinen et al., 2012); 3-hour TWA magnetic-field measurements of dentists and spot measurements near dental equipment in Taiwan (Huang et al., 2011); spot measurements and personal monitoring of magnetic fields in hospital personnel in Spain (Ubeda et al., 2011); spot measurements and personal monitoring of magnetic fields in railway workers in Italy (Contessa et al., 2010); and a study of electric fields, current densities, and contact currents at a 400-kV substation in Finland (Korpinen et al., 2011b). Two recent publications reported measured magnetic-field values inside 110-kV substations in Finland and the Ukraine (Korpinen L. and Pääkkönen; Okun et al., 2014). The highest measured field levels were 2500 and 4200 mG in the two papers, respectively, in the immediate vicinity of busbars and cables. In general, the measured magnetic fields were below the occupational reference values of ICNIRP in these studies. At some locations within substations, worker exposure to electric fields could exceed the reference level (Korpinen et al., 2011b; Korpinen et al., 2012; Korpinen et al., 2011b, 2012), but the induced current density in the central nervous system did not exceed the ICNIRP basic restriction value.

4 Methods for Evaluating Scientific Research

Science is more than a collection of facts. It is a method of obtaining information and of reasoning to ensure that the information and conclusions are accurate and correctly describe physical and biological phenomena. Many misconceptions in human reasoning occur when people casually interpret their observations and experience. Therefore, scientists use systematic methods to conduct and evaluate scientific research and assess the potential impact of a specific agent on human health. This process is designed to ensure that more weight is given to those studies of better quality and studies with a given result are not selected out from all of the studies available to advocate or suppress a preconceived idea of an adverse effect. Scientists and scientific agencies and organizations use these standard methods to draw conclusions about the many exposures in our environment.

Weight-of-evidence reviews

The scientific process entails looking at *all* the evidence on a particular issue in a systematic and thorough manner to evaluate if the overall data presents a logically coherent and consistent picture. This is often referred to as a weight-of-evidence review, in which all studies are considered together, giving more weight to studies of higher quality and using an established analytic framework to arrive at a conclusion about a possible causal relationship. Weight-of-evidence reviews are typically conducted within the larger framework of health risk assessments or evaluations of particular exposures or exposure circumstances that qualitatively and quantitatively define health risks. Weight-of-evidence and health risk assessment methods have been described by several agencies, including the IARC, which routinely evaluates substances such as drugs, chemicals, and physical agents for their ability to cause cancer; the WHO International Programme for Chemical Safety; and the US Environmental Protection Agency (EPA), which set guidance for public exposures (USEPA, 1993; WHO, 1994; USEPA, 1996). Two steps precede a weight-of-evidence evaluation: a systematic review to identify the relevant literature and an evaluation of each study to determine its strengths and weaknesses.

The following sections discuss important considerations in the evaluation of human health studies of ELF EMF in a weight-of-evidence review, including exposure considerations, study design, methods for estimating risk, bias, and the process of causal inference. The purpose of discussing these considerations here is to provide context for the later weight-of-evidence evaluations.

EMF exposure considerations

Exposure methods range widely in studies of EMF, including: the classification of residences based on the relative capacity of nearby power lines to produce magnetic fields (i.e., wire code categories); occupational titles; calculated magnetic-field levels based on job histories (a job-exposure matrix [JEM]; residential distance from nearby power lines; spot measurements of magnetic-field levels inside or outside residences; 24-hour and 48-hour measurements of magnetic fields in a particular location in the house (e.g., a child's bedroom); calculated magnetic-field levels based on the characteristics of nearby power installations; and, finally, personal 24-hour and 48-hour magnetic-field measurements.

Each of these methods has strengths and limitations (Kheifets and Oksuzyan, 2008). Since magnetic-field exposures are ubiquitous and vary over a lifetime as the places we frequent and the sources of EMF in those places change, making valid estimates of personal magnetic-field exposure is challenging. Furthermore, without a biological basis to define a relevant exposure metric (average, peak, etc.) and a defined critical period for exposure (*in utero*, shortly before diagnosis, etc.), relevant and valid assessments of exposure are problematic. Exposure misclassification is one of the most significant concerns in epidemiology studies of ELF EMF.

In general, long-term personal measurements are the metric recommended by epidemiologists to estimate exposure in their studies. Other methods are generally weaker because they may not be strong predictors of long-term exposure and do not take into account all magnetic-field sources. EMF can be estimated indirectly by assigning an estimated amount of EMF exposure to an individual based on calculations considering nearby power installations or a person's job title. For example, a relative estimate of exposure could be assigned to all machine operators based on historical information on the magnitude of the magnetic field produced by the machine. Indirect measurements are not as accurate as direct measurements because they do not contain information specific to that person or the exposure situation. In the example of machine operators, the indirect measurement may not account for how much time any one individual spends working at that machine or any potential variability in magnetic fields produced by the machines over time, and occupational measurements do not take into account the worker's residential magnetic-field exposures.

While an advance over earlier methods, JEMs still have some important limitations, as highlighted in a review by Kheifets et al. (2009) summarizing an expert panel's findings.[9] A person's occupation provides some relative indication of the overall magnitude of his or her occupational magnetic-field exposure, but it does not take into account the possible variation in exposure due to different job tasks within occupational titles, the frequency and intensity of contact to relevant exposure sources, or variation by calendar time. This was highlighted in a study of 48-hour magnetic-field measurements of 543 workers in Italy in a variety of occupational settings, including: ceramics, mechanical engineering, textiles, graphics, retail, food, wood and biomedical industries (Gobba et al., 2011). There was significant variation in this study between the measured TWA magnetic-field levels for workers in many of the International Standard Classification of Occupations' (ISCO) job categories, which the authors attributed to variation in industry within the task-defined ISCO categories.

Types of health research studies

Research studies can be broadly classified into two groups: 1) epidemiologic observations of people and 2) experimental studies on animals, humans, cells, and tissues in laboratory settings. Epidemiology studies investigate how disease is distributed in populations and what factors

[9] Kheifets et al. (2009) reports on the conclusions of an independent panel organized by the Energy Networks Association in the United Kingdom in 2006 to review the current status of the science on occupational EMF exposure and identify the highest priority research needs.

influence or determine this disease distribution (Gordis, 2000). Epidemiology studies attempt to establish causes for human disease while observing people as they go about their normal, daily lives. Such studies are designed to quantify and evaluate the associations between disease and reported exposures to environmental factors.

The most common types of epidemiology studies in the EMF literature are case-control and cohort studies. In case-control studies, the exposures of people with and without the disease of interest are compared. Often, people are interviewed or their personal records (e.g., medical records or employment records) are reviewed in order establish the exposure history for each individual. The exposure histories of the diseased and non-diseased populations are compared to determine whether any statistically significant differences in exposure histories exist. A difference in the exposure of the cases and control persons may suggest an association between the exposure and the disease. In cohort studies, on the other hand, individuals within a defined cohort of people (e.g., all persons working at a utility company) are classified as exposed or non-exposed and followed over time for the incidence of disease. Researchers then compare disease incidence in the exposed and non-exposed groups and so can directly estimate exposure related risks.

Experimental studies are designed to test specific hypotheses under controlled conditions and are vital to assessing cause-and-effect relationships. An example of a human experimental study relevant to this area of research would be a study that measures the impact of magnetic-field exposure on acute biological responses in humans, such as hormone levels. These studies are conducted in laboratories under controlled conditions.

In vivo and *in vitro* experimental studies are also conducted under controlled conditions in laboratories. *In vivo* studies expose laboratory animals to very high levels of a chemical or physical agent to determine whether exposed animals develop cancer or other effects at higher rates than unexposed animals, while attempting to control other factors that could possibly affect disease rates (e.g., diet and genetics). *In vitro* studies of isolated cells and tissues are also important because they can help scientists understand biological mechanisms as they relate to the same exposure in intact humans and animals.

The results of experimental studies of animals, and particularly those of isolated tissues or cells, however, may not always be directly extrapolated to human populations. In the case of *in vitro* studies, the responses of cells and tissues outside the body may not reflect the response of those same cells if maintained in a living system, so their relevance cannot be assumed. Therefore, it is both necessary and desirable to explore agents that could present a potential health threat in epidemiology studies as well.

Both of these approaches—epidemiology and experimental laboratory studies—have been used to evaluate whether exposure to EMF has any adverse effects on human health. Epidemiology studies are valuable because they are conducted in human populations, but they are limited by their non-experimental design and typical retrospective nature. In epidemiology studies of EMF, for example, researchers cannot control the amount of individual exposure to EMF, the contribution from different field sources, how exposure occurs over time, or individual behaviors that could affect disease risk, such as diet or smoking. In valid risk assessments of EMF, epidemiology studies are considered alongside experimental studies of laboratory animals, while studies of isolated tissues and cells are generally acknowledged as being supplementary.

Estimating risk

Epidemiologists measure the statistical association between exposures and disease in order to estimate risk. In this context, risk simply refers to an exposure that is associated with a health event and does not imply that a causal relationship has been established.[10] This brief summary of risk is included to provide a foundation for understanding and interpreting statistical associations in epidemiology studies as risk estimates.

Two common types of risk estimates are absolute risk and relative risk (RR). Absolute risk, also known as incidence, is the amount of new disease that occurs in a given period of time. For example, the absolute risk of invasive childhood cancer in children ages 0-19 years for 2004 was 14.8 per 100,000 children (Ries et al., 2007). RR estimates are calculated to evaluate whether a particular exposure or inherent quality (e.g., EMF, diet, genetics, race) is associated with a disease outcome. This is calculated by looking at the absolute risk in one group relative to a comparison group. For example, white children in the 0-19 year age range had an estimated absolute risk of childhood cancer of 15.4 per 100,000 in 2004, and African American children had an estimated absolute risk of 13.3 per 100,000 in the same year. By dividing the absolute risk of white children by the absolute risk of African American children, we obtain a RR estimate of 1.16. This RR estimate can be interpreted to mean that white children have a risk of childhood cancer that is 16% greater than the risk of African American children. Additional statistical analysis is needed to evaluate whether this association is statistically significant, as defined in the following sub-section.

It is important to understand that risk is estimated differently in cohort and case-control studies because of the way the studies are designed. Traditional cohort studies can provide a direct estimate of RR, while case-control studies can only provide indirect estimates of RR, called odds ratios (OR). For this reason, among others, cohort studies usually provide more reliable estimates of the risk associated with particular exposures. Case-control studies are more common than cohort studies, however, because of they are less costly and more time efficient.

Thus, the association between a particular disease and exposure is measured quantitatively in an epidemiology study as either the RR estimate (cohort studies) or OR (case-control studies). The general interpretation of a relative risk estimate equal to 1.0 is that the exposure is not associated with the occurrence of the disease. If the relative risk estimate is greater than 1.0, the inference is that the exposure is associated with an increased incidence of the disease. On the other hand, if the relative risk estimate is less than 1.0, the inference is that the exposure is associated with a reduced incidence of the disease. The magnitude of the relative risk estimate is often referred to as its strength (i.e., strong vs. weak). Stronger associations are given more weight because they are less susceptible to the effects of bias.

[10] The following definition is provided of a risk factor in a dictionary of epidemiology terms: "…an aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that, on the basis of epidemiological evidence, is known to be associated with health-related condition(s) considered important to prevent" (Last, 2001, p. 160).

Statistical significance

Statistical significance testing provides an idea of whether or not a statistical association is caused by chance alone, i.e., whether the association is likely to be observed this way upon repeated testing or whether it is simply a chance occurrence. The terms "statistically significant" or "statistically significant association" are used in epidemiology studies to describe the tendency of the level of exposure and the occurrence of disease to be linked, with chance as an unlikely explanation. Statistically significant associations, however, are not automatically an indication of cause-and-effect, because the interpretation of statistically significant associations depends on many other factors associated with the design and conduct of the study, including, how the data were collected and the size of the study.

Confidence intervals (CI) are typically reported along with RR and OR values. A CI is a range of values for an estimate of effect that has a specified probability (e.g., 95%) of including the "true" estimate of effect; CIs evaluate statistical significance, but do not address the role of bias, as described further below. A 95% CI indicates that, if the study were conducted a very large number of times, 95% of the measured estimates would be within the upper and lower confidence limits.

The range of the CI is also important for interpreting estimated associations, including the precision and statistical significance of the association. A very wide CI indicates great uncertainty in the value of the "true" risk estimate. This is usually due to a small number of observations. A narrow CI provides more certainty about where the "true" RR estimate lies. Another way of interpreting the CI is if the 95% CI does not include 1.0, the probability of an association being due to chance alone is 5% or lower and the result is considered statistically significant, as discussed above. Statistical variation, however, while easily estimated, is just one of the sources of uncertainty in the characterization of epidemiological associations. Additional uncertainties may result from bias (e.g., participation, selection or recall biases) and confounding by alternative exposures. These additional uncertainties are not quantified by statistical testing and the assessment of their influence on the overall interpretation requires expert evaluation of information from outside the studies themselves.

Meta-analysis and pooled analysis

In epidemiologic research, the results of studies with a smaller number of participants may be difficult to distinguish from normal, random variation. This is also the case for sub-group analyses where few cases are estimated to have high exposure levels, e.g., in case-control studies of childhood leukemia and TWA magnetic-field exposure greater than 3-4 mG. Meta-analysis is an analytic technique that combines the published results from a group of studies into one summary result. A pooled analysis, on the other hand, combines the raw, individual-level data from the original studies and analyzes all of the data from the studies together. These methods are valuable because they increase the number of individuals in the analysis, which allows for a more robust and stable estimate of association. Meta- and pooled analyses are also an important tool for qualitatively synthesizing the results of a large group of studies.

The disadvantage of meta- and pooled analyses is that they can convey a false sense of consistency across studies if *only* the combined estimate of effect is considered (Rothman and Greenland, 1998). These analyses typically combine data from studies with different study populations, methods for measuring and defining exposure, and disease definitions. This is particularly true for analyses that combine data from case-control studies, which often use very different methods for the selection of cases and controls and exposure assessment. Therefore, in addition to the synthesis or combining of data, meta- and pooled analyses should be used to understand what factors cause the results of the studies to vary (publication date, study design, possibility of selection bias, etc.), and how these factors affect the associations calculated from the data of all the studies combined (Rothman and Greenland, 1998).

Meta- and pooled analyses are a valuable technique in epidemiology; however, in addition to calculating a summary RR, they should follow standard techniques (Stroup et al., 2001) and analyze the factors that contribute to any heterogeneity between the studies.

Bias in epidemiologic studies

One key reason that results of non-experimental epidemiology studies cannot directly provide evidence for cause-and-effect is the presence of bias. Bias is defined as “any systematic error in the design, conduct or analysis of a study that results in a mistaken estimate of an exposure’s effect on the risk of disease” (Gordis, 2000, p. 204). In other words, sources of bias are factors or research situations that can mask a true association or cause an apparent association in the study that does not truly exist. As a result, the extent of bias, as well as its types and sources, is one of the most important considerations in the interpretation of epidemiology studies. Since it is not possible to fully control human populations, perfectly measure their exposures, or control for the effects of all other risk factors, bias will exist in some form in all epidemiology studies of human health. Experimental studies, on the other hand, more effectively manage bias because of the tight control the researchers have over most study variables.

One important source of bias occurs when a third variable confuses the relationship between the exposure and disease of interest because of its relationship to both. Consider an example of a researcher whose study finds that people who exercise have a lower risk of diabetes compared to people who do not exercise. It is known that people who exercise more also tend to consume healthier diets and healthier diets may lower the risk of diabetes. If the researcher does not control for the impact of diet, it is not possible to say with certainty that the lower risk of diabetes is due to exercise and not to a healthier diet. In this example, diet is the confounding variable.

Cause vs. association and evaluating evidence regarding causal associations

Epidemiology studies can help suggest factors that may contribute to the risk of disease, but they are not used as the sole basis for drawing inferences about cause-and-effect relationships. Since epidemiologists do not have control over the many other factors to which people are exposed in their studies (e.g., chemicals, pollution, infections) and diseases can be caused by a complex interaction of many factors, the results of epidemiology studies must be interpreted with caution.

A single epidemiology study is rarely unequivocally supportive or non-supportive of causation; rather, a weight is assigned to the study based on the validity of its methods and all studies (epidemiology, *in vivo*, and *in vitro*) must be considered together in a weight-of-evidence review to arrive at a conclusion about possible causality between an exposure and disease.

Scientific guidance for assessing the overall epidemiologic evidence for causality was formally proposed by Sir Austin Bradford Hill (Hill, 1965). Hill put forth nine criteria for use in an evaluation of causality for associations observed in epidemiologic studies. These criteria included strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy. Hill cautioned that, while none of these criteria are *sine qua non* of causality, the more the epidemiologic evidence meets these guidelines, the more convincing the evidence is for a potential causal interpretation. The use of these guidelines is recommended after chance is ruled out with reasonable certainty as a potential explanation for the observed epidemiologic association.

In 1964, the Surgeon General of the United States published a landmark report on smoking-related diseases (HEW, 1964). As part of this report, nine criteria, similar to those proposed by Hill for evaluating epidemiology studies (along with experimental data) for causality, were outlined. In a more recent version of this report, these criteria have been reorganized into seven criteria. In the earlier version, coherence, plausibility, and analogy were considered as distinct items, but are now summarized together because they have been treated in practice as essentially reflecting one concept (HHS, 2004). Table 2 provides a listing and brief description of each criterion.

Table 2. Criteria for evaluating whether an association is causal

Criteria	Description
Consistency	Repeated observation of an association between exposure and disease in multiple studies of adequate statistical power, in different populations, and at different times.
Strength of the association	The larger (stronger) the magnitude and statistical strength of an association is between exposure and disease, the less likely such an effect is the result of chance or unmeasured confounding.
Specificity	The exposure is the single (or one of a few) cause of disease.
Temporality	The exposure occurs prior to the onset of disease.
Coherence, plausibility, and analogy	The association cannot violate known scientific principles and the association must be consistent with experimentally demonstrated biologic mechanisms.
Biologic gradient	This is also known as a dose-response relationship, i.e., the observation that the stronger or greater the exposure is, the stronger or greater the effect.
Experiment	Observations that result from situations in which natural conditions imitate experimental conditions. Also stated as a change in disease outcome in response to a non-experimental change in exposure patterns in population.

Source: Department of Health and Human Services, 2004

The criteria were meant to be applied to statistically significant associations that have been observed in the cumulative epidemiologic literature, i.e., if no statistically significant association has been observed for an exposure then the criteria are not relevant. It is important to note that these criteria were not intended to serve as a checklist; rather, they were intended to serve as a guide in evaluating associations for causal inference. Theoretically, it is possible for an exposure to meet all seven criteria, but still not be deemed a causal factor. Also, no one criterion can provide indisputable evidence for causation, nor can any single criterion, aside from temporality, rule out causation.

In summary, the judicious consideration of these criteria is useful in evaluating epidemiology studies, but they cannot be used as the sole basis for drawing inferences about cause-and-effect relationships. In line with the criteria of "coherence, plausibility, and analogy," epidemiology studies are considered along with *in vivo* and *in vitro* studies in a comprehensive weight-of-evidence review. Epidemiologic support for causality is usually based on high-quality studies reporting consistent results across many different populations and study designs that are supported by the experimental data collected from *in vivo* and *in vitro* studies.

Biological response vs. disease in human health

When interpreting research studies, it is important to distinguish between a reported biological response and an indicator of disease. This is relevant because exposure to EMF may elicit a biological response that is simply a normal response to environmental conditions. This response, however, might not be a disease, cause a disease, or be otherwise harmful. There are many exposures or factors encountered in day-to-day life that elicit a biological response, but the response is neither harmful nor does it cause disease. For example, when an individual walks from a dark room indoors to a sunny day outdoors, the pupils of the eye naturally constrict to limit the amount of light passing into the eye. This constriction of the pupil is a biological response to the change in light conditions. Pupil constriction, however, is neither a disease itself, nor is it known to cause disease.

5 The WHO 2007 Report: Methods and Conclusions

The WHO is a scientific organization within the United Nations system whose mandate includes providing leadership on global health matters, shaping health research agendas, and setting norms and standards. The WHO established the International EMF Project in 1996, in response to public concerns about exposures to EMF and possible adverse health outcomes. The project's membership includes 8 international organizations, 8 collaborating institutions, and over 54 national authorities. The overall purpose of the Project is to assess health and environmental effects of exposure to static and time-varying fields in the frequency range 0-300 Gigahertz (GHz). A key objective of the EMF Project was to evaluate the scientific literature and make a status report on health effects to be used as the basis for a coherent international response, including the identification of important research gaps and the development of internationally acceptable standards for EMF exposure.

Methods

As part of their Environmental Health Criteria Programme, the WHO published a Monograph in June 2007 summarizing health research on exposures in the ELF range. The Monograph used standard scientific procedures, as outlined in its Preamble and described above in Section 4, to conduct the review. The Task Group responsible for the report's overall conclusions consisted of 21 scientists from around the world with expertise in a wide range of disciplines. The Task Group relied on the conclusions of previous weight-of-evidence reviews,[11] where possible, and mainly focused on evaluating studies published after an IARC review of ELF EMF (with regard to cancer) in 2002 .

The WHO Task Group and IARC use specific terms to describe the strength of the evidence in support of causality between specific agents and cancer. These categories are described here because, while they are meaningful to scientists who are familiar with the IARC process, they can be confusing and can create an undue level of concern with the general public.

Sufficient evidence of carcinogenicity is assigned to a body of epidemiologic research if a positive association has been observed in studies in which chance, bias, and confounding can be ruled out with reasonable confidence. *Limited evidence of carcinogenicity* describes a body of epidemiologic research where the findings are inconsistent or there are outstanding questions about study design or other methodological issues that preclude making a conclusion. *Inadequate evidence of carcinogenicity* describes a body of epidemiologic research where it is unclear whether the data is supportive or unsupportive of causation because there is a lack of data or there are major quantitative or qualitative issues. A similar classification system is used for evaluating *in vivo* studies and mechanistic data for carcinogenicity.

[11] The term "weight-of-evidence review" is used in this report to denote a systematic review process by a multidisciplinary, scientific panel involving experimental and epidemiologic research to arrive at conclusions about possible health risks. The WHO Monograph on EMF does not specifically describe their report as a weight-of-evidence review. Rather, they describe conducting a health risk assessment. A health risk assessment differs from a weight-of-evidence review in that it also incorporates an exposure and exposure-response assessment.

Summary categories are assigned by considering the conclusions of each body of evidence (epidemiologic, *in vivo*, and *in vitro*) together (Figure 3). *In vitro* research is not described in Figure 3 because it provides ancillary information and, therefore, is used to a lesser degree in evaluating carcinogenicity and is classified simply as strong, moderate, or weak. Categories include (from highest to lowest risk): carcinogenic to humans, probably carcinogenic to humans, possibly carcinogenic to humans, unclassifiable, and probably not carcinogenic to humans. These categories are intentionally meant to err on the side of caution, giving more weight to the possibility that the exposure is truly carcinogenic and less weight to the possibility that the exposure is not carcinogenic. The category "possibly carcinogenic to humans" denotes exposures for which there is limited evidence of carcinogenicity in epidemiology studies and less than sufficient evidence of carcinogenicity in studies of experimental animals.

	Epidemiology Studies				Animal Studies			
	Sufficient evidence	Limited evidence	Inadequate evidence	Evidence suggesting lack of carcinogenicity	Sufficient evidence	Limited evidence	Inadequate evidence	Evidence suggesting lack of carcinogenicity
Known Carcinogen	✔							
Probable Carcinogen		✔			✔			
Possible Carcinogen		✔				✔	✔	
Not Classifiable			✔			✔	✔	
Probably not a Carcinogen				✔				✔

Sufficient evidence in epidemiology studies—A positive association is observed between the exposure and cancer in studies, in which chance, bias and confounding were ruled out with "reasonable confidence."

Limited evidence in epidemiology studies—A positive association has been observed between the exposure and cancer for which a causal interpretation is considered to be credible, but chance, bias or confounding could not be ruled out with "reasonable confidence."

Inadequate evidence in epidemiology studies—The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

Evidence suggesting a lack of carcinogenicity in epidemiology studies—There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit close to the null value (e.g. a relative risk of 1.0). Bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up.

Sufficient evidence in animal studies—An increased incidence of malignant neoplasms is observed in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or indifferent laboratories or under different protocols. An increased incidence of tumors in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide sufficient evidence.

Limited evidence in animal studies—The data suggest a carcinogenic effect but are limited for making a definitive evaluation, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; etc.

Inadequate evidence in animal studies—The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available

Evidence suggesting a lack of carcinogenicity in animal studies—Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent is not carcinogenic.

Figure 3. Basic IARC method for classifying exposures based on potential carcinogenicity

The IARC has reviewed over 900 substances and exposure circumstances to evaluate their potential carcinogenicity. Over 80% of exposures fall in the categories possible carcinogen (28%) or non-classifiable (53%). This occurs because it is nearly impossible to prove that something is completely safe and few exposures show a clear-cut or probable risk, so most agents will end up in either of these two categories. Throughout the history of the IARC, only one agent has been classified as probably not a carcinogen, which illustrates the conservatism of the evaluations and the difficulty in proving the absence of an effect beyond all doubt.

Conclusions

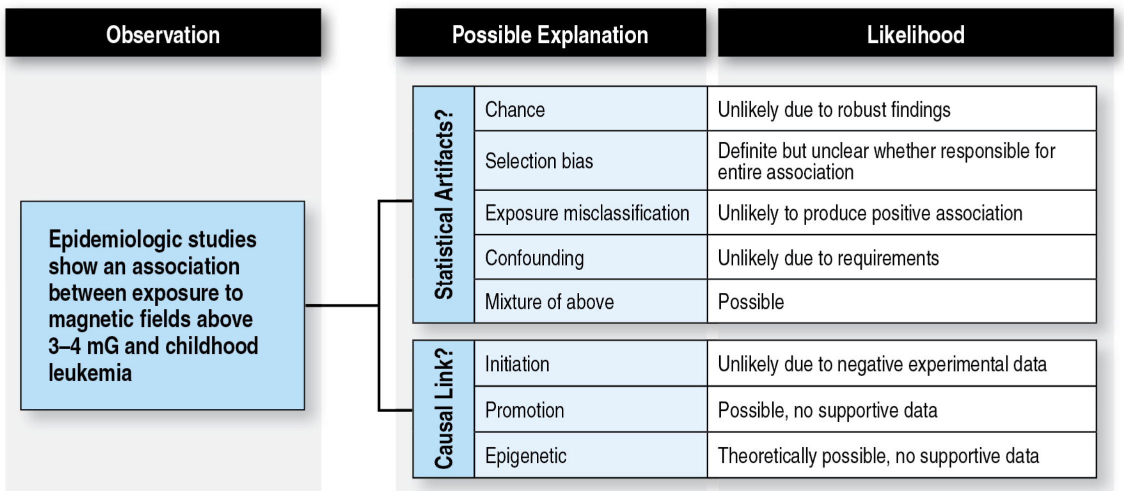
The WHO report provided the following overall conclusions with regard to ELF EMF:

> New human, animal, and in vitro studies published since the 2002 IARC Monograph, 2002 [sic] do not change the overall classification of ELF as a possible human carcinogen (WHO, 2007, p. 347).
>
> Acute biological effects [i.e., short-term, transient health effects such as a small shock] have been established for exposure to ELF electric and magnetic fields in the frequency range up to 100 kHz that may have adverse consequences on health. Therefore, exposure limits are needed. International guidelines exist that have addressed this issue. Compliance with these guidelines provides adequate protection. Consistent epidemiological evidence suggests that chronic low-intensity ELF magnetic field exposure is associated with an increased risk of childhood leukaemia. However, the evidence for a causal relationship is limited, therefore exposure limits based upon epidemiological evidence are not recommended, but some precautionary measures are warranted (WHO, 2007, p. 355).

With regard to specific diseases, the WHO concluded the following:

Childhood cancers. The WHO report paid particular attention to childhood leukemia because the most consistent epidemiologic association in the area of ELF EMF and health research has been reported between this disease and TWA exposure to high, magnetic-field levels. Two pooled analyses reported an association between childhood leukemia and TWA magnetic-field exposure >3-4 mG (Ahlbom et al., 2000; Greenland et al., 2000); it is this data, categorized as limited epidemiologic evidence, that resulted in the classification of ELF magnetic fields as possibly carcinogenic by the IARC in 2002.

The WHO report systematically evaluated several factors that might be partially, or fully, responsible for the consistent association, including: chance, misclassification of magnetic-field exposure, confounding from hypothesized or unknown risk factors, and selection bias (Figure 4). The authors concluded that chance is an unlikely explanation since the pooled analyses had a large sample size and decreased variability. Control selection bias probably occurs to some extent in these studies and would result in an overestimate of the true association, but would not explain the entire observed association. It is less likely that confounding occurs, although the possibility that some yet-to-be identified confounder is responsible for the association cannot be fully excluded. Finally, exposure misclassification would likely result in an underestimate of the true association, although that may not always be the case. The WHO concluded that reconciling the epidemiologic data on childhood leukemia and the negative experimental findings (i.e., no hazard or risk observed) through innovative research is currently the highest priority in the field of ELF EMF research. Given that few children are expected to have average magnetic-field exposures greater than 3-4 mG, however, the WHO stated that the public health impact of magnetic fields on childhood leukemia would likely be minimal, if the association was determined to be causal.



Source: Adapted from Schüz and Ahlbom (2008)

Figure 4. Possible explanations for the observed association between magnetic fields and childhood leukemia

Fewer studies have been published on magnetic fields and childhood brain cancer compared to studies of childhood leukemia. The WHO Task Group described the results of these studies as inconsistent and limited by small sample sizes and recommended a meta-analysis to clarify the research findings.

Breast cancer. The WHO concluded that recently published studies on breast cancer and ELF EMF exposure were higher in quality compared with previous studies, and for that reason, they provide strong support to previous consensus statements that magnetic-field exposure does not influence the risk of breast cancer. In summary, the WHO stated "[w]ith these [recent] studies, the evidence for an association between ELF magnetic-field exposure and the risk of female breast cancer is weakened considerably and does not support an association of this kind" (WHO, 2007, p. 9). The WHO recommended no further research with respect to breast cancer and magnetic-field exposure.

Adult leukemia and brain cancer. The WHO concluded, "In the case of adult brain cancer and leukaemia, the new studies published after the IARC monograph do not change the conclusion that the overall evidence for an association between ELF [EMF] and the risk of these diseases remains inadequate" (WHO, 2007, p. 307). The WHO panel recommended updating the existing cohorts of occupationally-exposed individuals in Europe and pooling the epidemiologic data on brain cancer and adult leukemia to confirm the absence of an association.

***In vivo* research on carcinogenesis.** The WHO concluded the following with respect to *in vivo* research, "[t]here is no evidence that ELF exposure alone causes tumours. The evidence that ELF field exposure can enhance tumour development in combination with carcinogens is inadequate" (WHO, 2007, p. 10). Recommendations for future research included the development of a rodent model for childhood acute lymphoblastic leukemia (ALL) and the continued investigation of whether magnetic fields can act as a co-carcinogen.

***In vitro* research on carcinogenesis.** The WHO concluded that magnetic-field exposure below 50,000 mG was not associated with genotoxicity *in vitro*. There was some evidence, however, to suggest that magnetic fields above these levels might interact with other genotoxic agents to induce damage. Evidence for an association between magnetic fields and altered apoptosis or expression of genes controlling cell cycle progression was considered inadequate.

Reproductive and developmental effects. The WHO concluded that, overall, the body of research does not suggest that maternal or paternal exposures to ELF EMF cause adverse reproductive or developmental outcomes. The evidence from epidemiology studies on miscarriage was described as inadequate and further research on this possible association was recommended, although it was designated as low priority.

***In vivo* research on reproductive and developmental effects.** The WHO Task Group concluded that the available *in vivo* studies were inadequate for drawing conclusions regarding the potential effects of magnetic fields on the reproductive system. Furthermore, the Task Group concluded that studies conducted in mammalian models showed no adverse developmental effects associated with magnetic-field exposure.

Neurodegenerative disease. The WHO reported that the majority of epidemiology studies have reported associations between occupational magnetic-field exposure and mortality from Alzheimer's disease and ALS, although the design and methods of these studies were relatively weak (e.g., disease status was based on death certificate data, exposure was based on incomplete occupational information from census data, and there was no control for confounding factors). The WHO concluded that there is inadequate data in support of an association between magnetic fields and Alzheimer's disease or ALS. The panel highly recommended that further studies be conducted in this area, particularly studies where the association between magnetic fields and ALS is estimated while controlling for the possible confounding effect of electric shocks.

***In vivo* research on neurological effects.** The WHO stated that various animal models were used to investigate possible field-induced effects on brain function and behavior. Few brief, transient responses had been identified.

Cardiovascular disease. It has been hypothesized that magnetic-field exposure reduces heart rate variability (HRV), which in turn increases the risk for acute myocardial infarction (AMI). With one exception (Savitz et al., 1999), however, none of the studies of cardiovascular disease morbidity and mortality has shown an association with exposure. Whether a specific association exists between exposure and altered autonomic control of the heart remains speculative and the overall evidence does not support an association. Experimental studies of both short- and long-term exposure indicate that, while electric shock is an obvious health hazard, other hazardous cardiovascular effects associated with ELF EMF are unlikely to occur at exposure levels commonly encountered environmentally or occupationally.

6 Current Scientific Consensus

The following sections identify and describe epidemiology and *in vivo* studies related to ELF EMF and health published from August 1, 2012 through July 31, 2014.[12] The purpose of this section is to evaluate whether the findings of these recent studies alter the conclusions published by the WHO in their 2007 report, as described in Section 5.

Literature search methodology

A structured literature search was conducted using PubMed, a search engine provided by the National Library of Medicine and the National Institutes of Health that includes over 15 million up-to-date citations from MEDLINE and other life science journals for biomedical articles (http://www.pubmed.gov). A well-defined search strategy was used to identify literature indexed August 1, 2012 through July 31, 2014.[13] While PubMed contains an extensive database of publications, some studies are indexed well after their publication date. For that reason, there may be studies included in this report that were actually published prior to August 1, 2012, but indexed after that date.

All fields (title, abstract, keywords, among others) were searched with various search strings that referenced the exposure[14] and diseases of interest,[15] as well as authors that regularly publish in this field. A scientist with experience in this area reviewed the titles and abstracts of these publications for inclusion in this evaluation. Only peer-reviewed, epidemiology studies, pooled- or meta-analyses, and human experimental studies of 50-Hz or 60-Hz AC ELF EMF and recognized disease entities are included. *In vivo* animal studies of 50-Hz or 60-Hz AC ELF EMF are also included, but only on the topic of cancer.

The following specific inclusion criteria were applied:

1. **Outcome**. Included studies evaluated one of the following diseases: cancer; reproductive and developmental effects; neurodegenerative diseases; or cardiovascular disease. Research on other outcomes is not included (psychological effects, behavioral effects, hypersensitivity). Few studies are available in these research areas and, as such,

[12] In March 2015, following the solicitation of comments and input on its preliminary opinion, the Scientific Committee commissioned by the European Union issued its review of health research on electromagnetic fields that included reviews of ELF EMF fields. Although this was after the cutoff date for the literature search, we reference this review in our report.

[13] While extensive efforts were made to identify relevant studies, it is possible that some studies reporting on the association between a disease and some measure of EMF exposure were missed. Many occupational and environmental case-control studies of cancer are published, some of which examine a large number of possible exposures; if no reference to EMF is made in the abstract, title, or keywords, for example, these studies may not have been identified using our search strategy. The most informative studies in this field, however, will be identified by our search strategy.

[14] EMF, magnetic fields, electric fields, or electromagnetic.

[15] Cancer (cancer, leukemia, lymphoma, carcinogenesis), neurodegenerative disease (neurodegenerative disease, Alzheimer's disease, amyotrophic lateral sclerosis, or Lou Gehrig's disease), cardiovascular effects (cardiovascular or heart rate), or reproductive outcomes (miscarriage, reproduction, or development).

research evolves more slowly.

2. **Exposure**. The study must have evaluated 50-Hz or 60-Hz AC ELF EMF.

3. **Exposure assessment methods**. To be included in this report, exposure must have been evaluated beyond self-report of an activity or occupation. Included studies estimated exposure through various methods including: calculated EMF levels using distance from power lines; time-weighted average EMF exposures; and average exposures estimated from JEMs.

4. **Study design**. Epidemiology, human experimental, and *in vivo* studies were included. *In vitro* studies were not systematically evaluated, since this field of study is less informative to the risk assessment process (IARC, 2002). We rely on the conclusions of the WHO report (as described in Section 5) with regard to mechanistic data from *in vitro* studies. Furthermore, only *in vivo* studies of carcinogenicity were evaluated in this review; the review relies on the conclusions of the WHO with regard to *in vivo* studies in the areas of reproduction, development, neurology, and cardiology.

5. **Peer-review**. The study must have been peer-reviewed and published in English. Therefore, no foreign language studies, conference proceedings, abstracts, or on-line material was included.

Methodological research is now being pursued in many areas of ELF EMF research to identify the possible impact of certain aspects of study design or biases on the studies' results. Therefore, articles evaluating the impact of methodological aspects of epidemiology studies in this field are discussed, where appropriate. Systematic review articles of relevant topics are also noted, where appropriate. Studies published prior to the scope of this update are noted in certain circumstances to provide context.

Epidemiology and human experimental studies are evaluated below by outcome (childhood cancer; adult cancer; reproductive or developmental effects; neurodegenerative diseases; and cardiovascular effects), followed by an evaluation of *in vivo* research in the field of cancer. Tables 3-11 list the relevant studies in these areas, including the study's first author and the title of the article.

Health outcomes

Childhood leukemia

In 2002, the IARC assembled and reviewed research related to ELF EMF to evaluate the strength of the evidence in support of carcinogenicity. The IARC expert panel noted that, when studies with the relevant information were combined in a pooled analysis, a statistically significant two-fold association was observed between childhood leukemia and estimated exposure to high, average levels of magnetic fields (i.e., greater than 3-4 mG of average 24- and 48-hour exposure). This evidence was classified as "limited evidence" in support of carcinogenicity, falling short of "sufficient evidence" because chance, bias, and confounding could not be ruled out with "reasonable confidence." Largely as a result of the findings related to childhood leukemia, the IARC classified magnetic fields as "possibly carcinogenic," a category that describes exposures with limited epidemiologic evidence and inadequate evidence from *in vivo* studies. The classification "possibly carcinogenic" was confirmed by the WHO in June 2007.

Recent studies (2012-2014)

Childhood leukemia continues to be the main focus of ELF EMF epidemiologic research. Three large case-control studies from France, Denmark, and the United Kingdom have assessed the risk of childhood leukemia in relation to residential proximity to high-voltage power lines (Sermage-Faure et al., 2013; Bunch et al., 2014; Pedersen et al., 2014). The French study used geocoded information on residential addresses and power line locations to examine the risk of childhood leukemia in association with distance to power lines between 2002 and 2007. Overall, the study included 2,779 cases of childhood leukemia and 30,000 control children (Sermage-Faure et al., 2013) and reported no statistically significant increase in leukemia risk with distance to power lines. The authors, however, noted a statistically non-significant risk increase in a sub-analysis within 50 meters of 225-400 kV lines, but this was based on a small number of cases (n=9). A similar study from Denmark included 1,698 cases of childhood leukemia and 3,396 healthy control children (Pedersen et al., 2014). The authors reported no risk increases for childhood leukemia with residential distance to power lines.

In the third publication, Bunch et al. (2014) reported on a study that updated and extended the 2005 study conducted by Draper et al. (2005) in the United Kingdom. The update extended the study period by 13 years, included Scotland in addition to England and Wales, and included 132-kV lines in addition to 275-kV and 400-kV transmission lines. Bunch et al. is the largest study to date—it included over 53,000 childhood cancer cases, diagnosed between 1962 and 2008, and over 66,000 healthy children as controls. Overall, the authors reported no association with residential proximity to power lines with any of the voltage categories. In the overall analysis of the updated data, the statistical association that was reported in the earlier study (Draper et al., 2005) was no longer apparent. An analysis by calendar time indicated that the association was evident only in the earlier decades (1960s and 1970s) but not present in the later decades starting from the 1980s (Bunch et al., 2014). This somewhat weakens the argument that the associations observed earlier are due to magnetic-field effects.

The strengths of these three studies include their large size and their population-based design that minimized the potential for selection bias. All of these studies, however, relied on distance to power lines as their main exposure metric, which is known to be a poor predictor of actual residential magnetic field exposure. The limitations of distance as an exposure proxy also have been discussed by several observers in the scientific literature in the context of the French study (Bonnet-Belfais et al., 2013; Clavel et al., 2013). In addition, Chang et al. (2014) recently provided a detailed discussion of the limitations of exposure assessment methods based on geographical information systems.

A hospital-based case-control study of EMF and childhood leukemia included 79 cases and 79 matched controls in the Czech Republic (Jirik et al., 2012). Exposure was measured in the participants' homes, in the "vicinity" of the residences, and the participants' schools. No association was reported between the measured magnetic field and leukemia risk. The study was small and provided insufficient information on the methods of case ascertainment, control selection, subject recruitment, and exposure assessment to fully assess its quality.

A recent pooled analysis (Schüz et al., 2012) aimed to follow up on two earlier studies that, based on small numbers of cases, reported poorer survival among cases of childhood leukemia with increased average exposure to magnetic fields, suggesting the magnetic fields may play a role in the progression in the disease following diagnosis (Foliart et al., 2006; Svendsen et al., 2007). The study included exposure and clinical data on more than 3,000 cases of childhood leukemia from Canada, Denmark, Germany, Japan, the United Kingdom, and the United States. The authors reported no association between magnetic-field exposure and overall survival or relapse of disease in children with leukemia after diagnosis.

Researchers also examined the association between occupational exposures of fathers and the risk of childhood leukemia in their children in the United Kingdom (Keegan et al., 2012). The study included a total of 15,785 cases of childhood leukemia diagnosed between 1962 and 2006 and a similar number of matched controls in the analyses. EMF exposure was among the 33 investigated occupational exposures. Occupational EMF exposure of the fathers was not statistically significantly related to leukemia in their children when all types of leukemia, lymphoid (the most common type), or myeloid leukemia were considered. The authors reported a statistically significant increase for leukemia classified as “other types,” which included but 7% of the leukemia cases.

Zhao et al. (2014) conducted a meta-analysis of nine case-control studies of EMF exposure and childhood leukemia published between 1997 and 2013. The authors reported a statistically significant association between average exposure above 4 mG and all types of childhood leukemia (OR 1.57, 95% CI, 1.03-2.4). The meta-analysis relied on published results from some of the same studies included in previous pooled analyses, thus provided little new insight.

Several methodological studies have also examined the potential role of causal and alternative, non-causal explanations for the reported epidemiologic associations. Swanson and Kheifets (2012) proposed that if the biological mechanism explaining the epidemiologic association involves free radicals then, due to the small timescale of the reactions, the effects of ELF EMF and the earth’s geomagnetic fields would be similar. Thus, to test this hypothesis the authors evaluated whether the magnitude of the earth’s geomagnetic field modifies the effects reported by ELF EMF childhood leukemia studies from various parts of the world. The results were not in full support of the hypothesis. Swanson (2013) examined differences in residential mobility among residents who lived at varying distances from power lines in order to assess if these differences in mobility may explain the statistical association of leukemia with residential proximity to power lines. The study reported some variations in residential mobility, “but only small ones, and not such as to support the hypothesis.” A third study evaluated whether selection bias may play a role in the association between childhood leukemia and residential magnetic-field exposure (Slusky et al., 2014). The authors used wire code categories to assess exposure among participant and nonparticipant subjects in the Northern California Childhood Leukemia Study. While the authors reported systematic differences between participant and nonparticipant subjects in both wire code categories and socioeconomic status, these differences did not appear to influence the association between childhood leukemia and exposure estimates. The limitations of the study include the use of wire code categories to assess exposure, which is known to be a poor predictor for actual magnetic-field exposure, and that the study showed no association between magnetic fields and childhood leukemia among the participant subjects.

Recent reviews continue to highlight that the observed epidemiologic association between EMF and childhood leukemia remains unexplained and there are no supportive data from laboratory animal studies or known biophysical mechanisms that could explain a carcinogenic effect (Ziegelberger et al., 2011; Teepen and van Dijck, 2012; Grellier et al., 2014).

Grellier et al.(2014) estimated that, if the association was causal, ~1.5% to 2% of leukemia cases might be attributable to ELF EMF in Europe. They conclude that "this contribution is small and is characterized by considerable uncertainty." Authors continue to emphasize that further understanding may be gained by studies of improved methodology and reduced potential for bias and by international and interdisciplinary collaborations (Ziegelberger et al., 2011; Teepen and van Dijck, 2012).

Assessment

In summary, while some of the recently published large and methodologically advanced studies showed no association (e.g., Bunch et al., 2014, Pedersen et al., 2014), the association between childhood leukemia and magnetic fields observed in some studies remains unexplained. Thus, the results of recent studies do not change the classification of the epidemiologic data as limited, which is also the assessment by the SCENIHR (2015) panel.

It should be noted that magnetic fields are just one small area in the large body of research on the possible causes of childhood leukemia. There are many other hypotheses under investigation that point to possible genetic, environmental, and infectious explanations for childhood leukemia, which have similar or stronger support in epidemiology studies (Ries et al., 1999; McNally and Parker, 2006; Belson et al., 2007; Rossig and Juergens, 2008; Eden, 2010).

Table 3. Relevant studies of childhood leukemia

Author	Year	Study Title
Bunch et al.	2014	Residential distance at birth from overhead high-voltage powerlines: childhood cancer risk in Britain 1962-2008.
Grellier et al.	2014	Potential health impacts of residential exposures to extremely low frequency magnetic fields in Europe
Jirik et al.	2012	Association between childhood leukaemia and exposure to power-frequency magnetic fields in middle Europe
Keegan et al.	2012	Case–control study of paternal occupation and childhood leukaemia in Great Britain, 1962–2006
Pedersen et al.	2014	Distance from residence to power line and risk of childhood leukemia: a population-based case-control study in Denmark
Schüz et al.	2012	Extremely low-frequency magnetic fields and survival from childhood acute lymphoblastic leukemia: an international follow-up study
Sermage-Faure et al.*	2013	Childhood leukaemia close to high-voltage power lines – the Geocap study, 2002–2007
Slusky et al.	2014	Potential role of selection bias in the association between childhood leukemia and residential magnetic fields exposure: a population-based assessment
Swanson	2013	Residential mobility of populations near UK power lines and implications for childhood leukaemia

Author	Year	Study Title
Swanson and Kheifets	2012	Could the geomagnetic field be an effect modifier for studies of power-frequency magnetic fields and childhood leukaemia?
Teepen and van Dijck	2012	Impact of high electromagnetic field levels on childhood leukemia incidence
Zhao et al.	2014	Magnetic fields exposure and childhood leukemia risk: a meta-analysis based on 11,699 cases and 13,194 controls
Ziegelberger et al.	2011	Review. Childhood leukemia: Risk factors and the need for an interdisciplinary research agenda
*Comments and Replies on Sermage-Faure et al.:		
Bonnet-Belfais et al.	2013	Comment: childhood leukaemia and power lines--the Geocap study: is proximity an appropriate MF exposure surrogate?
Magana Torres and Garcia	2013	Comment on 'Childhood leukaemia close to high-voltage power lines--the Geocap study, 2002-2007'--odds ratio and confidence interval.
Clavel and Hemon	2013	Reply: Comment on 'Childhood leukaemia close to high-voltage power lines--the Geocap study, 2002-2007'--odds ratio and confidence interval
Clavel et al.	2013	Reply: comment on 'Childhood leukaemia close to high-voltage power lines--the Geocap study, 2002-2007'--is proximity an appropriate MF exposure surrogate?

Childhood brain cancer

Compared to the research on magnetic fields and childhood leukemia, there have been fewer studies of childhood brain cancer. The data are less consistent and limited by even smaller numbers of exposed cases than studies of childhood leukemia. The WHO review recommended the following:

> As with childhood leukaemia, a pooled analysis of childhood brain cancer studies should be very informative and is therefore recommended. A pooled analysis of this kind can inexpensively provide a greater and improved insight into the existing data, including the possibility of selection bias and, if the studies are sufficiently homogeneous, can offer the best estimate of risk (WHO, 2007, p. 18).

Recent studies (2012-2014)

There has been one new publication that examined the potential relationship between residential proximity to transmission lines and childhood brain cancer. The previously described case-control epidemiologic study by Bunch et al. (2014) also included cases of brain cancer (n=11,968) and other solid tumors (n=21,985) among children in the United Kingdom between 1962 and 2008.

Assessment

The recent publication by Bunch et al. (2014) did not report an association between estimated magnetic-field exposure and brain tumors among children. This is in line with the previous assessment that the weight of the recent data does not support an association between magnetic-field exposures and the development of childhood brain cancer (Kheifets et al., 2010; SCENIHR, 2015). The recent data do not alter the classification of the epidemiologic data in this field as inadequate.

Table 4. Relevant studies of childhood brain cancer

Authors	Year	Study Title
Bunch et al.	2014	Residential distance at birth from overhead high-voltage powerlines: childhood cancer risk in Britain 1962-2008.

Breast cancer

The WHO reviewed studies of breast cancer and residential magnetic-field exposure, electric blanket usage, and occupational magnetic-field exposure. These studies did not report consistent associations between magnetic-field exposure and breast cancer. The WHO concluded that the recent body of research on this topic was less susceptible to bias compared with previous studies, and, as a result, it provided strong support to previous consensus statements that magnetic-field exposure does not influence the risk of breast cancer. Specifically, the WHO stated:

> Subsequent to the IARC monograph a number of reports have been published concerning the risk of female breast cancer in adults associated with ELF magnetic field exposure. These studies are larger than the previous ones and less susceptible to bias, and overall are negative. With these studies, the evidence for an association between ELF exposure and the risk of breast cancer is weakened considerably and does not support an association of this kind (WHO, 2007, p. 307).

The WHO recommended no specific research with respect to breast cancer and magnetic-field exposure.

Recent studies (2012-2014)

Researchers in the United Kingdom published a large case-control study that investigated risk of adult breast cancer, leukemia, brain tumors, and malignant melanoma, in relation to magnetic-field exposure and residential distance to high voltage power lines (Elliott et al., 2013). The study included incident cancer cases, including 29,202 female breast cancer cases, from England and Wales diagnosed between 1974 and 2008, and a total of over 79,000 controls between the age of 15 and 74 years. Location of power lines and residential addresses were identified based on data from geographical information systems. Magnetic-field exposure was calculated for each control address and for each case address for the year of and 5 years prior to diagnosis. Risk of female breast cancer showed no association with distance to power lines or with estimated magnetic fields. Following publication, the study received criticism regarding its exposure assessment, exposure categorization and the potential for confounding (de Vocht, 2013; Philips et al., 2013; Schüz, 2013).

Sorahan (2012) studied cancer incidence among more than 80,000 electricity generation and transmission workers in the United Kingdom between 1973 and 2008. Standardized registration rates were calculated among the workers compared to rates observed in the general population. No statistically significant increases were reported for breast cancer among either men or women. There was no trend for breast cancer incidence with year of hire, years of being employed, or years since leaving employment. The strengths of the study include its prospective nature and its large size. It is, however, limited in exposure assessment because risk was not calculated by magnetic-field exposure levels, and incidence rates were compared to an external reference group.

Koeman et al. (2014) investigated occupational exposure to ELF magnetic fields and cancer incidence in a cohort of about 120,000 men and women in the Netherlands Cohort study. The researchers used a case-cohort approach to analyze their data and identified 2,077 breast cancer cases among women and no breast cancer among men in the cohort. Exposure to ELF magnetic fields was assigned based on job title using a job-exposure matrix. Breast cancer showed no association with the level of estimated ELF magnetic-field exposure, or the length of employment, or cumulative exposure in the exposed jobs.

Li et al. (2013) conducted a nested case-cohort analysis of breast cancer incidence among more than 267,000 female textile workers in Shanghai. The researchers identified 1,687 incidence breast cancer cases in the cohort between 1989 and 2000 and compared their estimated exposure to 4,702 non-cases. Exposure was assessed based on complete work history and a job-exposure matrix specifically developed for the cohort. No association was observed between cumulative exposure and risk of breast cancer regardless of age, histological type, and whether lag period was used or not. An accompanying editorial opined that this well-designed study further adds to the already large pool of data not supporting an association between ELF EMF and breast cancer (Feychting, 2013). The editorial suggests that further studies in breast cancer "have little new knowledge to add," following the considerable improvement in study quality over time in breast cancer epidemiologic studies, and with the evidence being "consistently negative."

Meta-analyses for breast cancer were conducted by Chinese investigators for both female (Chen et al., 2013) and male breast cancers (Sun et al., 2013). The meta-analysis for female breast cancer included 23 case-control studies published between 1991 and 2007. Overall, the authors estimated a slight, but statistically significant association between breast cancer and ELF magnetic-field exposure (OR 1.07; 95% CI 1.02-1.013), which was slightly higher for estrogen receptor positive and premenopausal cancer (OR 1.11). The conclusion of the authors that ELF magnetic fields might be related to breast cancer is contrary to the conclusion of the WHO and other risk assessment panels, which may be due to their reliance on earlier and methodologically less advanced studies in the meta-analysis. Sun et al (2013) conducted a meta-analysis of male breast cancer including 7 case-control and 11 cohort studies. The combined analysis showed a statistically significant association between male breast cancer and exposure to ELF EMF (OR 1.32, 95% CI, 1.14-1.52). Methodological limitations, the small number of cases in the individual studies, and the potential for publication bias may contribute to the findings.

Assessment

The recent large case-control and cohort studies, which report no association with female breast cancer, add to growing support against a causal role for magnetic-field exposure, both in residential and occupational settings, in breast cancer development. A recent review by SCENIHR (2015) concluded that, overall, studies on "adult cancers show no consistent associations."

Table 5. Relevant studies of breast cancer

Authors	Year	Study
Chen et al.	2013	A meta-analysis on the relationship between exposure to ELF-EMFs and the risk of female breast cancer.
*Elliott et al.	2013	Adult cancers near high-voltage overhead power lines
Feytching	2013	Invited commentary: extremely low-frequency magnetic fields and breast cancer--now it is enough!
Koeman et al.	2014	Occupational extremely low-frequency magnetic field exposure and selected cancer outcomes in a prospective Dutch cohort
Li et al	2013	Occupational exposure to magnetic fields and breast cancer among women textile workers in Shanghai, China
Sorahan et al.	2012	Cancer incidence in UK electricity generation and transmission workers, 1973–2008
Sun et al.	2013	Electromagnetic field exposure and male breast cancer risk: a meta-analysis of 18 studies
*Comment and Replies on Elliot et al.		
Philips et al.	2013	Letter to the Editor: Adult cancers near high-voltage power lines
De Vocht	2013	Letter to the Editor: Adult cancers near high-voltage power lines
Schüz	2013	Commentary: power lines and cancer in adults: settling a long-standing debate?

Adult brain cancer

Brain cancer was studied along with leukemia in many of the occupational studies of EMF. The findings were inconsistent, and there was no pattern of stronger findings in studies with more advanced methods, although a small association could not be ruled out. The WHO classified the epidemiologic data on adult brain cancer as inadequate and recommended (1) updating the existing cohorts of occupationally-exposed individuals in Europe and (2) pooling the epidemiologic data on brain cancer and adult leukemia to confirm the absence of an association.

The WHO stated the following:

> In the case of adult brain cancer and leukaemia, the new studies published after the IARC monograph do not change the conclusion that the overall evidence for an association between ELF [EMF] and the risk of these disease remains inadequate (WHO 2007, p. 307).

Recent studies (2012-2014)

The Elliot et al. (2013) study of residential proximity and magnetic-field exposure from power lines, described above, also included 6,781 brain cancer cases. The risk of brain cancer showed no statistically significant increase with either distance or estimated magnetic-field levels in the study.

Sorahan (2012) also examined the incidence of brain cancer in his analyses in the cohort of electricity generation and transmission workers in the United Kingdom. He reported no increased risk for brain cancer among either men or women. No trend was reported for brain cancer with year of hire, years of employment, or years since employment in the study.

Koeman (2014) identified 160 male and 73 female cases of brain cancer in the Netherlands Cohort Study, described above. No statistically significant risk increase or trend was observed for cumulative ELF magnetic-field exposure either among men or women.

Turner et al. (2014) reported results from the INTEROCC study, which is an international case-control study of brain cancer and occupational exposure to ELF EMF. A total of 3,761 cases of brain cancer and 5,404 controls were included from Australia, Canada, France, Germany, New Zealand, the United Kingdom, and Israel between 2000 and 2004. Exposure was assessed based on individual job history and a job-exposure matrix. There was no association with lifetime cumulative exposure, average exposure, or maximum exposure for either glioma or meningioma. The authors, however, reported an association for both brain cancer types with exposure in the 1 to 4 year time-window prior to diagnosis. A statistical decrease in risk for glioma was also reported in the highest maximum exposure category.

Assessment

Recent studies did not report a consistent overall increase of brain cancer risk with either occupational or residential exposure to ELF EMF. While an association still cannot be ruled out *entirely* because of remaining deficiencies in exposure assessment methods, there is no strong evidence in support of a relationship between magnetic fields and brain cancer. The data remain inadequate as reported earlier (EHFRAN, 2012). As mentioned above, the most recent SCENIHR report (2015) states that, overall, studies on "adult cancers show no consistent associations."

Table 6. Relevant studies of adult brain cancer

Authors	Year	Study
Elliott et al.	2013	Adult cancers near high-voltage overhead power lines
Koeman et al.	2014	Occupational extremely low-frequency magnetic field exposure and selected cancer outcomes in a prospective Dutch cohort
Sorahan et al.	2012	Cancer incidence in UK electricity generation and transmission workers, 1973–2008
Turner et al	2014	Occupational exposure to extremely low frequency magnetic fields and brain tumour risks in the INTEROCC study

Adult leukemia and lymphoma

There is a vast amount of literature on adult leukemia and EMF, most of which is related to occupational exposures. Overall, the findings of these studies are inconsistent—with some studies reporting a positive association between measures of EMF and leukemia and other studies showing no association. No pattern has been identified whereby studies of higher quality or design are more likely to produce positive or negative associations. The WHO subsequently classified the epidemiologic evidence for adult leukemia as "inadequate." They recommended updating the existing occupationally-exposed cohorts in Europe and updating a meta-analysis on occupational magnetic-field exposure.

Recent studies (2012-2014)

Elliott et al (2013) included 7,823 cases of adult leukemia and reported no elevated risk or trend in association with distance or estimated magnetic-field exposure from high-voltage power lines in the United Kingdom. In the cohort of electricity power plant and transmission workers in the United Kingdom, Sorahan (2012) reported no increase in risk for leukemia either among men or women, and no increasing trend was observed with length of employment. Koeman et al. (2014) identified 761 and 467 hematopoietic malignancies among men and women, respectively, in the Netherlands Cohort Study. No increases in risk or trend were observed in association with cumulative exposure to ELF magnetic fields among either men or women.

Rodriguez-Garcia and Ramos (2012) reported inverse correlations between acute myeloid leukemia, acute lymphoblastic leukemia, and the distance to thermoelectric power plants and high-density power line networks in their study of hematologic cancers in a region of Spain from 2000 to 2005. This study, however, has severe limitations due to the use of aggregated data, rudimentary methods of exposure assessment, and the lack of an adequate comparison group.

Assessment

Recent studies did not provide strong evidence in support of an association. While the possibility that there is a relationship between adult lymphohematopoietic malignancies and magnetic-field exposure still cannot be entirely ruled out, because of the remaining deficiencies in study methods, the current database of studies provides inadequate evidence for an association (EFHRAN, 2012; SCENIHR, 2015).

Table 7. Relevant studies of adult leukemia/lymphoma

Authors	Year	Study
Elliott et al.	2013	Adult cancers near high-voltage overhead power lines
Koeman et al.	2014	Occupational extremely low-frequency magnetic field exposure and selected cancer outcomes in a prospective Dutch cohort
Rodriguez-Garcia et al.	2012	High incidence of acute leukemia in the proximity of some industrial facilities in El Bierzo, northwestern Spain
Sorahan	2012	Cancer incidence in UK electricity generation and transmission workers, 1973–2008

Reproductive/developmental effects

Over a decade ago, two studies received considerable attention because of a reported association between peak magnetic field exposure greater than approximately 16 mG and miscarriage: a prospective cohort study of women in early pregnancy (Li et al., 2002) and a nested case-control study of women who miscarried compared to their late-pregnancy counterparts (Lee et al., 2002).

These two studies improved on the existing body of literature because average exposure was assessed using 24-hour personal magnetic-field measurements (early studies on miscarriage were limited because they used surrogate measures of exposure, including visual display terminal use, electric blanket use, or wire code data). The Li et al. study was criticized by the NRPB *inter alia* because of the potential for selection bias, a low compliance rate, measurement of exposure after miscarriages, and the selection of exposure categories after inspection of the data (NRPB, 2002).

Following the publication of these two studies, however, a hypothesis was put forth that the observed association may be the result of behavioral differences between women with “healthy” pregnancies that went to term (less physically active) and women who miscarried (more physically active) (Savitz, 2002). It was proposed that physical activity is associated with an increased opportunity for peak magnetic-field exposures, and the nausea experienced in early, healthy pregnancies and the cumbersomeness of late, healthy pregnancies would reduce physical activity levels, thereby decreasing the opportunity for exposure to peak magnetic fields. Furthermore, nearly half of women who had miscarriages reported in the cohort by Li et al. (2002) had magnetic-field measurements taken after miscarriage occurred, when changes in physical activity may have already occurred, and all measurements in Lee et al. (2002) occurred post-miscarriage.

The scientific panels that have considered these two studies concluded that the possibility of this bias precludes making any conclusions about the effect of magnetic fields on miscarriage (NRPB, 2004; FPTRPC, 2005; WHO, 2007). The WHO concluded, "There is some evidence for increased risk of miscarriage associated with measured maternal magnetic-field exposure, but this evidence is inadequate" (WHO, 2007, p. 254) and recommended further epidemiologic research.

Recent studies (2012-2014)

Three epidemiologic studies investigated the relationship between ELF EMF exposure and miscarriage or stillbirth. A study in China (Wang et al., 2013), identified 413 pregnant women at 8 weeks of gestation between 2010 and 2012. The researchers measured magnetic-field levels at the front door and the alley in front of the participants' homes. No statistically significant association was seen with average exposure at the front door, but the authors reported an association with maximum magnetic-field values measured in the alleys in front of the homes. Magnetic-field levels measured at the front door are very poor predictors of home and personal exposure, thus the study provides fairly limited contribution to current knowledge.

A study from Iran (Shamsi Mahmoudabadi et al., 2013) reported results of a hospital-based case-control study that included 58 women with spontaneous abortion and 58 pregnant women. The measured magnetic-field levels were reported as statistically significantly higher among the cases than among controls. The study provides little weight to an overall assessment, however, due to limited information provided on subject recruitment, exposure assessment, type of metric used and potential confounders, and the small number of subjects.

A Canadian study (Auger et al., 2012) investigated the association between stillbirth and residential proximity to power lines. The authors identified over 500,000 births and 2,033 stillbirths in Québec and determined distance between postal code at birth address and the closest power line. No consistent association or trend was reported between stillbirth and residential distance. Reliance on distance to power lines and using the postal code for address information is a major limitation of the study's exposure assessment.

Two studies examined various birth outcomes in relation to ELF EMF exposure. A study from the United Kingdom investigated birth outcomes in relation to residential proximity to power lines during pregnancy between 2004 and 2008 in Northwest England (de Vocht et al., 2014). The researchers examined hospital records of over 140,000 births and distance to the nearest power lines were determined using geographical information systems. The authors reported moderately lower birth weight within 50 meters of power lines, but observed no statistically significant increase in risk of any adverse clinical birth outcomes (such as preterm birth, small for gestational age, or low birth weight). The limitations of the study include its reliance on distance for exposure assessment and the potential for confounding by socioeconomic status as also discussed by the authors. A study from Iran reported no association between ELF EMF and pregnancy and developmental outcomes, such as duration of pregnancy, birth weight and length, head circumference, and congenital malformations (Mahram and Ghazavi, 2013). The study, however, provided little information on subject selection and recruitment, thus it is difficult to assess its quality.

An Italian study reported that blood melatonin levels statistically significantly increased among 28 newborns 48 hours after being taken out from incubators with assumed elevated ELF EMF exposure, but not among 28 control newborns who were not in incubators (Bellieni et al., 2012). Neither the before nor the after values were statistically different from each other in the two groups (incubator vs. control), however, thus the clinical significance of the findings, if any, is unclear.

Assessment

The recent epidemiologic studies on pregnancy and reproductive outcomes provided little new insight in this research area and do not change the classification of the data from earlier assessments as inadequate (EFHRAN, 2012). The recent review by (SCENIHR, 2015) concluded that "recent results do not show an effect of ELF MF [magnetic field] exposure on reproductive function in humans."

Table 8. Relevant studies of reproductive and developmental effects

Authors	Year	Study
Auger et al.	2012	Stillbirth and residential proximity to extremely low frequency power transmission lines: a retrospective cohort study
Bellieni et al.	2012	Is newborn melatonin production influenced by magnetic fields produced by incubators?
de Vocht et al.	2014	Maternal residential proximity to sources of extremely low frequency electromagnetic fields and adverse birth outcomes in a UK cohort
Gye and Park	2012	Effect of electromagnetic field exposure on the reproductive system
Mahram and Ghazavi	2013	The effect of extremely low frequency electromagnetic fields on pregnancy and fetal growth, and development
Mortazavi et al.	2013	The study of the effects of ionizing and non-ionizing radiations on birth weight of newborns to exposed mothers
Shamsi Mahmoudabadi et al.	2013	Exposure to Extremely Low Frequency Electromagnetic Fields during Pregnancy and the Risk of Spontaneous Abortion: A Case-Control Study
Wang et al.	2013	Residential exposure to 50 Hz magnetic fields and the association with miscarriage risk: a 2-year prospective cohort study

Neurodegenerative diseases

Research into the possible effect of magnetic fields on the development of neurodegenerative diseases began in 1995, and the majority of research since then has focused on Alzheimer's disease and a specific type of motor neuron disease called amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease. Early studies on ALS, which had no obvious biases and were well conducted, reported an association between ALS mortality and estimated occupational magnetic-field exposure. The review panels, however, were hesitant to conclude that the associations provided strong support for a causal relationship. Rather, they felt that an alternative explanation (i.e., electric shocks received at work) may be the source of the observed association.

The majority of the more recent studies discussed by the WHO reported statistically significant associations between occupational magnetic-field exposure and mortality from Alzheimer's disease and ALS, although the design and methods of these studies were relatively weak (e.g., disease status was based on death certificate data, exposure was based on incomplete occupational information from census data, and there was no control for confounding factors). Furthermore, there was no biological data to support an association between magnetic fields and neurodegenerative disease. The WHO panel concluded that there is "inadequate" data in support of an association between magnetic fields and Alzheimer's disease or ALS. The panel recommended more research in this area using better methods; in particular, studies that enrolled incident Alzheimer's disease cases (rather than ascertaining cases from death certificates) and studies that estimated electrical shock history in ALS cases were recommended. Specifically, the WHO concluded, "When evaluated across all the studies, there is only very limited evidence of an association between estimated ELF exposure and [Alzheimer's] disease risk" (WHO, 2007, p. 194) and "overall, the evidence for an association between ELF exposure and ALS is considered inadequate" (WHO, 2007, p. 206).

Recent studies (2012-2014)

A population-based case-control study (Frei et al., 2013) examined the relationship between residential distance to power lines and neurodegenerative diseases covering the entire population of Denmark between 1994 and 2010. Distance from the nearest power line to the residential address for all newly-reported cases and matched controls were determined using geographical information systems. Overall, none of the investigated diseases, including Alzheimer disease and other types of dementia, ALS, Parkinson's disease, of multiple sclerosis was related to residential proximity to power lines. The inclusion of newly-diagnosed cases from hospital discharge records represents a significant methodological improvement over mortality studies. The study, however, was limited by the methods used for the exposure assessment.

Weak to no evidence of an association was presented in two recent meta-analyses of occupational exposure to ELF magnetic fields and neurodegenerative disease (Zhou et al., 2012; Vergara et al., 2013); hence, the authors concluded that potential within-study biases, evidence of publication bias, and uncertainties in the various exposure assessments greatly limit the ability to infer an association, if any, between occupational exposure to magnetic fields and neurodegenerative disease. In sum, these recent meta-analyses provide no convincing evidence of a relationship between ELF EMF and neurodegenerative disease.

Several recent studies addressed the issue of the potential role of electric shocks in the development of neurodegenerative and neurological diseases, but none of them presented convincing evidence for an association (Das et al., 2012; Grell et al., 2012; Vergara et al., 2013; van der Mark et al., 2014). It has been previously suggested that the weak and inconsistent association between ELF EMF and ALS might be explained by electric shocks.

Assessment

The recent studies continue to be limited by uncertainties about the estimates of magnetic-field exposure. Further research in this area will be needed to address the limitations of research to date on neurodegenerative disease (SSM, 2010; EHFRAN, 2012).

The most recent SCENIHR report (2015) concluded that newly published studies "do not provide convincing evidence of an increased risk of neurodegenerative diseases or dementia related to ELF-EMF exposure."

Table 9. Relevant studies of neurodegenerative disease

Authors	Year	Study
Das et al.	2012	Familial, environmental, and occupational risk factors in development of amyotrophic lateral sclerosis
Frei et al.	2013	Residential distance to high-voltage power lines and risk of neurodegenerative diseases: a Danish population-based case-control study
Grell et al.	2012	Risk of neurological diseases among survivors of electric shocks: a nationwide cohort study, Denmark, 1968-2008
Van der Mark et al.	2014	Extremely low-frequency magnetic field exposure, electrical shocks and risk of Parkinson's disease
Vergara et al.	2013	Occupational exposure to extremely low-frequency magnetic fields and neurodegenerative disease: A meta-analysis
Zhou et al.	2012	Association between extremely low-frequency electromagnetic fields occupations and amyotrophic lateral sclerosis: A meta-analysis

Cardiovascular disease

It has been hypothesized that magnetic-field exposure reduces heart rate variability, which in turn is a marker of increased susceptibility for AMI. In a large cohort of utility workers, Savitz et al. (1999) reported an increased risk of arrhythmia-related deaths and deaths due to AMI. Previous and subsequent studies did not report a statistically significant increase in cardiovascular disease (CVD) mortality or incidence related to occupational magnetic-field exposure (WHO, 2007). The WHO concluded, "Overall, the evidence does not support an association between ELF exposure and cardiovascular disease." (WHO, 2007, p. 220)

Recent studies (2012-2014)

One study from the Netherlands evaluated the relationship between occupational exposure to ELF EMF and cardiovascular disease mortality (Koeman et al., 2013). The study identified more than 8,000 cardiovascular deaths among the more than 120,000 men and women in the Netherlands Cohort Study during a 10-year period. Occupational exposure was determined by linking occupational histories to an ELF-magnetic-field job-exposure matrix. The authors reported no association between cumulative occupational ELF-magnetic-field exposure and cardiovascular mortality or death due to any of the subtypes of cardiovascular disease. The authors concluded that their results add "to the combined evidence that exposure to ELF-MF [magnetic fields] does not increase the risk of death from CVD."

Assessment

The recent study reported no association between ELF magnetic fields and CVD, thus confirming earlier conclusions about the lack of an association between magnetic fields and CVD.

Table 10. Relevant studies of cardiovascular disease

Authors	Year	Study Title
Koeman et al.	2013	Occupational exposure to extremely low-frequency magnetic fields and cardiovascular disease mortality in a prospective cohort study

In vivo studies related to carcinogenesis

In the field of ELF EMF research, a number of research laboratories have exposed rodents, including those with a particular genetic susceptibility to cancer, to high levels of magnetic fields over the course of the animals' lifetime and performed tissue evaluations to assess the incidence of cancer in many organs. In these studies, magnetic-field exposure has been administered alone (to test for the ability of magnetic fields to act as a complete carcinogen), in combination with a known carcinogen (to test for a promotional or co-carcinogenetic effect), or in combination with a known carcinogen and a known promoter (to test for a co-promotional effect).

The WHO review described four large-scale, long-term studies of rodents exposed to magnetic fields over the course of their lifetime that did not report increases in any type of cancer (Mandeville et al., 1997; Yasui et al., 1997; McCormick et al., 1999; Boorman et al., 1999a; Boorman et al., 1999b). No directly relevant animal model for childhood ALL existed at the time of the WHO report. Some animals, however, develop a type of lymphoma similar to childhood ALL and studies exposing predisposed transgenic mice to ELF magnetic fields did not report an increased incidence of this lymphoma type (Harris et al., 1998; McCormick et al., 1999; Sommer and Lerchl, 2004).

Studies investigating whether exposure to magnetic fields can promote cancer or act as a co-carcinogen used known cancer-causing agents, such as ionizing radiation, ultraviolet radiation, or other chemicals. No effects were observed for studies on chemically-induced preneoplastic liver lesions, leukemia or lymphoma, skin tumors, or brain tumors; however, the incidence of 7,12-dimethylbenz[a]anthracene (DMBA)-induced mammary tumors was increased with magnetic-field exposure in a series of experiments in Germany (Löscher et al., 1993; Mevissen et al., 1993a, 1993b; Löscher et al., 1994; Baum et al., 1995; Löscher and Mevissen, 1995; Mevissen et al., 1996a; Mevissen et al., 1996b; Löscher et al., 1997; Mandeville et al., 1997; Mevissen et al., 1998), suggesting that magnetic-field exposure increased the proliferation of mammary tumor cells. These results were not replicated in a subsequent series of experiments in a laboratory in the United States (Anderson et al., 1999; Boorman et al., 1999a; Boorman et al., 1999b), possibly due to differences in experimental protocol and the species strain. In Fedrowitz et al. (2004), exposure enhanced mammary tumor development in one sub-strain (Fischer 344 rats), but not in another sub-strain that was obtained from the same breeder, which argues against a promotional effect of magnetic fields.[16]

Some studies have reported an increase in genotoxic effects among exposed animals (e.g., DNA strand breaks in the brains of mice at very high field levels (1 mT) [Lai and Singh, 2004]), although the results have not been replicated.

In summary, the WHO concluded the following with respect to *in vivo* research: "There is no evidence that ELF [EMF] exposure alone causes tumours. The evidence that ELF field exposure can enhance tumour development in combination with carcinogens is inadequate" (WHO, 2007, p. 322). Recommendations for future research included the development of a rodent model for childhood ALL and the continued investigation of whether magnetic fields can act as a promoter or co-carcinogen.

Recent studies (2012-2014)

Eighteen studies indexed by PubMed since Exponent's 2012 update have investigated the effects of electric- and magnetic-field exposure in animals on processes related to carcinogenesis (Table 11). As noted above, none of the past large-scale, long-term bioassays of magnetic-field exposures have reported that lifetime exposure to magnetic fields do not initiate or promote tumor development in rodents. Some other studies in which DMBA-initiated mammary tumors were increased in a particular strain of rats exposed to magnetic fields in a single laboratory. To further investigate this phenomenon, Fedrowitz and Löscher (2012) evaluated gene expression in pooled samples of mammary tissue from both Fischer 344 rats (F344; magnetic-field susceptible)[17] and Lewis rats (magnetic-field insensitive) following 2 weeks of continuous exposure to 1,000 mG, 50-Hz magnetic fields. Control rats of both strains were sham exposed and analyses were conducted in a blinded manner. Based on a 2.5-fold change in gene expression as the cut-off for establishing an exposure-related response, only 22 of 31,100 gene transcripts were found to be altered with magnetic-field exposure in the two rat strains combined. Genes showing the greatest change in expression in response to magnetic-field exposure in F344 rats (with no change in gene expression observed in Lewis rats) were α-amylase (a 832-fold decrease), parotid secretory protein (a 662-fold decrease), and carbonic anhydrase 6 (a 39-fold decrease). To follow-up on these findings, Fedrowitz et al. (2012) examined α-amylase activity in mammary tissues collected from the two rat strains in previous experiments. In initial experiments using tissues collected in 2005 through 2006, magnetic-field exposure was associated with increased α-amylase activity in cranial mammary tissues, but not caudal mammary tissues, from both F344 and Lewis rats. Thus, the response did not appear to correlate with the observed rat strain susceptibility to magnetic-field exposure. In later experiments using tissues collected in 2007 through 2008, α-amylase activity in the cranial tissues was unaffected by magnetic-field exposure, but increased in the caudal tissues of F344 rats (and not the tissues of Lewis rats) in response to magnetic-field treatment. Additional experiments looked at α-

[16] The WHO concluded with respect to the German studies of mammary carcinogenesis, "Inconsistent results were obtained that may be due in whole or in part to differences in experimental protocols, such as the use of specific substrains" (WHO 2007, p. 321).

amylase protein expression and its correlation with tissue differentiation following treatment with diethylstilbestrol. Overall, the findings of this study are contradictory, making interpretation difficult regarding the potential role of α-amylase expression in the observed sensitivity of F344 rats to magnetic-field exposure.

Another study investigated the therapeutic potential of high magnetic-field exposures in the treatment of tumors. El-Bialy and Rageh (2013) injected female mice with Ehrlich ascites carcinoma cells, then treated them with 3 mg/kg cisplatin on days 1, 4, and 7, or exposed them to 100,000 mG, 50-Hz magnetic fields for 14 days (1 hour per day), or both. A control group was saline-treated, but not sham exposed to magnetic fields, and analyses were not reported to have been conducted in a blinded manner. Both magnetic-field exposure and cisplatin treatment, alone or in combination, were associated with reduced tumor volume; the strongest response was observed with the combination treatment. This response appeared to be associated with reduced cell proliferation, but also increased DNA damage (as assessed using the Comet and micronucleus assays). These results suggest that magnetic-field exposure may have therapeutic applications in the treatment of tumors; however, because the field strength was relatively high, it is possible that the observed response was due to an induced electric field.

Two recent studies examined the genotoxic potential of magnetic-field exposures. Miyakoshi et al. (2012) continuously exposed 3-day old rats to 100,000 mG, 50-Hz magnetic fields for 72 hours, treated them with 5 or 10 mg/kg bleomycin, or both; control animals were sham exposed (with the exposure system turned off). Brain astrocytes were then examined in culture for the presence of micronuclei. In other experiments, the animals were treated as just described, but also administered tempol, an antioxidant. Magnetic-field exposure alone or in combination with 5 mg/kg bleomycin appeared to have no effect on micronuclei formation, but was reported to increase the frequency of micronuclei resulting from co-treatment with 10 mg/kg bleomycin. Tempol co-exposure was reported to reduce micronuclei formation, suggesting a role for activated oxygen species in their formation. In a study by Villarini et al. (2013), male mice were exposed to 1,000 to 20,000 mG, 50-Hz for 7 days (15 hours per day), then sacrificed immediately after exposure or 24 hours later. The striatum, hippocampus and cerebellum were evaluated for DNA damage using the Comet assay. Control mice were sham-exposed (with the exposure system turned off), mice exposed to whole-body X-irradiation served as DNA damage positive controls, and the Comet assay data were evaluated in a blinded manner. Mice exposed to 10,000 or 20,000 mG, but not lower strength magnetic fields, showed evidence of DNA fragmentation in the brain tissues when sacrificed immediately following exposure. By 24 hours post-exposure, however, the levels of DNA fragmentation were back to baseline, indicating either that any associated DNA damage was reversible or the fragmentation was an indicator of apoptosis (as observed in Focke et al.. 2010), which disappeared as the apoptotic cells were removed during the 24-hour recovery period. In other investigations in this same study, magnetic field exposures had no effect on the expression of heat shock proteins.[18]

Oxidative stress is a condition in which oxygen free radical levels in the body are elevated and is one mechanism by which DNA damage, as well as other forms of cellular damage, may occur. Numerous recent *in vivo* studies have evaluated whether magnetic-field exposure may be

[18] The WHO report described the results of *in vitro* studies on the expression of heat shock genes as “inconsistent or inconclusive” (WHO, 2007, p. 347).

associated with oxidative stress, with mixed results. The primary focus for many of these studies was the potential role of oxidative stress in disease processes other than cancer, including neurodegenerative disorders and reproduction. Nonetheless, the findings related to oxidative stress are also relevant to understanding the potential for inducing cancer development; results from these studies related to other assessments (e.g., learning and memory behavioral assays) are not relevant to cancer, and thus, not discussed here.

Cui et al. (2012) exposed male mice (n=24/group) to 1,000 or 10,000 mG, 50-Hz for 4 hours per day for 12 weeks, after which the expression of oxidative stress markers was evaluated in the hippocampus and striatum. Control mice were sham-exposed. Although exposure to 1,000 mG was not reported to have produced any differences from control mice, 10,000 mG increased levels of malondialdehyde (MDA), a marker of lipid peroxidation, and reduced levels of the anti-oxidant enzymes catalase (CAT) and glutathione peroxidase (GSH-Px). The total anti-oxidant capacity (TAC) of these tissues was also reported to be reduced. In a similar study, Deng et al. (2013) exposed male mice (n=15/group) to 20,000 mG, 50-Hz for 4 hours per day (6 days per week) for 8 weeks. Other groups of mice were treated with aluminum or both aluminum and magnetic fields; control mice were not reported to have been sham-exposed. Following magnetic-field exposure, levels of the anti-oxidant enzyme superoxide dismutase (SOD) were reduced and MDA levels increased in both brain tissue and serum.

Duan et al. (2013) examined the expression of oxidative stress markers in the hippocampus and serum of male mice (n=10/group) continuously exposed to a higher intensity magnetic field of 80,000 mG, 50-Hz for 28 days. Control mice were reported to have been sham-exposed. Additional groups of mice were co-exposed to lotus seedpod procyanids to evaluate their anti-oxidant potential; only the findings associated with magnetic-field exposure alone are discussed here. As in the above studies, MDA levels were increased and antioxidant enzymes (SOD, CAT, and GSH-Px) were reduced with exposure. Nitric oxide (NO), an important intracellular messenger molecule and free radical compound, and NO synthase were also increased with treatment. It is interesting to note that the magnetic-field-exposed animals also weighed approximately 10 grams less than controls by the end of study.

Using the rat (n=6/group), Manikonda et al. (2014) examined the effects of 90 days continuous exposure to 500 or 1,000 mG, 50-Hz on markers of oxidative stress in the hippocampus, cerebellum, and cortex. Controls were sham-exposed. Results were similar across tissues, but the cortex was a bit less responsive than the other two tissues. No significant changes were observed at 500 mG. At 1,000 mG, reactive oxygen species were increased and GSH levels reduced. In contrast with the other studies described here, however, SOD and GSH-Px levels were increased. It was also observed that the animals in both magnetic-field-exposed groups were more physically active than controls; how this increased activity may have contributed to the observed alterations, however, is not known.

To examine the possible acute effects of magnetic-field exposure, Martínez-Sámano et al. (2012) exposed rats (n=8/group) that were either restrained or unrestrained to a 24,000 mG, 60-Hz magnetic field for 2 hours only. Control animals were sham-exposed (with the exposure system turned off), but analyses were not reported to have been conducted in a blinded manner. None of the examined markers of oxidative stress were affected by magnetic-field exposure in the liver. Kidney and heart tissues showed decreases in glutathione (GSH) levels; plasma and brain exhibited reduced SOD activity. CAT enzymes were also reduced and lipid peroxidation increased in the brain following magnetic-field exposure. No effects on brain NO, lipid content or plasma corticosterone levels were observed. In another study, (Akdag et al., 2013a) examined the effects of 1,000 and 5,000 mG, 50-Hz exposure for 2 hours per day over 10 months on the rat brain. Control rats were sham-exposed (with the magnetic-field generator turned off) and investigators were blinded as to the exposure status of the animals. Exposure to both 1,000 and 5,000 mG magnetic fields (n=10/group) was associated with increased levels of MDA and protein carbonyl, an oxidative product. In another study by the same group of investigators and using the same exposure regimen (Akdag et al., 2013b), markers of oxidative stress were unaffected by magnetic-field exposure in the testes; these markers included MDA, myeloperoxidase, CAT, TAC, total oxidant status (TOS), and the oxidative stress index (OSI). The higher exposure of 5,000 mG, however, was associated with increased levels of apoptosis compared to controls. Finally, Kiray et al. (2013) exposed rats (n=14/group) to a 30,000 mG, 50-Hz magnetic field 4 hours per day for 2 months. From the study report, it is not clear if control rats were sham-exposed and blinded analyses were not reported. Lipid peroxidation was reported to be increased and levels of anti-oxidative enzymes (SOD and GSH-Px) decreased in the heart. Markers of apoptosis (programmed cell death) were increased and morphological changes in the heart were also observed.

One study looked at the effects of electric-field exposures on antioxidant status in the brain and retina of rats (Akpinar et al., 2012). Rats (n=10/group) were exposed to either 12 kV/m or 18 kV/m for 1 hour per day for 14 days. The magnetic fields associated with these exposures were not reported. From the study report, it is not clear if controls were sham exposed or if blinded analyses were conducted. Both electric-field strengths were associated with increased lipid peroxidation in the brain and retina of exposed rats. TAS levels were reduced and TOS and OSI levels increased in both tissues; these three markers, however, are interrelated and likely represent separate measurements of the same phenomenon.

Overall, it is hard to draw any firm conclusions from these studies of oxidative stress markers because the numbers of animals per group were generally low, the exposure parameters and oxidative stress markers examined varied across the studies, negative controls were not always sham-exposed, positive controls were not implemented, and few of the analyses were reported to have been conducted in a blinded manner. Although markers of oxidative stress were generally increased with higher rather than lower magnetic-field exposures, it is not known if this effect is reversible or even biologically relevant. Independent replication of findings in studies with greater sample sizes and blinded analyses is needed.

The immune system is thought to play an important role in the immunosurveillance against cancer cells. Further, ALL, one of the cancers of concern for EMF exposures in children, arises in cells of the immune system. Thus, there is an interest in the potential effects of EMF exposures on immune function. To address this, Salehi et al. (2013) examined the effects of long-term magnetic-field exposure on the expression of various cytokines (including certain interleukins and interferon-γ [IFN-γ]), which are important factors in regulating immune function. Male rats were exposed to a 100 mG, 50-Hz magnetic field for 2 hours per day for 3 months. Control rats were sham exposed (with the exposure system turned off), but analyses were not reported to have been conducted in a blinded manner. No differences in body weight, or weights of the spleen and thymus (two important immune organs) were noted between the two groups. Serum concentrations of interleukin (IL)-12 were reduced with exposure, but levels of IFN-γ, IL-4 and IL-6 were unaffected. Spleen and blood cells were also collected from the animals after exposure to measure *in vitro* cytokine production. IL-6 production, but not production of the other cytokines, was increased in both cell types in response to phytohemagglutinin stimulation. In another study, Selmaoui et al. (2011) examined the effects of both continuous and intermittent exposure to a 100 mG, 50-Hz magnetic field on interleukins in human subjects. The control subjects were sham exposed, but in a separate room from that of the exposed group. In the intermittent condition, the exposure apparatus was 1 hour 'on' and 1 hour 'off', with the magnetic field switched on and off over a 15-second cycle during the 'on' operation. No exposure-related changes were observed with continuous exposure. In the intermittent condition, IL-6 expression was increased while the expression of four other interleukins (IL-1β, IL-1RA, IL-2 and IL-2R) was unaffected. The study authors cautioned that further study was required before any firm conclusions could be drawn from these findings.

A well-designed double-blind study (Kirschenlohr et al., 2012) examined gene expression in the white blood cells of 17 pairs of human subjects following exposure to a 620 mG, 50-Hz magnetic field on four different days (2 hours per day) over 2 weeks. On each exposure day, one member of each pair was exposed to the magnetic field and the other either exposed to sham conditions (with the current passing through the two coils of the exposure apparatus in opposing directions so that the magnetic field was cancelled, but the total current remained the same) or not exposed. On the next day, the exposures were reversed (the previously exposed subject was sham exposed or not exposed, and vice-versa). Blood samples were collected just prior to and following exposures, as well as at multiple times throughout the exposure period. Gene expression in one set of the collected blood samples (collected in week 1) was determined via microarray analysis with an emphasis on genes previously reported to respond to EMF exposure (i.e., immediate early genes involved in stress, inflammatory, and proliferative and apoptotic responses). The samples collected just prior to exposure were used as reference samples. Any indications of a possible positive finding were verified using the second set of collected blood samples. Based on their analyses, the study investigators reported that no genes showed a consistent response to magnetic-field exposure.

In a similarly well-conducted study, Kabacik et al. (2013) looked for changes in the expression of genes in the bone marrow of juvenile mice exposed to a 1,000 mG, 50-Hz magnetic field for 2 hours. The premise for conducting this research was that many types of leukemia are derived from cells in the bone marrow; thus, changes in gene expression in the bone marrow may relate to the development of these cancers. Control mice were sham-exposed and the experiment repeated in multiple groups of exposed and unexposed mice. In order to confirm consistent changes with exposure, gene expression in these replicate samples was analyzed in a blinded manner using multiple methods and in different laboratories. Again, no consistent changes in gene expression in response to magnetic-field exposure were found.

Assessment

As previously noted, no new animal bioassays of long-term magnetic-field exposure or of ELF EMF as a possible carcinogen or co-carcinogen have been conducted since the last update. Rather, various shorter-term, mechanistic studies have been conducted to investigate potential mechanisms related to carcinogenesis, including genotoxicity, oxidative stress, alterations in gene expression, and immune functional changes. Many of these studies suffer from various methodological deficiencies, including small samples sizes, the absence of sham-exposure treatment groups, and analyses that were not conducted in a blinded manner. Further, consistency across the body of studies is commonly lacking, with some studies reporting effects and other studies showing no change. These studies do not change the WHO conclusion that the overall evidence from *in vivo* studies does not support a role of EMF exposures in direct genotoxic effects; however, the potential for non-genotoxic effects remains inconclusive. Two particularly well-conducted studies evaluated potential differences in gene expression resulting from magnetic-field exposure. These studies employed sham exposures, replicate samples, and blinded analyses using multiple experimental methods of measuring gene expression in multiple laboratories; they also took into consideration the potential statistical power of the studies. Neither of these studies reported consistent changes in gene expression due to magnetic-field exposure. Another study looked at the possible anti-carcinogenic therapeutic potential associated with high magnetic field strengths, an area for which more research is still warranted to address the influence of potential confounding variables on observed outcomes. Overall, the *in vivo* studies published since the last update do not alter the previous conclusion that there is inadequate evidence of carcinogenicity due to ELF EMF exposure.

Table 11. Relevant *in vivo* studies related to carcinogenesis.

Authors	Year	Study
Akdag et al.	2013a	Do 100- and 500-μT ELF magnetic fields alter beta-amyloid protein, protein carbonyl and malondialdehyde in rat brains?
Akdag et al.	2013b	Can safe and long-term exposure to extremely low frequency (50 Hz) magnetic fields affect apoptosis, reproduction, and oxidative stress?
Akpinar et al.	2012	The effect of different strengths of extremely low-frequency electric fields on antioxidant status, lipid peroxidation, and visual evoked potentials
Cui et al.	2012	Deficits in water maze performance and oxidative stress in the hippocampus and striatum induced by extremely low frequency magnetic field exposure
Deng et al.	2013	Effects of aluminum and extremely low frequency electromagnetic radiation on oxidative stress and memory in brain of mice
Duan et al.	2013	The preventative effect of lotus seedpod procyanidins on cognitive impairment and oxidative damage induced by extremely low frequency electromagnetic field exposure
El-Bialy and Rageh	2013	Extremely low-frequency magnetic field enhances the therapeutic efficacy of low-dose cisplatin in the treatment of Ehrlich carcinoma
Fedrowitz and Löscher	2012	Gene expression in the mammary gland tissue of female Fischer 344 and Lewis rats after magnetic field exposure (50 Hz, 100 μT) for 2 weeks
Fedrowitz et al.	2012	Effects of 50 Hz magnetic field exposure on the stress marker α-amylase in the rat mammary gland
Kabacik et al.	2013	Investigation of transcriptional responses of juvenile mouse bone marrow to power frequency magnetic fields
Kiray et al.	2012	The effects of exposure to electromagnetic field on rat myocardium
Kirschenlohr et al.	2012	Gene expression profiles in white blood cells of volunteers exposed to a 50 Hz electromagnetic field
Manikonda et al.	2014	Extremely low frequency magnetic fields induce oxidative stress in rat brain
Martínez-Sámano et al.	2012	Effect of acute extremely low frequency electromagnetic field exposure on the antioxidant status and lipid levels in rat brain
Miyakoshi et al.	2012	Tempol suppresses micronuclei formation in astrocytes of newborn rats exposed to 50-Hz, 10-mT electromagnetic fields under bleomycin administration
Salehi et al.	2012	Exposure of rats to extremely low-frequency electromagnetic fields (ELF-EMF) alters cytokines production
Selmaoui et al.	2011	Acute exposure to 50-Hz magnetic fields increases interleukin-6 in young healthy men
Villarini et al.	2013	Brain hsp70 expression and DNA damage in mice exposed to extremely low frequency magnetic fields: Adose-response study

7 Reviews by Scientific Organizations

Two national and international scientific organizations have published a report with regard to the possible health effects of ELF EMF since 2012 (SCENIHR, 2015[19]; SSM, 2013). Although none of these documents represents a cumulative weight-of-evidence review of the caliber of the WHO review published in June 2007, their conclusions are of relevance. In general, the conclusions of these reviews are consistent with the scientific consensus articulated in Sections 5 and 6.

The WHO and other scientific organizations have not found any *consistent* associations with regard to ELF EMF exposure and any type of cancer or disease, except childhood leukemia, nor have they concluded that there is a cause-and-effect link with any health effect, including childhood leukemia (WHO, 2007; SCENIHR, 2009; EFHRAN, 2010; ICNIRP, 2010; SSM, 2010; EFHRAN, 2012).

In summary, over the past decades, reviews published by scientific organizations using weight-of-evidence methods have concluded that the cumulative body of research to date does not support the hypothesis that ELF EMF causes any long-term adverse health effects at the levels we encounter in our everyday environments. An evaluation of current research does not point to better quality or stronger evidence that would change these assessments.

[19] Following the completion of the current report, a Scientific Committee (SCENIHR) commissioned by the European Union updated its previous review on EMF that included reviews of health-related research on ELF EMF fields (SCENIHR, 2013). For completeness we updated the report to reference the SCENIHR review issued in its final form in March 2015. The conclusions of the SCENIHR review are consistent with those of the NIEHS and WHO reviews mentioned above. The European report did not conclude that the available scientific evidence confirms a causal link between any adverse health effects (including both cancer and non-cancer health outcomes) and EMF exposure. With respect to childhood leukemia epidemiologic results, the review concludes that: *"…no mechanisms have been identified and no support is existing from experimental studies that could explain these findings, which, together with shortcomings of the epidemiological studies prevent a causal interpretation"* **(http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_041.pdf).**

8 Summary

A number of epidemiology and *in vivo* studies have been published on EMF and health since Exponent's 2012 update. The weak statistical association between high, average magnetic fields and childhood leukemia remains largely unexplained and unsupported by the experimental data. The recent *in vivo* studies confirm the lack of experimental data supporting a leukemogenic risk associated with magnetic-field exposure.

Overall, the current body of research supports the conclusion that there is no association between magnetic fields and adult cancer or cardiovascular disease, although future research is needed that improves upon exposure estimations. Recent literature does not confirm an earlier suggestion that there is an association between magnetic fields and Alzheimer's disease.

In conclusion, no recent studies provide evidence to alter the conclusion that the scientific evidence does not confirm that EMF exposure is the cause of cancer or any other disease process at the levels we encounter in our everyday environment.

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