Appendix AF

Current Status of Research on Extremely Low Frequency Electric and Magnetic Field and Health, Merrimack Valley Reliability Project, April 27, 2015

Health Sciences Practice

Exponent®

Current Status of Research on Extremely Low Frequency Electric and Magnetic Fields and Health

Merrimack Valley Reliability Project

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Merrimack Valley Reliability Project

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Acronyms and Abbreviations

AC	Alternating current
ALL	Acute lymphoblastic leukemia
AMI	Acute myocardial infarction
CAT	Catalase
CI	Confidence interval
DMBA	Dimethylbenz[a]anthracene
EHC	Environmental Health Criteria
ELF	Extremely low frequency
EMF	Electric and magnetic fields (or electromagnetic fields)
G	Gauss
GSH	Glutathione
GSH-Px	Glutathione peroxidase
GHz	Gigahertz
HCN	Health Council of the Netherlands
Hz	Hertz
IARC	International Agency for Research on Cancer
ICES	International Committee on Electromagnetic Safety
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
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 antioxidant capacity
TOS	Total oxidant status
TWA	Time weighted average
V/m	Volts per meter
WHO	World Health Organization

Limitations

At the request of Public Service of New Hampshire, 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.[1]

[1] The report was prepared on January 13, 2015; however, in March 2015, the European Commission's Scientific Committee on Emerging and Newly Identified Health Risks released its final "Opinion on Potential health effects of exposure to electromagnetic fields (EMF)," thus, the report has been updated to reference this document.

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 New Hampshire Public Utilities Commission at the request of Public Service of New Hampshire as an appendix to its Application for the Merrimack Valley Reliability Project.

Section 1 introduces the topic of this report, health research on ELF EMF. 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 2 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 electricity in biological processes (i.e., the role of electrical potentials across cell membranes and current flows between cells in our bodies). Over the past 35 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, compared to healthy children, 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 entirety of the relevant 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. Such reviews are particularly helpful to policy makers and the general public because they are prepared for a public health agency by scientists representing the various disciplines required to understand the topic at hand using validated scientific standards and systematic methods.

The WHO report is one of the most recent comprehensive health agency reviews that provide guidance to stakeholders and policymakers. The relevant scientific literature published since the WHO report until July 2012 has been systematically summarized in in reports submitted to state agencies on behalf of Northeast Utilities for previous projects.[2]

In a health risk assessment of any exposure, it is essential to consider the type and strength of relevant 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. These studies include those using different methods to understand possible health risks. Epidemiologic studies conducted in human populations and *in vivo* (experimental whole animals) studies play the primary role in human health risk assessments. Secondary information is provided by *in vitro* experimental studies, conducted in tissues and cells, which may contribute to our better understanding of potential biophysical mechanisms.

Section 3 of this report provides a summary of the methods used to conduct a health risk assessment. Section 4 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 relevant epidemiology studies in these areas of research and *in vivo* studies relevant for carcinogenicity published between August 2012 and November 2014 (Section 5).[3]

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2 Exponent, Inc. "Current Status of Research on Extremely Low Frequency Electric and Magnetic Fields and Health: Interstate Reliability Project, June 10, 2011" and Exponent, Inc. "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" (Connecticut Siting Council Dockets No. 424 and 435).

3 In March 2015, the Scientific Committee on Emerging and Newly Identified Health Risks commissioned by the European Union updated its previous review on EMF that included reviews of ELF EMF fields. They 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, which is consistent with the conclusions of the WHO review mentioned above.

1 Introduction

Extensive scientific research on extremely low frequency (ELF) electric and magnetic fields (EMF) and health has been conducted over the past 35 years. The available body of scientific evidence has been periodically and systematically reviewed, using the weight-of-evidence scientific process, by a number of expert panels on behalf of national and international scientific, health, and government organizations. One of the most comprehensive reviews was conducted by the World Health Organization (WHO) in 2007. 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, 2007a, 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, 2007a, p. 355).

These conclusions are consistent with conclusions of 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 National Radiological Protection Board of Great Britain (NRPB) in 2004, and the Health Council of the Netherlands in 2005. The WHO in its review also concluded that scientifically based exposure limits, such as the limits established by International Commission on Non-Ionizing Radiation Protection (ICNIRP) and the International Committee on Electromagnetic Safety (ICES), protect the public from all established health effects. With respect to precautionary measures, the WHO states that given the weakness of the evidence and the very limited public health impact, if any, the cost of any measures to reduce ELF EMF exposure should be very low.

The subsequent relevant scientific literature published until July 2012 was systematically reviewed in previous documents submitted by Northeast Utilities with previous applications.[4]

[4] Exponent, Inc. "Current Status of Research on Extremely Low Frequency Electric and Magnetic Fields and Health: Interstate Reliability Project, June 10, 2011" and Exponent, Inc. "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" (Connecticut Siting Council Dockets No. 424 and 435).

Public Service of New Hampshire requested that Exponent prepare a document that provides an update to these earlier summaries of the relevant literature.

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 2012 and November 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 November 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 that the research does not support the conclusion that ELF EMF at the levels we encounter in our everyday environment is a cause of cancer or any other disease. As the WHO website currently states "[b]ased on a recent in-depth review of the scientific literature, the WHO concluded that current evidence does not confirm the existence of any health consequences from exposure to low level electromagnetic fields." The WHO website continues to state that "[w]ith more and more research data available, it has become increasingly unlikely that exposure to electromagnetic fields constitutes a serious health hazard."[5]

There are no national guidelines or standards in the United States to regulate ELF EMF. The WHO recommends adherence to ICNIRP standards or those developed by ICES for the prevention of acute short-term 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 recommendation is consistent with policies adopted by some states in the United States (e.g., California and Connecticut).

[5] http://www.who.int/peh-emf/about/WhatisEMF/en/index1.html

2 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. ELF EMF from these AC sources is often referred to as power-frequency 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 milligauss (mG), where 1 G = 1,000 mG.[6] 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 distribution 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 are surrounded by these fields (Figure 1). While EMF levels decrease with distance from the source, any home, school, or office will have

[6] 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.

a background EMF level as a result of the combined effect of the numerous EMF sources present in these locations.

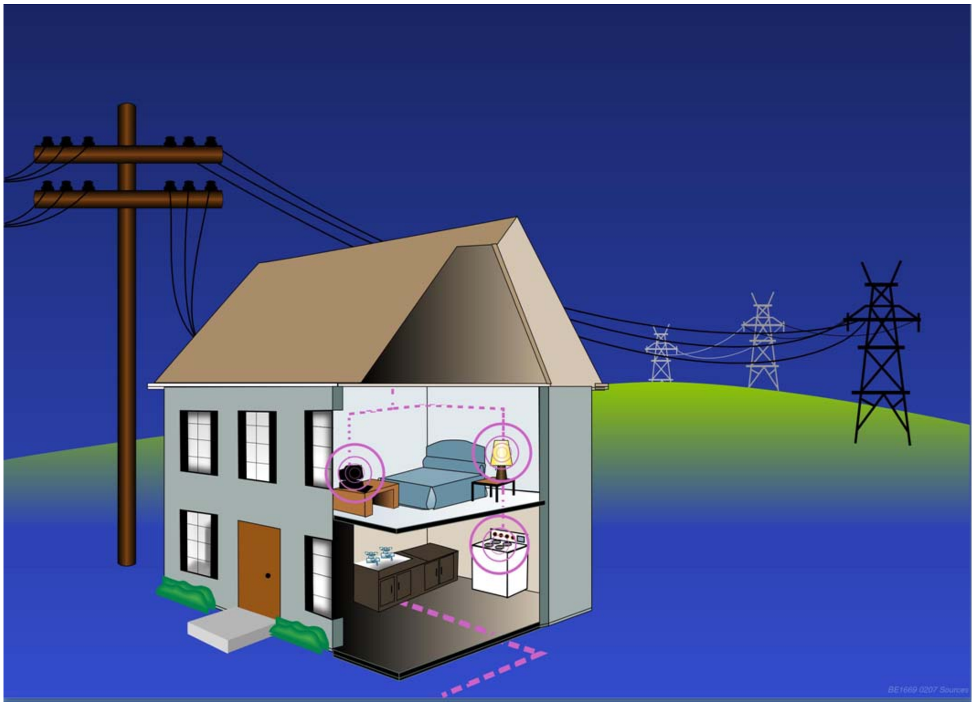

Figure 1. Common sources of ELF EMF in the home (appliances, wiring, currents running on water pipes, and nearby distribution and transmission lines)

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 on the right of way (ROW) of a typical transmission line. The fields from underground transmission lines are not included in this figure since they are a rare source of EMF exposure in most locations. While the magnetic field over buried conductors can be as high, or even higher, than an overhead line, the magnetic field will diminish more quickly with distance. No electric field is produced above ground by underground cables because the fields are blocked by the metallic sheaths around the conductors and by the ground covering the cables.

In general, the background magnetic-field level as estimated from the average of measurements throughout a typical 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).

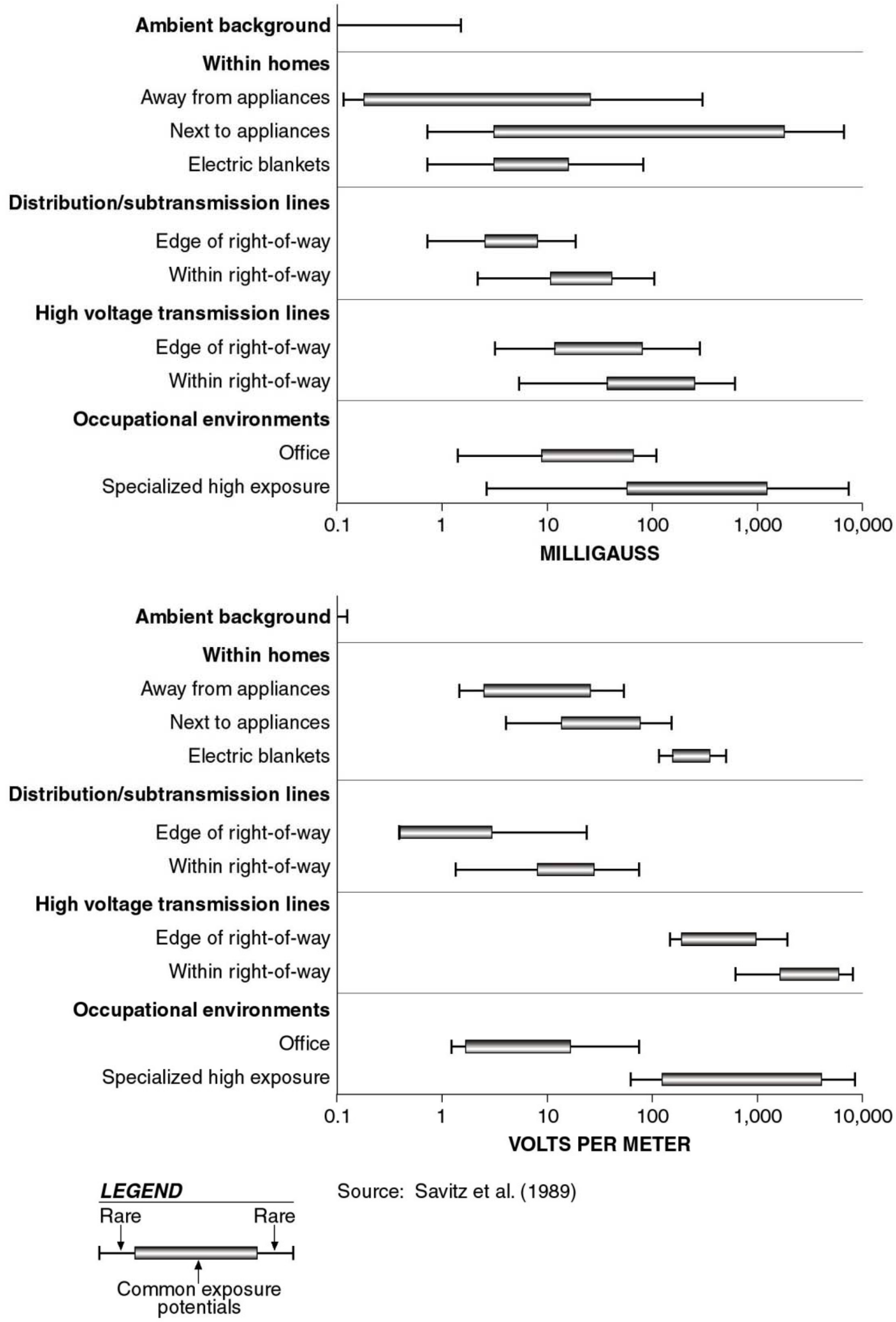

Figure 2. Magnetic and electric field levels in the environment

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, 2007a). 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).[7]
  - 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).

[7] 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.

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

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. International exposure guidelines and standards have been developed to protect the public from all known adverse effects.

3 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 about 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 present 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, 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 (e.g., average, peak) and a defined critical period for exposure (e.g., *in utero*, shortly before diagnosis), 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 machine 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.[8] 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' job categories, which the authors attributed to variation in industry within those task-defined 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

[8] 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.[9] 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 below.

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 the 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 RR 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 RR 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 RR 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.

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[9] The definition a risk factor in epidemiology is: "…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)" (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 (e.g., publication date, study design, possibility of selection bias), 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 introduce an association in the study that does not truly exist in the underlying population. 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 reported 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 epidemiology studies. These criteria include 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 1 provides a listing and brief description of each criterion.

Table 1. 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 cause of disease, or one of its few causes.
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 the 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 for 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 criterion 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 sunlight 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.

4 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 . 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

In 2007, the WHO published their Environmental Health Criteria (EHC) 238 on EMF summarizing health research on exposures in the ELF range. The EHC used standard scientific procedures, as outlined in its Preamble and described above in Section 3, 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,[10] 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 are 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.

[10] 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 EHC 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 close to 1,000 substances and exposure circumstances to evaluate their potential carcinogenicity. Over 80% of exposures fall in the categories possible carcinogen (29%) or non-classifiable (52%). 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

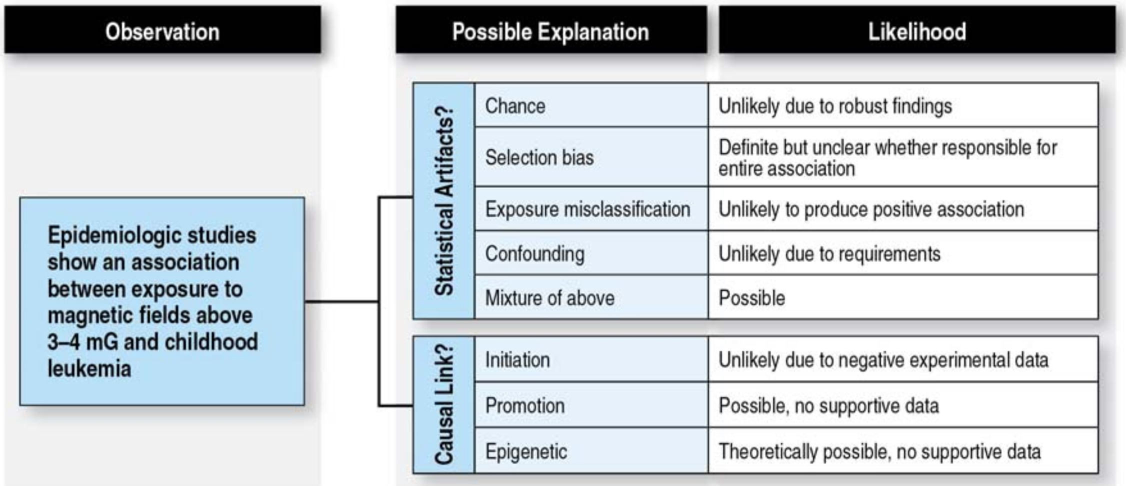
The WHO report provided the following overall conclusions with regard to ELF EMF:

> 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, 2007a, 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, 2007a, 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, 2007a, 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, 2007a, 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, 2007a, 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.

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.

Cardiovascular disease. It has been hypothesized that magnetic-field exposure reduces heart rate variability, 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.

Electric fields. As discussed earlier, ELF electric fields, unlike ELF magnetic fields, are easily shielded by common conductive objects, thus there is less opportunity for long-term exposure to electric fields. It is also more difficult to measure electric fields than magnetic fields, because electric fields are significantly disturbed by conductive objects ,including the person conducting the measurements, and therefore, special training and precautions are needed for electric field measurements. Also, at ELF frequencies, the induced internal electric field is several magnitudes lower than the external electric field, thus the potential internal exposures are reduced more than for magnetic fields that propagate almost unperturbed in most materials including the body. For all of the above reasons, most of the ELF EMF research focused on ELF magnetic fields as opposed to ELF electric fields. The relevant research o ELF electric fields, however, has also been reviewed by the WHO. Overall, no long-term health effects were identified with respect to ELF electric fields. Human and laboratory studies evaluated potential effects of ELF electric fields on the neuroendocrine system, but overall the WHO concluded that the data does not indicate that ELF electric (and/or magnetic) fields affect the neuroendocrine system. The evidence for developmental or reproductive effects in laboratory animals with exposure to ELF electric fields was judged inadequate, that is, no consistent evidence was reported for these outcomes. The evidence was also considered inadequate for carcinogenicity from human studies, and overall, exposure to ELF electric field was considered not classifiable as to potential carcinogenicity to humans (Group 3).

5 Current Scientific Research

The following sections identify and describe relevant epidemiology studies related to ELF EMF and health and *in vivo* carcinogenicity studies published between August 2012 and November 2014.[11] 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 4.

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 2012 through November 2014.[12] 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[13] and diseases of interest.[14] A researcher 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 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 outcomes: cancer; reproductive and developmental effects; neurodegenerative diseases; or cardiovascular disease. Research on other outcomes is not included (e.g., psychological effects, behavioral effects, hypersensitivity). Few studies are available in these research areas and, as such, research evolves more slowly.

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[11] 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.

[12] 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 or other search string used 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.

[13] EMF, magnetic fields, electric fields, electromagnetic, transmission line, or power line.

[14] 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 developmental effects).

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 studies and *in vivo* laboratory animal studies relevant for carcinogenicity 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 4) with regard to mechanistic data from *in vitro* studies. 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 also 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 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 2-10 list the relevant studies in these areas, including the study's first author and the title of the study.

As most research studies focus on ELF magnetic fields, as opposed to ELF electric fields, the following summary addresses ELF magnetic field studies. The research on ELF electric fields relating to cancer was systematically reviewed by Kheifets et al. (2010b). The authors concluded that the very few laboratory studies do not indicate that electric fields should be an "exposure of interest." The epidemiologic studies on residential and occupational exposures and cancer development, according to the authors, did not provide any consistent support for a carcinogenic effect, and the authors conclude that "there seems little basis for continued research into electric fields."

The latest assessment of ELF electric fields by the WHO is that "Following a standard health risk assessment process, the Task Group concluded that there are no substantive health issues related to ELF electric fields at levels generally encountered by members of the public." (WHO, 2007b).

Childhood 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 approximately 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 (August 2012 to November 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. Swanson et al. (2014a) have provided additional empirical data to demonstrate the limitations of distance assessments in childhood cancer epidemiologic studies basing the exposure assessment on distance from power lines. They concluded that reliance on postcode without the exact address, which may be the case for some of the study subjects in epidemiologic studies, are probably not acceptable for accurate magnetic-field assessment in the subjects' homes.

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 after diagnosis in children with leukemia.

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 leukemia (the most common type), or myeloid leukemia were considered. The authors reported a statistically significant increase for leukemia classified as "other types," which included only 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.

Swanson et al. (2014b) investigated the potential role of corona ions from power lines in childhood cancer development in the largest-to-date epidemiologic study of childhood cancer conducted in the United Kingdom. The authors used an improved model to predict exposure to corona ions using meteorological data on wind conditions, power line characteristics, and proximity to residential address. The authors concluded that their results provided no empirical support for the corona ion hypothesis.

Several methodological studies have also examined the potential role of causal and alternative, non-causal explanations for 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." Another 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 (Teepen and van Dijck, 2012; Mezei et al., 2014).

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 reached in 2015 by the Scientific Committee on Emerging and Newly Idenfied Health Risks (SCENIHR) 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 2. 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
Swanson et al.	2014a	Relative accuracy of grid references derived from postcode and address in UK epidemiological studies of overhead power lines
Swanson et al.	2014b	Childhood cancer and exposure to corona ions from power lines: an epidemiological test
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
*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, 2007a, p. 18).

Recent studies (August 2012 to November 2014)

There has been one new publication that examined the potential relationship between residential proximity to transmission lines and childhood brain cancer. The case-control epidemiologic study by Bunch et al. (2014), described above, 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.

The results of the methodological study that investigated the accuracy of distance assessment in childhood cancer studies (Swanson et al., 2014a) are also relevant for childhood brain cancer. The study that investigated the role of corona ions in childhood cancer development, similarly to childhood leukemia, reported no consistent associations for childhood brain cancer (Swanson et al., 2014b).

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., 2010a; SCENIHR, 2015). The recent data do not alter the classification of the epidemiologic data in this field as inadequate.

Table 3. 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.
Swanson et al.	2014a	Relative accuracy of grid references derived from postcode and address in UK epidemiological studies of overhead power lines
Swanson et al.	2014b	Childhood cancer and exposure to corona ions from power lines: an epidemiological test

Adult health outcomes

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, 2007a, p. 307).

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

Recent studies (August 2012 to November 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 diagnosis 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 JEM. 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 JEM 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; Zhao et al., 2014b) 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 (Chen et al., 2013). 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. Zhao et al. (2014b) reported the results of their meta-analysis of 16 case-control epidemiologic studies of ELF EMF and breast cancer published between 2000 and 2007. They reported a weak but statistically significant association, which appeared to be stronger among non-menopausal women. 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. Similar to the previous meta-analysis, their conclusion may be due to the inclusion of 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 4. 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
Zhao et al.	2014b	Relationship between exposure to extremely low-frequency electromagnetic fields and breast cancer risk: a meta-analysis
*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 (August 2012 to November 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.

Sorahan (2014a) reported results of further analyses of brain cancer incidence between 1973 and 2010 among more than 70,000 British electricity supply workers in a cohort analysis. The study reported no consistent association between brain cancer risk (glioma and meningioma) and estimated cumulative, recent, and distant occupational exposure to ELF EMF.

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, Israel, New Zealand, and the United Kingdom between 2000 and 2004. Exposure was assessed based on individual job history and a JEM. 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 5. 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
Sorahan	2014a	Magnetic fields and brain tumour risks in UK electricity supply workers
Turner et al	2014	Occupational exposure to extremely low frequency magnetic fields and brain tumour risks in the INTEROCC study

Adult leukemia

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 (August 2012 to November 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. Sorahan also completed detailed analyses for leukemia incidence in the cohort of over 70,000 British electricity supply employees (Sorahan, 2014b). For all leukemia, overall, there was no indication for risk increases with cumulative, recent, or distant occupational exposure to magnetic fields. In some sub-analyses, however, the authors reported a statistically significant association for ALL.

Koeman et al. (2014) identified 761 and 467 hematopoietic malignancies among men and women, respectively, in the Netherlands Cohort Study. Although in some sub-type sub-analyses statistically significant associations were noted for acute myeloid leukemia and follicular lymphoma, overall 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, ALL, 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 new evidence to support of an association with adult leukemia overall or with any leukemia subtype. 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, there is no new evidence to alter the overall conclusion and the evidence overall remains inadequate for adult leukemia (EFHRAN, 2012; SCENIHR, 2015).

Table 6. Relevant studies of adult leukemia

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
Sorahan	2014b	Magnetic fields and leukaemia risks in UK electricity supply workers

Reproductive and 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, 2007a). 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, 2007a, p. 254) and recommended further epidemiologic research.

Recent studies (August 2012 to November 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 was 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.

Su et al. (2014) conducted a cross-sectional study in Shanghai to examine correlations between magnetic-field exposure and embryonic development. The authors identified 149 pregnant women who were seeking induced abortion during the first trimester. Personal 24-hour measurements were conducted for women within four weeks of the abortion. Ultrasound was used to determine embryonic bud and sac length prior to the abortion. The authors reported an association with maternal daily magnetic-field exposure and embryonic bud length. The study has a number of severe limitations, including the cross-sectional design, which cannot distinguish whether exposure measured after abortion described exposure during the first trimester making it impossible to assess causality, and the lack of careful consideration of gestational age, which is a major determinant of embryonic bud length. Thus, the study provides little, if any weight in a weight-of-evidence assessment.

Lewis et al. (2014) analyzed magnetic-field exposure data over 7 consecutive days among 100 pregnant women from an earlier study. They reported that measures of central tendency (e.g., mean, median) were relatively well correlated day-to-day, and a measurement on one day could be used reasonably well to predict exposure on another day. Peak exposure measures (e.g., maximum value) showed poorer performance than measures of central tendency. The study did not examine the outcomes of the pregnancies, but these results have implications for earlier studies that reported an association for spontaneous abortions with peak measures but not with measures of central tendency.

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 concluded that "recent results do not show an effect of the ELF fields on the reproductive function in humans" (SCENIHR, 2015, p. 7).

Table 7. 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
Lewis et al.	2014	Temporal variability of daily personal magnetic field exposure metrics in pregnant women
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

Authors	Year	Study
Shamsi Mahmoudabadi et al.	2013	Exposure to Extremely Low Frequency Electromagnetic Fields during Pregnancy and the Risk of Spontaneous Abortion: A Case-Control Study
Su et al.	2014	Correlation between exposure to magnetic fields and embryonic development in the first trimester
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, 2007a, p. 206).

Recent studies (August 2012 to November 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, or 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.

Davanipour et al. (2014) have reported on a study of severe cognitive dysfunction and occupational ELF magnetic-field exposure, in which "[t]he study population consisted of 3,050 Mexican Americans, aged 65+, enrolled in Phase I of the Hispanic Established Population for the Epidemiologic Study of the Elderly (H-EPESE) study." Occupational history, along with data on other socio-demographic information, was obtained via in-home personal interviews. Occupational exposure to magnetic fields was classified as low, medium, and high. Cognitive function was evaluated with the use of the mini-mental state exam and cognitive dysfunction was defined as an exam score below 10. While the authors describe their study as a population-based case-control study, based on the provided description in the paper, the study appears to be a cross-sectional study. Based on their analyses, the authors report a statistically significant association between estimated occupational magnetic-field exposure and severe cognitive dysfunction. The study had a number of limitations, including the cross-sectional study design, the lack of clear clinical diagnosis for case-definition, and the crude assessment of occupational exposure.

Seelen et al. (2014) conducted a large population-based case-control study of ALS and residential proximity to high-voltage power lines in the Netherlands. The authors included 1,139 ALS cases diagnosed between 2006 and 2013 and 2,864 frequency-matched controls selected from general practitioners' rosters. Lifetime residential history was determined for all cases and controls using data from the Municipal Personal Records Database. Addresses were geocoded and the shortest distance to a high-voltage power was determined for each address. High-voltage power lines with voltage between 50 kV and 150 kV (high voltage) and between 220 kV and 380 kV were analyzed. No statistically significant association was reported for ALS with residential proximity to power lines with any of the voltages included. The authors also conducted a meta-analysis including their own results along with two previously published studies (Marcilio et al., 2011; Frei et al., 2013) and reported an overall OR of 0.9 (95% CI 0.7-1.1) for living within 200 meters of a high voltage power line. Similar to the previous power-line studies, the main limitation of the current study is the use of distance to power lines as a surrogate for magnetic-field exposure. The authors, however, reconstructed lifetime residential history, which represents a methodological improvement.

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 a couple of earlier studies based on limited methodology and small numbers presented no convincing evidence for an association (Das et al., 2012; Grell et al., 2012). It has been previously suggested that the weak and inconsistent association between ELF EMF and ALS might be explained by electric shocks.

Researchers in the Netherlands conducted a hospital-based case-control study of Parkinson's disease and occupational exposure to electric shocks and ELF magnetic fields (van der Mark et al., 2014). The study included 444 cases of Parkinson's disease and 876 matched controls. Occupational history was determined based on telephone interviews. JEMs were used to categorize jobs for exposure to both electric shocks and magnetic fields. The authors reported no risk increases with any of the two investigated exposures and concluded that their results suggest no association with Parkinson's disease.

A mortality case-control study using death certificates between 1991 and 1999 was conducted in the United States (Vergara et al., 2014). The study analyzed 5,886 ALS deaths and 10-times as many matched control deaths. Exposure to electric shocks and ELF magnetic fields was classified based on job titles reported on the death certificates and using corresponding JEMs. While a statistically significant association was reported for "electrical occupations," no consistent associations were observed for either magnetic field or electric shock exposures. The main limitation of the study is its reliance on death certificates that may result in disease and exposure misclassifications.

Huss et al. (2014) reported results of their analysis of ALS mortality in the Swiss National Cohort between 2000 and 2008. The cohort included about 2.2 million workers with high, medium, or low exposure to ELF magnetic fields and electric shocks. For exposure classification, JEMs for magnetic-field exposure and electric shocks were applied to occupations reported by the subjects at the 1990 and 2000 censuses. The authors reported a statistically significant association of ALS mortality with estimated medium or high occupational magnetic-field exposure based at both censuses, but not with estimates of electric shock exposure. The main limitations of the study include the reliance on mortality data, which may result in disease misclassification, and the use of census data for exposure assessment, which may result in exposure misclassification.

Assessment

Overall, the recent literature does not alter the conclusion that there are inadequate data for a causal link between exposure to ELF magnetic fields and neurodegenerative diseases. Most of the recent studies provided no support for a potential association. Several recent studies have investigated the potential role of electric shocks in neurodegenerative disease development. None of these studies reported results that would support the hypothesis that electric shocks play an etiologic role.

The recent studies continue to be limited by uncertainties about the estimates of magnetic-field exposure. With respect to Alzheimer's disease, the main limitations of the available literature remains the difficulty in diagnosing Alzheimer's disease; the difficulty of identifying a relevant exposure window given the long and nebulous course of this disease; the difficulty of estimating magnetic-field exposure prior to the appearance of the disease; the under-reporting of Alzheimer's disease on death certificates; crude exposure evaluations that are often based on the recollection of occupational histories by friends and family given the cognitive impairment of the study participants; and the lack of consideration of both residential and occupational exposures or confounding variables. Further research in this area will be needed to address the limitations of research to date on neurodegenerative disease (SSM, 2010; EHFRAN, 2012).

Although the studies published in 2014 were not available for the most recent review and assessment by SCENIHR released in 2015, the authors concluded that newly published studies that they reviewed "do not provide convincing evidence of an increased risk of neurodegenerative diseases, including dementia, related to ELF MF [magnetic field] exposure" (SCENIHR, 2015, p.186). Consideration of the 2014 publications that we reviewed does not change this conclusion.

Table 8. Relevant studies of neurodegenerative disease

Authors	Year	Study
Das et al.	2012	Familial, environmental, and occupational risk factors in development of amyotrophic lateral sclerosis
Davanipour et al.	2014	Severe cognitive dysfunction and occupational extremely low frequency magnetic field exposure among elderly Mexican Americans
Frei et al.	2013	Residential distance to high-voltage power lines and risk of neurodegenerative diseases: a Danish population-based case-control study
Huss et al.	2014	Occupational exposure to magnetic fields and electric shocks and risk of ALS: The Swiss National Cohort
Grell et al.	2012	Risk of neurological diseases among survivors of electric shocks: a nationwide cohort study, Denmark, 1968-2008
Seelen et al.	2014	Residential exposure to extremely low frequency electromagnetic fields and the risk of ALS
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
Vergara et al.	2014	Case-control study of occupational exposure to electric shocks and magnetic fields and mortality from amyotrophic lateral sclerosis in the US, 1991–1999
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 mortality or incidence related to occupational magnetic-field exposure (WHO, 2007a). The WHO concluded, "Overall, the evidence does not support an association between ELF exposure and cardiovascular disease." (WHO, 2007a, p. 220)

Recent studies (August 2012 to November 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 deaths due to cardiovascular disease 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 JEM. 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 [cardiovascular disease]."

Assessment

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

Table 9. 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.[15]

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 millitesla] reported by 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, 2007a, 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 (August 2012 to November 2014)

No new animal bioassays of tumor development due to magnetic-field exposure alone or in combination with known cancer initiators have been conducted since the study by Bernard et al. (2008) that was the first study to use an animal model of ALL, the most common leukemia type in children, which was reviewed in the previous update. Instead, various *in vivo* studies examining potential mechanisms that could precipitate cancer development have been conducted. These studies are listed in Table 10.

Some previous studies from a single laboratory, but not others, reported that DMBA-initiated mammary tumors were increased in a particular strain of rats exposed to magnetic fields. To further investigate this phenomenon, Fedrowitz and Löscher (2012) evaluated gene expression in pooled samples of mammary tissue from both Fischer 344 rats (F344) and Lewis rats 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-amylase protein expression and its correlation with tissue differentiation

[15] 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).

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.

Four recent animal studies examined the ability of magnetic-field exposure to cause DNA damage. 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 magnetic fields 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, 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.[16]

In another study, Saha et al. (2014) examined the effects of magnetic-field exposure on DNA during gestational development. Pregnant mice were exposed to one of three different magnetic field (50-Hz) exposure conditions: 1,000 mG for 2 hours on day 13.5 of gestation; 3,000 mG

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

(continuous) for 15 hours on day 12.5 of gestation; or 3,000 mG (intermittent: 5 minutes on, 10 minutes off) for 15 hours on day 12.5 of gestation. Controls were either untreated or sham-exposed under these same conditions, but with the exposure equipment turned off. Additional animals were exposed to either 10 or 25 Gray of X-irradiation on day 13.5 of gestation; however, the amount of time for which these treatments were given is not known. Although X-irradiation was associated with increased DNA double strand breaks and cell apoptosis in the embryonic brain cells of the ventricular and subventricular zones, none of the magnetic field conditions had a significant effect on these parameters. These analyses were not conducted in a blinded manner; however, the potential influence of the animal litter was taken into account in the statistical analysis.

Finally, Korr et al. (2014) continuously exposed mice for 8 weeks to either 1,000 mG or 10,000 mG 50-Hz magnetic fields. Controls were not sham-exposed, but maintained in the same room as the magnetic-field-exposed animals. At the end of the exposure period, the animals were injected with radiolabeled thymidine to look for DNA single-strand breaks and unscheduled DNA synthesis in the liver, kidneys, and brain using an autoradiographic method. A slight reduction in mitochondrial DNA synthesis was observed in the epithelial cells of the kidney collecting ducts at 1,000 mG, but no increase in DNA single-strand breaks was observed. At 10,000 mG, a slight reduction in unscheduled DNA synthesis (likely related to the reduced mitochondrial DNA synthesis) was observed in the epithelial cells of the choroid plexus of the brain's fourth ventricle and the kidney collecting duct, but again, there was no difference in the degree of DNA single-strand breaks observed between treated and control animals. These investigations were conducted in a blinded manner. Overall, these studies suggest that magnetic-field exposures do not cause direct DNA damage and that any measured DNA damage after exposure may be due to cell apoptosis. As suggested in earlier investigations, however, some evidence suggests very high magnetic-field exposure may affect the DNA-damaging capacity of other, known genotoxicants.

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 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.

To examine the possible acute effects of magnetic-field exposure, Martínez-Sámano et al. (2012) exposed rats 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 activity of the antioxidant enzyme superoxide dismutase (SOD). Catalase (CAT) enzymes were also reduced and lipid peroxidation increased in the brain following magnetic-field exposure. No effects on brain levels of nitric oxide (NO)—an important intracellular messenger molecule and free radical compound)—or lipid content, or plasma corticosterone levels were observed.

In another acute exposure study, Seifirad et al. (2014) examined the expression of various markers, including the lipid peroxidation markers malondialdehyde (MDA)—a marker of lipid peroxidation)—conjugated dienes, and total antioxidant capacity (TAC) in the blood following exposure of rats to a 5,000 mG, 60-Hz magnetic fields for either 4 hours (acute) or 14 days (chronic). The acute exposure was associated with increased TAC, while the chronic exposure was associated with increased MDA levels and a reduced TAC. Although the controls were reportedly sham-exposed, it is not known if this was for the acute or chronic exposure condition, making interpretation difficult. Blinded analyses and control of environmental conditions also were not reported.

Glinka et al. (2013) examined the expression of various antioxidant markers in the blood and liver of male rats following 30 minutes of exposure to 100,000 mG, 40-Hz magnetic fields, for 6, 10, or 14 days. The purpose of this analysis was to examine the potential role of magnetic fields in the treatment of wounds; thus, the rats were first wounded surgically prior to exposure. Controls were sham exposed, but blinded analyses were not reported. Further, no details on the preparation of liver homogenates or the methods used to analyze the various samples were reported. Differences from control in the expression of the antioxidant markers SOD, glutathione peroxidase (GSH-Px), and MDA were reported in either the blood or the liver on various days, but no clear pattern of expression was apparent. No differences in the expression of glutathione S-transferase was observed. It should be noted, however, that control values varied considerably across the different study days, which may be related to a confounding effect associated with the wound healing process. Duan et al. (2013) examined the expression of oxidative stress markers in the hippocampus and serum of male mice continuously exposed to 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. MDA levels were increased and the antioxidant enzymes SOD, GSH-Px, and CAT were reduced with exposure. NO 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.

Hassan and Abdelkawi (2014) conducted a similar study in which male rats were exposed to 100,000 mG, 50-Hz magnetic fields for 1 hour per day for 30 days. Other groups of rats were treated with cadmium chloride or both cadmium chloride and magnetic-field exposure. Although it was reported that the controls were sham-exposed, based on the methods description, this does not appear to be the case; also, analyses were not conducted in a blinded manner. Both magnetic-field exposure and cadmium treatment were reported to increase the total oxidant status and protein carbonyls present in the blood; both exposures combined resulted in an increased response over either single condition alone.

Manikonda et al. (2014) examined the effects of 90 days continuous exposure to much lower magnetic field strengths of 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 were reduced. In contrast with the other studies described here, however, SOD and GSH-Px levels were increased instead of reduced. 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.

Deng et al. (2013) exposed mice to 20,000 mG, 50-Hz magnetic fields for 4 hours per day, 6 days per week for 8 weeks. Other treatment groups were exposed to aluminum or both magnetic fields and aluminum. Control mice were not reported to have been sham-exposed and analyses were not reported to have been conducted in a blinded manner. Both brain and serum SOD levels were reported to be lower in all exposure conditions compared to controls. In contrast, MDA levels were increased in all exposure groups. Other analyses looking at behavior and brain pathology were also conducted in this study, but are not reported here. Similarly, Kiray et al. (2013) exposed rats 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; 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.

Cui et al. (2012) exposed male mice 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 MDA levels and reduced the TAC of these tissues as well as levels of the anti-oxidant enzymes CAT and GSH-Px. In another study (Akdag et al., 2013a), the effects on the rat brain of 1,000 and 5,000 mG, 50-Hz exposure for 2 hours per day over 10 months were examined. 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 was associated with increased levels of MDA and protein carbonyls, 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.

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 were exposed to either 12 kV/m or 18 kV/m electric fields 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. TAC 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

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, and inflammatory, 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 fields 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's conclusion that the overall evidence from *in vivo* studies does not support a role of EMF exposure 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. One particularly well-conducted study on genotoxicity found no effect of magnetic-field exposure on DNA double strand breaks. This study employed positive control X-irradiation, sham exposure of negative controls, and blinded analyses. Further, the results are generally consistent with those of another recent investigation that found no influence of magnetic-field exposure on the induction of DNA single strand breaks in the brain, liver, or kidneys of exposed mice.

Overall, the *in vivo* studies published since the last update do not alter the previous conclusion of the WHO that there is inadequate evidence of carcinogenicity due to ELF EMF exposure. Further, the limited recent investigations suggest that DNA single and double strand breaks do not occur as a result of magnetic-field exposure.

Table 10. 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
Glinka et al.	2013	Influence of extremely low-frequency magnetic field on the activity of antioxidant enzymes during skin wound healing in rats
Hassan and Abdelkawi	2014	Assessing of plasma protein denaturation induced by exposure to cadmium, electromagnetic fields and their combined actions on rat
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
Korr et al.	2014	No evidence of persisting unrepaired nuclear DNA single strand breaks in distinct types of cells in the brain, kidney, and liver of adult mice after continuous eight-week 50 Hz magnetic field exposure with flux density of 0.1 mT or 1.0 mT
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
Saha et al.	2014	Increased apoptosis and DNA double-strand breaks in the embryonic mouse brain in response to very low-dose X-rays but not 50 Hz magnetic fields
Salehi et al.	2012	Exposure of rats to extremely low-frequency electromagnetic fields (ELF-EMF) alters cytokines production
Seifirad et al.	2014	Effects of extremely low frequency electromagnetic fields on paraoxonase serum activity and lipid peroxidation metabolites in rat
Villarini et al.	2013	Brain hsp70 expression and DNA damage in mice exposed to extremely low frequency magnetic fields: Adose-response study

6 Consensus 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[17]; SSM, 2013). Although neither of these reports represents a cumulative weight-of-evidence review with the breadth 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 4 and 5.

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, 2007a; SCENIHR, 2009, 2015; 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.

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[17] Following the completion of our current report in January 2015, SCENIHR released its review on EMF that included reviews of health-related research on ELF EMF fields and updated its report released in 2009. (This 2015 review had been previously released in 2013 as a Preliminary Opinion). For completeness we updated our 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 epidemiologic results on childhood leukemia, 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 epidemiologic studies prevent a causal interpretation" (SCENIHR, 2015, p. 7). (http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_041.pdf).

7 Standards and Guidelines

Following a thorough review of the research, scientific agencies develop exposure standards to protect against known health effects. The major purpose of a weight-of-evidence review is to identify the lowest exposure level below which no health hazards have been found (i.e., a threshold). Exposure limits are then set well below the threshold level to account for any individual variability or sensitivities that may exist.

Several scientific organizations have published guidelines for exposure to ELF EMF based on acute health effects that can occur at very high field levels.[18] The ICNIRP reviewed the epidemiologic and experimental evidence and concluded that there was insufficient evidence to warrant the development of standards or guidelines on the basis of hypothesized long-term adverse health effects such as cancer; rather, the guidelines put forth in their 2010 document set limits to protect against acute health effects (i.e., the stimulation of nerves and muscles) that occur at much higher field levels. The ICNIRP recommends a residential screening value of 2,000 mG and an occupational exposure screening value of 10,000 mG (ICNIRP, 2010). If exposure exceeds these screening values, then additional dosimetry evaluations are needed to determine whether basic restrictions on induced current densities are exceeded. For reference, in a national survey conducted by Zaffanella and Kalton (1998) for the National Institute for Environmental Health and Safety's EMF Research and Public Information Dissemination program, only about 1.6% of the general public in the United States experienced exposure to magnetic fields of at least 1,000 mG during a 24-hour period.

The ICES also recommends limiting magnetic field exposures at high levels because of the risk of acute effects, although their guidelines are higher than ICNIRP's guidelines; the ICES recommends a residential exposure limit of 9,040 mG and an occupational exposure limit of 27,100 mG (ICES, 2002). Both guidelines incorporate large safety factors.

The ICNIRP and ICES guidelines provide guidance to national agencies and only become legally binding if a country adopts them into legislation. The WHO strongly recommends that countries adopt the ICNIRP guidelines, or use a scientifically sound framework for formulating any new guidelines (WHO, 2006).

There are no national or state standards in the United States limiting exposures to ELF EMF based on health effects. Two states, Florida and New York, have enacted standards to limit magnetic fields at the edge of the right-of-way from transmission lines (NYPSC, 1978; FDER, 1989; NYPSC, 1990; FDEP, 1996), however, the basis for these limits was to maintain the "status quo" so that fields from new transmission lines would be no higher than those produced by existing transmission lines.

[18] Valberg et al. (2011) provides a listing of guidelines provided by health and safety organizations.

Table 11. Screening levels for whole body exposure to 60-Hz fields that assure compliance with basic restrictions: general public

Organization recommending limit	Magnetic fields	Electric fields
ICNIRP reference level	2,000 mG	4.2 kV/m
ICES maximum permissible exposure	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).

8 Summary

A number of epidemiology and *in vivo* studies have been published on EMF and health since the WHO 2007 report. The weak statistical association between high, average magnetic fields and childhood leukemia remains largely unexplained and unsupported by the experimental data. Most recent epidemiologic studies of childhood leukemia, and childhood cancer in general, however, tend to show no overall associations providing no new evidence for a potential relationship. {discuss that consideration of Hill's criteria does not support a causal association.}The recent *in vivo* studies confirm the lack of experimental data supporting a leukemogenic risk associated with magnetic-field exposure. Recent publications on other cancer and non-cancer outcomes provided no substantial new information to alter the previous conclusion that the evidence is inadequate to link outcomes to ELF EMF.

In conclusion, recent studies when considered in context of previous research do not provide evidence to alter the conclusion that ELF EMF exposure at the levels we encounter in our everyday environment including transmission lines is not a cause of cancer or any other disease process.

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