

Written Evidence to the  
Independent Expert Group on Mobile Phones

An Assessment of the Evidence Relating to  
Radio-frequency Radiation and Cancer

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REPORT BY DR. JOHN E. MOULDER

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on behalf of the  
Federation of the Electronics Industry

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## **An Assessment of the Evidence Relating to Radio-Frequency Radiation and Cancer**

### **1) Introduction and Purpose of Report**

This report was prepared by Dr. John E. Moulder, Professor of Radiation Oncology, for the Independent Expert Group on Mobile Phones. The report was prepared at the request of the Federation of the Electronics Industry.

#### 1.1) What does this report cover?

This report reviews the evidence relevant to the question of whether exposure to radio-frequency radiation causes or contributes to the development of cancer.

Specifically, the report reviews:

1. The types of evidence that are relevant to determining whether radio-frequency radiation could cause or contribute to cancer.
2. The biophysics of radio-frequency radiation with emphasis on why biological effects of other types of electromagnetic radiations or fields (such as ionizing radiation and power-frequency fields) are of little relevance to evaluating biological effects of radio-frequency radiation.
3. Epidemiological studies of people exposed to radio-frequency radiation.
4. Studies of whether exposure to radio-frequency radiation alone causes cancer in animals.
5. Studies of whether exposure to radio-frequency radiation, along with exposure to other known carcinogens, increases the ability of these other carcinogens to cause cancer in animals.
6. Studies of whether exposure to radio-frequency radiation directly damages the genetic material of cells, animals or humans.
7. Studies of whether exposure to radio-frequency radiation, along with exposure to other known carcinogens, increases the damage that these other carcinogens cause to the genetic material of cells, animals or humans.
8. A weight-of-evidence summary of how the epidemiological and experimental evidence bears on the question of whether exposure to radio-frequency radiation causes, or contributes to the development of, cancer.

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### 1.2) What does this report conclude about radio-frequency fields and cancer?

The report concludes that the existing body of epidemiological and experimental data does not suggest that radio-frequency radiation either causes cancer or contributes to the development of cancer.

Specifically, the report concludes that:

1. There is an extensive body of published peer-reviewed studies that are relevant to assessing the carcinogenic potential of radio-frequency radiation.
2. The relevant peer-reviewed literature includes epidemiology, long-term animal exposure studies, cellular studies of genotoxic potential, and cellular studies of epigenetic activity.
3. The epidemiological studies of radio-frequency radiation and cancer do not suggest a causal association.
4. The long-term animal exposure studies present no compelling evidence that long-term exposure to radio-frequency radiation is genotoxic.
5. Some of the long-term animal exposure studies suggest the possibility that radio-frequency radiation might have epigenetic activity at high (possibly thermal) exposure levels.
6. Cellular studies of genotoxicity have been extensive, and the weight of evidence is that radio-frequency radiation is not genotoxic.
7. Assessment of the epigenetic potential of radio-frequency radiation in cell culture has been limited, and the results are equivocal.
8. An overall weight-of-evidence evaluation indicates that the current evidence for a causal association between exposure to radio-frequency radiation and cancer is weak to non-existent.

## **2) Qualifications and Experience**

My name is John E. Moulder. I am a research scientist specializing in cancer biology and radiation biology. I am Professor in the Departments of Radiation Oncology, Radiology, and Pharmacology/Toxicology at the Medical College of Wisconsin (MCW) in Milwaukee, Wisconsin, U.S.A. I have conducted research on the effects of ionizing radiation since 1973, including studies of tissue injury after irradiation, and of causes of radiation sensitivity and radiation resistance. Much of my academic work has been directed towards assessing whether various types of ionizing and non-ionizing radiations and fields can be, or have been, the cause of injuries.

I received an undergraduate degree, Magna Cum Laude, in chemistry and biology from Carleton College, Northfield, Minnesota, U.S.A. I then earned a Masters and Ph.D. from the Department of

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Biology at Yale University, New Haven, Connecticut, U.S.A. My graduate research was on cellular regulation of protein synthesis.

After completing my academic training in 1972, I conducted research and taught courses in radiation biology and cancer biology in the Departments of Radiology and Therapeutic Radiology at Yale Medical School. In 1975 I served as a Visiting Scientist at the Gray Laboratory of the Cancer Research Campaign, Mount Vernon Hospital, Northwood, Middlesex, U.K. In 1978, I joined the Radiation Biology and Biophysics Section of the Radiology Department at the Medical College of Wisconsin as a teacher and researcher. In a 1980 reorganization, this became the Radiation Biology Section of the Department of Radiation Oncology; and in 1988 I was promoted to Full Professor with tenure. Also in 1988, I spent a sabbatical as a Visiting Professor in the Department of Radiation Oncology at the University of Washington, Seattle, Washington, U.S.A.

As a Professor at the Medical College of Wisconsin, I conduct laboratory research on the biological effects of radiation and on the biology of cancer, participate in the development and analyses of clinical cancer trials, and teach courses in radiation biology and cancer biology. I have taught courses for medical students, graduate students, allied health students, residents, and physicians. The topics include cancer biology, radiation biology, carcinogenesis, mutagenesis, risk assessment and tumor biology; and include electromagnetic sources that range from static fields to power-frequency fields to radio-frequency radiation to x-rays.

Over the past decade I have been an invited lecturer at institutions that include Children's Hospital of Wisconsin, University of Wisconsin, University of Washington, Yale University, Tufts University, Colorado State University, Northwestern University, Brookhaven National Laboratory, Queensland Radium Institute (Australia), University of Minnesota, and Universidad de Valladolid (Spain). I have also been an invited lecturer at annual meetings of societies that include: the American Society of Therapeutic Radiology and Oncology, the Australian Radiation Protection Association, the Health Physics Society, the Radiation Therapy Oncology Group, the American Association of Physicists in Medicine, the Radiation Research Society (U.S.), the European Radiation Research Society, the Wisconsin Safety and Health Association, the International Congress of Radiation Research, and the Wisconsin State Medical Society. Topics of these lectures have included: health effects of non-ionizing radiations and fields in the workplace, the health consequences of radiation accidents, biological effects of power-frequency magnetic fields, biological effects of exposure to radio-frequency radiation, the biological basis of cancer therapy, the radiobiology of bone marrow transplantation, and the treatment of radiation injuries.

As part of my research, I have published more than 85 peer-reviewed papers on the therapeutic use of ionizing radiation and on the effects of ionizing and non-ionizing radiation on humans, animals,

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tissues and cells. This research has been supported by grants from the U.S. National Cancer Institute, other branches of the U.S. National Institutes of Health, and the American Cancer Society. My research has been published in scientific journals that include: *American Journal of Physiology*, *Archives of Physiology and Biochemistry*, *Biochimica et Biophysica Acta*, *Bone Marrow Transplantation*, *British Journal of Cancer*, *Cancer*, *Cancer and Metastasis Reviews*, *Cancer Research*, *Cancer Treatment and Research*, *Critical Reviews in Biomedical Engineering*, *Engineering in Medicine and Biology*, *International Journal of Radiation Biology*, *International Journal of Radiation Oncology Biology and Physics*, *Journal of Cell Biology*, *Journal of Laboratory and Clinical Medicine*, *Journal of Neurosurgery*, *Magnetic Resonance in Medicine*, *National Cancer Institutes (U.S.) Monographs*, *Nephron*, *Proceeding of the IEEE*, *Radiation Research*, *Radiology*, *Radiotherapy and Oncology*, *Radiation Oncology Investigations*, and *Transplantation*. In addition, I have contributed to a number of medical and scientific texts on radiation biology and on the use of radiation in medicine.

Among the articles I have published are a number that are of direct relevance to the issue of whether non-ionizing radiations and fields cause or contribute to cancer:

- JE Moulder, KR Foster: Biological effects of power-frequency fields as they relate to carcinogenesis. *Proceedings of the Society for Experimental Biology and Medicine* 209:309-324, 1995.
- JE Moulder: Biological studies of power-frequency fields and carcinogenesis. *Engineering in Medicine and Biology* 15:31-40, 1996.
- KR Foster, LS Erdreich, JE Moulder: Weak electromagnetic fields and cancer in the context of risk assessment. *Proceedings of the IEEE* 85:733-746, 1997.
- JE Moulder: The power line – cancer debate: Is it a conflict between physics and biology? *Radiation Research* 148:1, 1997.
- JE Moulder: Book review: Possible Health Effects of Exposure to Residential Electric and Magnetic Fields, by the National Research Council (U.S.). *Radiation Research* 148:101-103, 1997.
- JE Moulder: Book review: Non-Ionizing Radiation, edited by Rüdiger Matthes. *Radiation Research* 148:104-105, 1997.
- JE Moulder: Power-frequency fields and cancer. *Critical Reviews in Biomedical Engineering* 26:1-116, 1998.
- SC Miller, JE Moulder: Publication of negative results is an essential part of the scientific process. *Radiation Research* 150:1-2, 1998.
- JE Moulder: Une approche biomédicale: le point de vue d'un chercheur en cancérologie. In: J Lambrozo, I Le Bis (Eds.), *Champs Électriques et Magnétique de Très Basse Fréquence*: Electricité de France, 1998, pp. 73-78.

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- JE Moulder, KR Foster: Is there a link between exposure to power-frequency electric fields and cancer. *Engineering in Medicine and Biology* 18(2):109-116, 1999.
- JE Moulder, LS Erdreich, RS Malyapa, J Merritt, WF Pickard, Vijayalaxmi: Cell phones and cancer: What is the evidence for a connection? *Radiation Research* 151:513-531, 1999.
- JE Moulder: La controversia sobre líneas eléctricas y cáncer: Perspectiva histórica. In: J Represa, C Llanos (Eds.), *Campos Electromagnéticos y Salud Humana*. Universidad de Valladolid, In press.
- JE Moulder: Epidemiología sobre cáncer y exposición residencial a los campos generados por las líneas eléctricas. In: J Represa, C Llanos (Eds.), *Campos Electromagnéticos y Salud Humana*. Universidad de Valladolid, In press.

In addition to publishing in conventional peer-reviewed journals, I maintain an Internet site <<http://www.mcw.edu/gcrc/cop.html>> at the Medical College of Wisconsin that provides Question-and-Answer documents<sup>1</sup> on the biological effects of static magnetic fields, power-frequency fields and cellular telephone base station antennas. The FAQs are referenced by Internet sites including: the Australian Radiation Protection Agency, the Bioelectromagnetics Society (U.S.), the Canadian Center for Occupational Health and Safety, the Federation of the Electronics Industry (U.K.), Harvard University, the Institute of Electrical and Electronics Engineers (U.S.), the Leukemia Research Fund (U.K.), the New Scientist (U.K.), the New Zealand National Radiation Laboratory, Princeton University, the Radiation Research Society (U.S.), Stanford University, the Swedish Association for the Electrosensitive, the U.S. Federal Communication Commission, the U.S. National Institute of Environmental Health Sciences, the U.S. Health Physics Society, the U.S. National Aeronautics and Space Administration, the University of Pennsylvania Cancer Center, and the World Health Organization. Currently the Web site is accessed by over 15,000 people per month.

I have served on the Editorial Board of *Radiation Research*, *Proceedings of the Society for Experimental Biology and Medicine*, and the *International Journal of Radiation Oncology Biology and Physics*. I also serve as a peer-reviewer for a number of journals, including: *Acta Oncologica*, *Cancer Research*, *Free Radical Medicine and Biology*, *International Journal of Radiation Biology*, *Journal of the American Medical Association*, and *Radiotherapy and Oncology*. As a peer reviewer and editor, I review manuscripts that cover both ionizing and non-ionizing radiation biology.

The reviewing of requests for funding (“grant proposals”) plays a role in science that is perhaps as important as the review of manuscripts. I have served as a reviewer of such grant proposals for the

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<sup>1</sup>Called FAQs, Frequently Asks Questions (or FAQs), in the language of the Internet.

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U.S. National Institutes of Health, the U.S. National Electric and Magnetic Field Health Effects Research Program, the Medical Research Council of Canada, the Netherlands Cancer Research Foundation, and the National Cancer Institute of Canada. As part of work done for the U.S. National Institutes of Health and the U.S. National Electric and Magnetic Field Health Effects Research Program, I participated in the review of most of the grant proposals that were submitted for funding under the EMF-RAPID<sup>2</sup> program.

I have served as a consultant for a number of companies, public utilities, and governmental bodies, including the Wisconsin Department of Justice, the U.S. National Research Council, the Wisconsin Radiation Protection Service, the National Council on Radiation Protection and Measurement, Alpha Therapeutic Corporation, the Wisconsin Utilities Association, the Wauwatosa (Wisconsin) School District, Wisconsin Electric Power Corporation, Journal Communications, the Seattle City Attorney's Office, Kaiser Aluminum and Chemical Corporation, the Milwaukee County Parks Department, the Milwaukee Police Department, Florida Power & Light, the City of Brookfield (Wisconsin), Vodacom (South Africa), Northern States Power, British Nuclear Fuels, PrimeCo Personal Communications, Cellular One, and The National Grid Company (U.K.). The topics of these consultations include: design of clinical trials, the alleged hazards of power lines, the alleged hazards of computer terminals, the alleged hazards of cellular telephone towers, the hazards of radio and TV broadcast antennas, and the biological effects of low doses of ionizing radiation.

I am a Full Member of the Radiation Research Society, in which I was elected to the governing Council, and served as the Chair of the Constitution and Bylaws Committee, and then of the Membership Committee. I am an Active (full) Member of the American Society of Therapeutic Radiology and Oncology, where I served for 11 years on the Radiation Biology Committee. I am also a member of the American Association for the Advancement of Science, the Bioelectromagnetics Society, the Environmental Mutagen Society, the Institute of Electrical and Electronics Engineers (IEEE), and the Radiation Therapy Oncology Group. In 1995 I was elected to membership in the IEEE Committee on Man and Radiation (COMAR); and in 1997 I was appointed to the IEEE Medical Technology Policy Committee, where I serve as the chair of the Technology Impact Assessment Committee.

I have served on a number of state and local government advisory committees, including the Wisconsin Legislative Council Committee on Environmental Health, the Wisconsin Pesticide Advisory Council, the Committee on Non-Ionizing Radiation of the Wisconsin Radiation Protection

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<sup>2</sup>The Electric and Magnetic Fields (EMF) Research and Public Information Dissemination (RAPID) program was authorized by the U.S. Congress in 1993 "to determine whether or not exposure to EMF produced by the generation, transmission and use of electric energy affects human health".

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Council, and the Wisconsin Radiation Protection Council (where I was Vice-Chairman for 4 years). At the Medical College I have served on the Radiation Safety Committee, the Safety Committee, the Carcinogen Committee (which I chaired for 8 years), and the Animal Care and Use Committee.

### 3) Identifying Carcinogens

Epidemiology provides the most direct evidence for carcinogenic potential in humans, but the mechanisms of carcinogenesis are sufficiently well established that laboratory studies can also provide information relevant to assessing whether radio-frequency radiation has the potential to cause or contribute to cancer (Table I).

When the epidemiological evidence for an association between a physical agent and cancer is weak and/or the link is biophysically implausible, laboratory studies are critical for risk evaluation [1-3]. If there is strong cellular (*in vitro*) and/or animal (*in vivo*) evidence that an agent is carcinogenic, it can make even weak epidemiology evidence for an association credible. Conversely, if appropriate laboratory studies are done and these studies fail to show any consistent evidence for carcinogenic activity, then we tend to dismiss weak epidemiological evidence, particularly if the association is biophysically implausible.

Our current understanding of cancer is that it is initiated by damage to the genetic information of a cell (the DNA), and agents which cause such injury are called genotoxins. It is extremely unlikely that a single genetic injury to a cell will result in cancer, as it appears that a series of very specific genetic injuries are required [3-5]. In fact, genotoxic injury to cells occurs all the time because of random errors during cell replication, and because of daily exposure to natural and artificial genotoxins. Most of this genetic injury has no deleterious effect on the cell it occurs in; and many other genetic injuries result in death of the cell. Only a very small fraction of the genetic injuries that occur push cells along the path towards cancer.

It is also clear that non-genotoxic agents can contribute to the development of cancer, even though these agents may not cause cancer by themselves. Epigenetic (non-genotoxic) carcinogens affect carcinogenesis by increasing the probability that other agents will cause genotoxic injury, or that genotoxic injury caused by other agents will lead to cancer [3-8]. The actions of epigenetic agents can be tissue- and species-specific, and evidence exists that epigenetic agents have thresholds for their effects [3-7]. Thus evidence that an agent has epigenetic activity must be evaluated carefully for its relevance to human carcinogenicity under real-world exposure conditions.

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Current research indicates that carcinogenesis is a multi-step process driven by a series of injuries to the genetic material of cells [3-9]. This multi-step model replaces an earlier model, called the “initiation-promotion” model. The initiation-promotion model proposed that carcinogenesis was a two-step process, with the first step being a genotoxic injury (called “initiation”) and the second step being non-genotoxic (called “promotion”). There are important differences between these models:

- 1) The multi-step model recognizes that multiple genotoxic injuries may be required for carcinogenesis, while the initiation-promotion model implied that a single genotoxic event was sufficient for carcinogenesis.
- 2) The multi-step model recognizes that some cancers may be produced solely by a series of genotoxic injuries (i.e., promotion is not required).
- 3) The multi-step model recognizes that there are epigenetic effects on carcinogenesis that do not meet the standard definition of promotion.
- 4) Because genotoxic injury can be the result of random errors in DNA replication and cell division, the multi-step model recognizes that exposure to epigenetic agents can increase the incidence of cancer even in the absence of exposure to genotoxins.

Because there are multiple mechanisms of carcinogenesis, there is no single test that can identify carcinogens. Conversely, there is no test, or set of tests, that can prove the absence of carcinogenic activity [3-11]. In assessing carcinogenic potential, scientists consider seven main lines of evidence (Table I):

- 1) evidence from human populations (i.e., epidemiology, clinical studies, and case reports);
- 2) long-term animal exposure studies (i.e., does long-term exposure of animals cause cancer);
- 3) animal assays for genotoxicity (i.e., does exposure of animals cause mutations, DNA damage or chromosome aberrations);
- 4) cellular assays for genotoxicity (i.e., does exposure of cells cause mutations, DNA damage or chromosome aberrations);
- 5) animal assays for epigenetic activity (i.e., does exposure enhance or “promote” the action of known carcinogens);
- 6) cellular assays for epigenetic activity (i.e., does exposure increase the probability that other genotoxins will cause genotoxic injury, or that genotoxic injury caused by other agents will lead to cancer);
- 7) biochemical and/or biophysical plausibility (i.e., is a causal connection compatible with what we know about carcinogenesis and about the biochemistry and/or biophysics of the agent).

In the absence of definitive tests for carcinogenicity, scientists must consider all of these lines of evidence, and must consider all relevant data (both positive and negative) in a weight-of-evidence assessment.

#### **4) Radio-frequency Radiation**

##### 4.1) The electromagnetic spectrum

X-rays, ultraviolet light, visible light, infrared light, microwaves, radio-frequency radiation (RF or RFR), and electromagnetic fields from electric power systems are all part of the electromagnetic spectrum. The parts of the electromagnetic spectrum are characterized by their frequency (or wavelength), and different electromagnetic frequencies produce fundamentally different types of biological effects. We usually talk about electromagnetic sources as though they produced waves of energy. However, electromagnetic energy can also act like particles, particularly at high frequencies; and the energy of these particles (photons) increases as the frequency increases. The particle nature of electromagnetic energy is important because the energy per particle (photon energy) is a major determinant of what biological effects a particular frequency of electromagnetic energy will have [11].

At the very high frequencies characteristic of X-rays, electromagnetic particles (photons) have sufficient energy to break chemical bonds. This breaking of bonds is termed ionization, and this part of the electromagnetic spectrum is termed ionizing. The well-known hazards of ionizing radiations such as X-rays are due to the breakage of chemical bonds in the genetic material of cells (the DNA). At lower frequencies, such as those characteristic of visible light, radio-frequency radiation, and microwaves, the energy of a photon is very much below that needed to disrupt chemical bonds, and this part of the electromagnetic spectrum is termed non-ionizing.

Non-ionizing electromagnetic radiations and fields can produce biological effects. Many of the biological effects of non-ionizing ultraviolet, visible, and infrared frequencies also depend on the photon energy; but they involve electronic excitation rather than ionization, and do not occur at frequencies below that of infrared light (below 300,000 MHz). Radio-frequency and microwave radiation can cause effects by inducing electric currents in tissue and increasing molecular motion, both of which cause heating. The efficiency with which non-ionizing electromagnetic radiation causes heating depends on the frequency of the source, and the size and orientation of the object being heated. At frequencies below that used for broadcast AM radio (about 1 MHz), electromagnetic fields are poorly absorbed by humans and animals, and thus are very inefficient (ineffective) at causing heating [11-14].

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Thus in terms of potential biological effects, the electromagnetic spectrum can be divided into four portions:

1. The ionizing radiation portion, where direct chemical damage can occur (e.g., X-rays).
2. The non-ionizing portion of the spectrum, which can be subdivided into:
  - a. The optical radiation portion, where electron excitation can occur (e.g., visible light, infrared light).
  - b. The portion where the wavelength is smaller than the body, and heating can occur (e.g., microwave ovens, mobile phones, broadcast TV, FM radio).
  - c. The portion where the wavelength is much larger than the body, and heating seldom occurs (e.g., AM radio, power frequency fields, static fields).

### 4.2) Terminology and units for measuring radio-frequency radiation

For radio-frequency radiation, the energy flux, in watts per square meter ( $\text{W}/\text{m}^2$  or  $\text{mW}/\text{cm}^2$ ), across a surface is called the “power density”. Power density measures the strength of the incident radio-frequency radiation and is the favored metric of external exposure to radio-frequency radiation; in part because it is relatively easy to measure. However, power density is an imperfect indicator of the relevant conditions inside an irradiated organism. Instead, scientists specify a metric of internal exposure, the specific absorption rate, SAR (in  $\text{W}/\text{kg}$ ). The SAR is generally used as the dose metric in laboratory experiments, and SAR serves as the scientific basis of modern radio-frequency radiation safety standards.

SAR can be estimated in three ways:

1. Small antennas can be used to determine the local electric field in tissue, and if the effective conductivity of the tissue is known, the SAR can be computed [15]. However, it is often difficult to place the antenna where it is needed, and technology has yet to develop suitable antennas with sub-millimeter dimensions. In addition, the effective conductivity of tissue may not be known for the tissue and frequency of interest.
2. Radio-frequency radiation causes heating of tissue which can be detected and used to infer the SAR in the neighborhood of a miniature temperature probe. However, because heat diffuses, a spatially non-uniform SAR can, over the time needed to produce a measurable temperature offset, be significantly confounded by thermal diffusion. Moreover, the “non-perturbing” temperature probes presently available are in reality only “minimally perturbing”, and the technical prospects of developing a probe system which matches tissue both thermally and electromagnetically seem remote.

3. Fortunately, the numerical modeling of the absorption of radio-frequency radiation is well-developed and offers a way around the obstacles to experimental determination of SAR. Given an organism and a well-characterized irradiation geometry, finite difference time domain (FDTD) simulations can predict SAR. For geometries within which robust field measurements can be made, FDTD predictions have been found to be accurate when tested [16].

#### 4.3) Possible mechanisms for biological effects of radio-frequency radiation

To effect a change in biological material through which it is passing, radio-frequency radiation must deposit enough energy to significantly alter some biological structure. However, every biological structure within the body already possesses thermal kinetic energy, and these structures continually collide with other structures of similar energy. For a change to occur in biological material, radio-frequency radiation seemingly should transfer energy considerably above this thermal energy. Because the photon energy of radio-frequency radiation is far less than either thermal energy or the bond energy, it would appear that there is little prospect of radio-frequency irradiation having biological activity (let alone carcinogenic sequelae) at sub-thermal power levels [14,15].

### **5) The Epidemiology of Radio-frequency Radiation**

Although radio-frequency radiation has been part of our society for many decades, and several occupations have clear exposure [17], no epidemiological study has clearly shown radio-frequency radiation to be carcinogenic. Voluntary occupational exposure limits, and the thermal hazard, have kept exposures relatively low; and there are unlikely to be any long-term population exposures at high doses. In addition, although sophisticated instruments have been developed to measure radio-frequency radiation, no completely satisfactory methods exist to continuously monitor individual exposures, or to estimate exposures retrospectively. Because of the relatively low levels of exposure, the relatively small populations, and the lack of reliable dose estimates, proving or disproving the existence of carcinogenic effects of radio-frequency radiation through epidemiology alone will probably be impossible. Despite these limitations, some information regarding the question of cancer can be obtained from existing epidemiological studies.

#### 5.1) Studies of “cancer clusters” and radio-frequency radiation

Reports of isolated cases, or even clusters of disease cases, provide limited information. The major steps in evaluating reports of “cancer clusters” are [18]: define a logical (as opposed to arbitrary)

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boundary in space and time to define the population to be studied, determine whether an excess of a specific type of cancer has actually occurred, and identify common exposures and characteristics.

A number of “cancer clusters” have been reported as involving exposure to radio-frequency radiation. However, the steps outlined above have not been followed in most of these studies, and these studies are not given much weight. Well-known examples of such clusters include a report of excess testicular cancer in police who used hand-held radars [19], a report of childhood leukemia near radio towers in Hawaii [20], and a report of excess brain cancer around FM/TV antennas in Colorado [21]. In 1993, Davis and Mostofi [19] reported an excess of testicular cancer in a self-reported group of Washington State traffic police who used hand-held radars; but no such excess has been reported among radar users elsewhere in the United States. In 1994, Maskarinec et al. [20] reported a cluster of childhood leukemia near radio towers in Hawaii. A follow-up case-control study [20] found that the excess was not statistically significant. More recently, the Colorado (U.S.) Department of Public Health and Environment [21] reported a cluster of adult brain cancers around the Lookout Mountain antenna farm. A standard incidence ratio study [21] found that the excess was not statistically significant.

None of these “cancer cluster” reports present convincing evidence that radio-frequency radiation is carcinogenic.

### 5.2) Geographical correlation studies with radio-frequency radiation

Geographic correlation studies estimate the strength of radio-frequency radiation in geographic areas and correlate these estimates with disease rates in those areas. Even when the design of such studies is optimal, they are considered exploratory and are not used for determining causality.

In 1996, Hocking et al. [22] published a geographic correlation study that compared municipalities “near TV towers” to those further away. No radio-frequency radiation exposures were actually measured. No other sources of exposure to radio-frequency radiation were taken into account, the study was based on only a single metropolitan area, and “near TV towers” and “not near TV towers” groups may not have had similar age distributions or socioeconomic status. The authors reported an elevated incidence of childhood leukemia, but no significant increase in adult leukemia, adult brain cancer, or childhood brain cancer.

In 1998, McKenzie et al. [23] repeated the Hocking et al. [22] study. McKenzie and colleagues looked at the same area, and at the same time period; but they made actual measurements of the radio-frequency radiation levels in various residential areas. They found increased childhood leukemia in one area near the TV antennas, but not in other similar areas near the same TV antennas;

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and they found no significant correlation between exposure to radio-frequency radiation and the incidence of childhood leukemia. They also found that much of the “excess childhood leukemia” reported by Hocking et al. [22] occurred before high-power 24-hour TV broadcasting had started at the site.

In 1997, Dolk et al. [24] investigated a reported leukemia and lymphoma cluster near a single high-power FM/TV broadcast antenna in the U.K. They found that the incidence of adult leukemia and skin cancer were elevated within 2 km of the antenna. No association was seen for brain cancer, breast cancer, lymphoma or any other type of cancer. Because of this finding, Dolk and colleagues [25] extended their study to all other high-power FM/TV broadcast antennas in the UK. No statistically-significant increases in total cancer, leukemia or brain cancer were found near these antennas.

### 5.3) Cohort and case-control studies of occupational and military exposure to radio-frequency radiation

Hill [26] studied cancer incidence in employees of the Massachusetts Institute of Technology who worked on radar development during the Second World War. Exposure was estimated for each individual based on work history and the characteristics of the contemporary radar systems. The maximum exposure was estimated to be 2-5 mW/cm<sup>2</sup>. The mortality rate for brain cancer, leukemia and lymphoma were not significantly elevated in these workers, and there was no evidence for an exposure-response trend.

From 1953 to 1976, the American Embassy building in Moscow was bathed in low-intensity radio-frequency radiation. Lilienfeld et al. [27] surveyed cancer mortality in employees at the embassy, and compared their cancer risk to workers assigned to other Eastern European embassies. Measurements in the Moscow embassy indicated that the maximum exposure was 0.015 mW/cm<sup>2</sup> at 500 to 9000 MHz. Lilienfeld et al. [27] found no evidence that individuals in the Moscow group experienced higher mortality from cancer in general or from any cancer subtype. Although this study was well-designed, the relatively small cohort size and short follow-up time limited its power.

Robinette et al. [28] studied the cancer mortality of U.S. Navy personnel who were likely to have been exposed to radio-frequency radiation. Exposure was estimated from occupation, based on shipboard monitoring and documented accidental exposures. The high-exposure categories included opportunity for exposure above 10 mW/cm<sup>2</sup>. In the high-exposure occupations, mortality rates were not significantly elevated for overall cancer or for lymphoma and leukemia; and no exposure-response trends were apparent. Garland et al. [29,30] also studied the relationship between

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occupation and lymphoma and leukemia in U.S. Navy personnel, and found that the occupations that Robinette [28] had identified as the high radio-frequency radiation exposure group had lower rates of lymphoma and leukemia than the general male population. Grayson [31] assessed the occurrence of brain tumors in male Air Force personnel with possible exposure to radio-frequency radiation; and found that brain tumor incidence was elevated for “probable” and “possible” exposure categories combined, but that no exposure-response trend was seen.

Milham [32] considered possession of an amateur radio operator’s license to be evidence for exposure to both radio-frequency radiation and power-frequency fields. Milham had no information on the operators’ exposure or the hours of use, and noted that amateur operators could be exposed to cancer-causing substances when they maintain their equipment. Overall mortality, as well as cancer mortality, was lower than in the general population, and this decrease was statistically significant. Mortality for leukemia plus lymphoma was significantly increased, but mortality from brain cancer was not.

Many epidemiological studies address “electrical workers”, but in the vast majority of these studies exposure to radio-frequency radiation is not specifically identified. Two exceptions are the studies by Tynes et al. [33] and Thomas et al. [34]. Tynes et al. [33] classified “electrical occupations” into categories, one of which specified exposure to radio-frequency radiation. The group whose jobs were assumed to result in exposure to radio-frequency radiation did not have an elevated risk of brain cancer, but did have an increased risk of leukemia. Thomas et al. [34] classified “electrical occupations” in categories with presumed exposure to power-frequency fields, radio-frequency radiation, or both power-frequency fields and radio-frequency radiation. Workers with presumed exposure only to radio-frequency radiation did not have an increased risk of brain tumors.

Szmigielski [35] studied cancer in Polish military personnel, some of whom had worked with devices that produced radio-frequency radiation. Exposure was determined from assessments of field levels at various service posts, but no consideration was given to the length of time at the post, or to the job at the post. The study has not been published in the peer-reviewed epidemiology literature, and the methods of data collection and analysis are inadequately described. Epidemiological methods suitable to studying a population over time were not used, there is no evidence of age adjustment, and neither the actual number of cases nor the total number of the personnel at risk are known. Cancer of all types, brain cancer, and cancer of the lymphatic and hematopoietic organs were reported to be greater in exposed personnel. Because of the missing design information and the lack of basic data such as numbers of cases observed and expected, the report does not meet basic epidemiological criteria for acceptability. In addition, Elwood [36] notes that more information about possible radio-frequency radiation exposure was available for the cases in the Szmigielski

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study than for the controls, and that “This raises the possibility of systematic bias; such a bias would be expected to produce an increased relative risk for all types of cancer.”

Lagorio et al. [37] studied the cancer mortality of female radio-frequency heat sealer operators. Exposure assessment was based on the time assigned to jobs using the heaters. Exposure estimates were based on a survey carried out in the past, which indicated that power density had sometimes exceeded 1 mW/cm<sup>2</sup>. Among the heat sealer operators in this small cohort, there was a higher than expected overall rate of cancer deaths. However, the six cancers found in the exposed group were all different types of cancer, which does not give much support to their having a common cause. The authors report that the work area also included exposure to chemicals associated with cancer.

Several studies have examined lymphocytes from workers with occupational exposure to radio-frequency radiation from telecommunications facilities. Garaj-Vrhovac et al. [38] found an increase in the incidence of chromosomal abnormalities and micronuclei in exposed workers, but Garson et al. [39] and Maes et al. [40] found no evidence for such an effect.

### 5.4) Case-control studies of cell phone users

To date, only one published epidemiological study has evaluated cancer in mobile phone users<sup>3</sup>. In 1999, Hardell et al. [41] published a case-control study of brain tumors in Swedish mobile phone users. Exposure was assessed by questionnaires, and analyses were based on “use of cellular

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<sup>3</sup>In a report issued 20 October 1999, the U. S. Food and Drug Administration (FDA) provided the following summary of an additional as-yet unpublished case-control study of mobile phone users. "In a hospital-based, case-control study, researchers looked for an association between mobile phone use and either glioma (a type of brain cancer) or acoustic neuroma (a benign tumor of the nerve sheath). No statistically significant association was found between mobile phone use and acoustic neuroma. There was also no association between mobile phone use and gliomas when all types of types of gliomas were considered together. It should be noted that the average length of mobile phone exposure in this study was less than three years. When 20 types of glioma were considered separately, however, an association was found between mobile phone use and one rare type of glioma, neuroepitheliomatous tumors. It is possible with multiple comparisons of the same sample that this association occurred by chance. Moreover, the risk did not increase with how often the mobile phone was used, or the length of the calls. In fact, the risk actually *decreased* with cumulative hours of mobile phone use. Most cancer causing agents increase risk with increased exposure. An ongoing study of brain cancers by the National Cancer Institute is expected to bear on the accuracy and repeatability of these results. [Muscat et al: Epidemiological Study of Cellular Telephone Use and Malignant Brain Tumors. In: State of the Science Symposium; 1999 June 20; Long Beach, California]"

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telephones”. No elevation of brain tumor incidence was found in users of either digital or analog phones, and no exposure-response trend was observed. When analysis was restricted to tumors on the same side of the brain where the cell phone had been used, a non-significant excess incidence was found for use of the analog phones, but not for use of the digital phones.

### 5.5) Summary of the epidemiology of radio-frequency radiation

In general, the higher the quality of the exposure assessment, the greater the confidence that can be placed in the results of an epidemiology study. Unfortunately, in the majority of the studies of radio-frequency radiation, exposure was not actually measured, so that occupation or job title had to be used as a surrogate measure of exposure. Although some of the studies provided some information on exposure at the job site, none included systematic measurements of exposures for individuals.

The most weight can be given to the three epidemiology studies (Robinette et al. [28], Hill [26], and Milham [32]) with acceptable design and analysis, larger sample size, and longer follow-up time. Four other studies (Lilienfeld et al. [27], Tynes et al. [33], Thomas et al. [34], and Hardell et al. [41]) used acceptable designs, but had significant limitations in exposure assessment and/or follow-up. These seven studies do not show statistically-significant associations between exposure to radio-frequency radiation and either cancer in general or any specific type of cancer.

Overall, the results of the epidemiology studies of radio-frequency radiation do not fare well when viewed in the context of cancer causation criteria [1-3]: the associations are not strong, consistent, or specific for any type of cancer; and exposure-response trends are not evident.

### **6) Whole Organism Studies with Radio-frequency Radiation**

There have been no long-term animal studies using exposure to radio-frequency radiation that meet the optimal criteria for carcinogenesis studies (i.e., normal animals, multiple exposure levels and life-time exposure); but a number of studies have been published that bear on the issue of whether radio-frequency radiation has carcinogenic potential. Some of the studies of radio-frequency radiation exposure have been of less than one year’s duration, and some have assessed life span and/or overall health status rather than cancer incidence. Three general types of studies have been done: exposure of normal rodents to radio-frequency radiation, exposure of cancer-prone rodents to radio-frequency radiation, and studies of rodents also treated with chemical carcinogens plus exposure to radio-frequency radiation.

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### 6.1) Carcinogenesis in normal animals treated with radio-frequency radiation

Prausnitz and Susskind [42] exposed mice to 9270 MHz radio-frequency radiation at 100 mW/cm<sup>2</sup> for 59 weeks. The SAR was later estimated to be 40-50 W/kg (equivalent to about half the lethal SAR for a mouse [43]), and the exposure caused body temperature to increase by 2-5° C. The authors described the presence of a leukocyte neoplasm, which they termed “leucosis”, in the exposed animals; but the animals exposed to radio-frequency radiation had a longer mean life span than the control group. Numerous flaws in this study, as pointed out by Roberts and Michaelson [43], greatly diminish its value for an assessment of the risk of exposure to radio-frequency radiation. Among the problems are: the heat stress from the exposure procedure, the lack of statistical analysis, the lack of histopathological characterization of the “leucosis”, and the occurrence of a pneumonia epidemic in the mice during the study.

Spalding et al. [44] exposed mice to 800 MHz radio-frequency radiation for 35 weeks at a power density of 43 mW/cm<sup>2</sup> (estimated SAR of 13 W/kg). Cancer incidence was not explicitly addressed, but the mean life span of the exposed group was not significantly different than that of the sham-exposed group. No significant differences between the exposed and sham-exposed groups were seen for hematological parameters or body weight.

Chou et al. [45] exposed rats to 2450 MHz radio-frequency radiation for 25 months at an SAR of 0.15 to 0.4 W/kg. An excess of overall malignant tumors was found in the exposed animals, but there were no differences between the exposed and sham-exposed animals for any specific type of tumor, or when benign tumors were added to the count. The mean life span of the exposed group was not significantly different than that of the control group. Because the comparison of overall malignant tumor incidence was just one of the 155 comparisons in the study, the increase was not statistically significant.

Liddle et al. [46] exposed mice to 2450 MHz radio-frequency radiation throughout their life at 3 or 10 mW/cm<sup>2</sup> (SARs of 2 and 6.8 W/kg). Life span was significantly shortened in mice exposed at 10 mW/cm<sup>2</sup>, but at 3 mW/cm<sup>2</sup> the exposed animals lived slightly longer than the sham-exposed group. The authors indicated that the heating from exposure at 10 mW/cm<sup>2</sup> might have been stressful enough to decrease life span.

Adey et al. [47] exposed rats to pulse-modulated 837 MHz radio-frequency radiation. Exposure started with whole-body exposure of pregnant rats and continued with whole-body exposure of the litter through weaning. Starting at 7 weeks of age, the rats were given radio-frequency radiation to the head that continued for 22 months. Brain SAR ranged from 0.7 to 1.6 W/kg, and whole-body SAR ranged from 0.2 to 0.7 W/kg. The authors reported that the number of brain tumors was non-

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significantly decreased in the groups exposed to radio-frequency radiation. At a meeting in 1997, Adey et al. [48] reported a similar lack of effect on brain tumor incidence when frequency-modulated radio-frequency radiation was used in the same protocol (but possibly a higher SAR); and at a meeting in 1999, Zook [49] reported the absence of an effect on brain tumor incidence in rats exposed to pulsed or continuous-wave 860 MHz radio-frequency radiation at 1.0 W/kg.

### 6.2) Carcinogenesis in cancer-prone animals treated with radio-frequency radiation

Toler et al. [50] examined the effect of long-term radio-frequency radiation exposure on mammary tumor-prone mice. In this animal model, virus-induced mammary tumors normally develop in about 50% of the animals. The mice were exposed for 20 months to 435 MHz radio-frequency radiation at a power density of 1 mW/cm<sup>2</sup> (SAR of 0.32 W/kg). There were no differences in mammary tumor incidence between the mice exposed to radio-frequency radiation and sham-exposed mice; and there were no differences between the groups in the numbers of malignant, metastatic, or benign tumors. There was also no difference in survival between the two groups.

Frei et al. [51,52] used a design similar to that of Toler et al. [50], except that the mammary tumor-prone mice were exposed at 2450 MHz for 18 months at 0.3 W/kg [52] or 1.0 W/kg [51]. No significant differences were noted in mammary tumor incidence or in the number of malignant, metastatic, or benign tumors. Analysis of survival also revealed no difference between the two groups.

Repacholi et al. [53] examined the possibility that long-term exposure to radio-frequency radiation would enhance the incidence of lymphomas in mice that were genetically predisposed to develop lymphomas. The animals were exposed to 900 MHz radio-frequency radiation for 18 months. Depending upon the size of the mice and their orientation in the field, the power density ranged from 0.26 to 1.3 mW/cm<sup>2</sup> (SARs from 0.008 to 4.2 W/kg). The incidence of lymphoma in the mice exposed to radio-frequency radiation was significantly higher than in the controls. No similar excess incidence of lymphoma (or leukemia) has been seen in the long-term animal exposure studies that did not use lymphoma-prone animals (i.e., Chou et al. [45], Toler et al. [50], Frei et al. [51,52], Adey et al. [47]).

### 6.3) Carcinogenesis in animals treated with chemical carcinogens plus radio-frequency radiation

Szmigielski et al. [54] exposed mice to 2450 MHz radio-frequency radiation for up to 10 months to examine whether radio-frequency radiation could “promote” various types of cancer. Exposures were at 5 or 15 mW/cm<sup>2</sup> (estimated SAR of 2-3 and 6-8 W/kg). Controls included both normal

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animals, and animals subject to “confinement stress”. In a study of skin tumor promotion, a carcinogen (benzopyrene) was painted on the backs of the mice, and the animals were exposed to radio-frequency radiation (Szudzinski et al. [55] appears to be a report of the same study). Both exposure to radio-frequency radiation and confinement stress significantly accelerated the appearance of the chemically-induced skin tumors. In a study of mammary-tumor prone mice, both exposure to radio-frequency radiation and confinement stress significantly accelerated the appearance of tumors. Finally, the investigators injected tumor cells into mice and looked for lung metastases, and again both exposure to radio-frequency radiation and confinement stress significantly increased the number of metastases.

The implications of the Szmigielski et al. [54] study are difficult to assess; and the mammary cancer promotion studies are contradicted by recent studies by Toler et al. [50] and Frei et al. [51,52]. The similarities between the 5 mW/cm<sup>2</sup> group and the confinement stress group suggest that the changes in tumor latency and lung metastasis may have been caused by stress rather than by exposure to radio-frequency radiation. Such stress effects are not unexpected, as stress has been shown to both decrease the latency for mammary tumors in this animal model [56,57], and to increase the rate of lung metastases [58]. The dosimetry in this study is also questionable, and it seems likely that the mice exposed at 15 mW/cm<sup>2</sup> were highly stressed and subject to at least localized heating [15].

Wu et al. [59] investigated the possibility that exposure to radio-frequency radiation could promote chemically-induced colon tumors in mice. The animals were injected with a colon tumor carcinogen (dimethylhydrazine) before and during exposure to 2450 MHz radio-frequency radiation. Exposure was for 5 months at 10 mW/cm<sup>2</sup> (SAR of 10-12 W/kg). The study found no differences in the number or size of tumors in the carcinogen-treated group compared to the group treated with carcinogen plus radio-frequency radiation.

Imaida et al. [60,61] examined the possibility that exposure to radio-frequency radiation could promote chemically-induced liver cancer in rats. Rats were injected with a liver tumor carcinogen (diethylnitrosoamine) and then exposed to radio-frequency radiation for 6 weeks. The first study [61] used 929 MHz radio-frequency radiation with an SAR of 1.7-2.0 W/kg; and the second study [60] used 1439 MHz radio-frequency radiation with an SAR of 0.9-1.9 W/kg. There were no statistically significant differences in liver tumor frequency between the exposed and the sham-exposed rats in either study.

In parallel to the study on normal animals (Section 6.1), Adey et al. [47] also exposed rats to pulse-modulated 837 MHz radio-frequency radiation plus a brain tumor carcinogen (ethylnitrosourea). The authors reported that the number of brain tumors was not enhanced (“promoted”) in the groups exposed to radio-frequency radiation plus carcinogen compared to those treated with the chemical

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carcinogen alone. At a meeting in 1997, Adey et al. [48] reported a similar lack of brain tumor promotion when frequency-modulated radio-frequency radiation was used in a similar protocol; and at a meeting in 1999, Zook [49] reported the absence of brain tumor promotion in rats exposed to 860 MHz pulsed or continuous-wave radio-frequency radiation at 1.0 W/kg.

### 6.4) In vivo assessment of the genotoxic activity of radio-frequency radiation

Multiple studies have shown that radio-frequency radiation is not mutagenic in fruit flies (*Drosophila melanogaster*) [62-67]. Non-thermal radio-frequency radiation also does not appear to be mutagenic in rodents [68-70]. Radio-frequency radiation with sufficient intensity to raise body (and/or testicular) temperature may be mutagenic in rodents [71], although there is evidence to the contrary [69,70].

Radio-frequency radiation exposure of rodents also does not appear to cause chromosome aberrations [72,73] or sister chromatid exchanges [73,74] in hematopoietic cells. For chromosome damage in spermatocytes of animals exposed to radio-frequency radiation, there is contradictory data, with one group reporting increases in chromosome damage [75,76], and another group reporting no effects [68,77].

Of three studies of the ability of radio-frequency radiation to cause DNA strand breaks in irradiated animals, two have found no evidence for such an effect [78,79]. The one positive report of DNA strand breaks is from Lai and Singh [80,81] who reported that exposure of rats to 2450 MHz radio-frequency radiation at 0.6-1.2 W/kg caused DNA strand breaks. Malyapa et al. [78] have reported that they cannot replicate the work of Lai and Singh [80,81], and that the method of killing animals used by Lai and Singh is itself a cause of DNA strand breaks.

More recently, Vijayalaxmi et al. [82] assessed chromosome damage in cancer-prone mice that were chronically exposed to 2450 MHz radio-frequency radiation at an SAR of 1.0 W/kg. The incidence of chromosome damage in the exposed animals was slightly increased, but the increase was not correlated with a carcinogenic outcome, as there was no evidence that this radio-frequency radiation exposure was carcinogenic in these animals [51,52].

Vijayalaxmi et al. [83] also found no increase in chromosome damage in mice exposed to ultra-wideband radio-frequency radiation, and Huuskonen et al. [84] found a similar lack of increase in chromosome damage in mice exposed to 0.02 MHz radio-frequency radiation.

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### 6.5) Summary of in vivo studies with radio-frequency radiation

Taken together, the in vivo studies present no compelling evidence that exposure to radio-frequency radiation is genotoxic. The evidence that radio-frequency radiation has epigenetic activity is contradictory. Repacholi et al. [53] reported promotion of lymphoma in genetically lymphoma-prone mice, and Szmigielski et al. [54] reported promotion of skin and mammary tumors. In contrast, the studies by Toler et al. [50] and Frei et al. [51,52] found that long-term exposure to radio-frequency radiation is not associated with promotion of mammary tumors, Wu et al. [59] reported that long-term exposure to radio-frequency radiation did not promote chemically-induced colon tumors, Imaida et al. [60,61] showed that exposure to radio-frequency radiation did not promote chemically-induced liver cancer, and Adey et al. [47,48] and Zook [49] reported that exposure to radio-frequency radiation did not promote brain cancer.

In summary, the whole organism exposure studies conducted to date provide no replicated evidence that exposure of whole organisms to radio-frequency radiation at non-thermal intensities produces genotoxic injuries. Exposures to radio-frequency radiation at intensities sufficient to substantially raise body temperature may be genotoxic; but this is not unexpected, as there is independent evidence that whole-body hyperthermia is genotoxic [85,86].

## **7) Cellular Studies with Radio-frequency Radiation**

### 7.1) Genotoxicity studies with radio-frequency radiation

Of the many studies of the mutagenic potential of radio-frequency radiation done in microbial systems [67,87-94] only one, Blevins et al. [90], shows evidence for mutagenesis. Blevins et al. [90] exposed *Salmonella typhmuri* to 2450 MHz radio-frequency radiation at 5000 mW/cm<sup>2</sup> in a standard microwave oven and found an increase in the mutation rate. However, because temperatures were not recorded, hyperthermia cannot be ruled out as the cause of the increased mutation rate.

In mammalian and plant systems, exposure to radio-frequency radiation does not appear to increase mutation frequency [95,96], to increase the frequency of sister chromatid exchanges [97-104], or to cause DNA damage [105-109]. Of particular note are studies by Malyapa et al. [106,107] that were designed to extend the studies of Lai and Singh [80,81] who had reported that exposure of animals to radio-frequency radiation caused DNA strand breaks. Although the results reported by Lai and Singh [80,81] were based on in vivo exposures, in vitro studies are valuable because these systems allow careful monitoring and control of cell growth, temperature (to avoid thermal artifacts),

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dosimetry and other experimental conditions. Malyapa et al. [106,107] exposed mammalian cells at 0.6 - 1.9 W/kg to 2450 MHz continuous-wave radio-frequency radiation, to 836 MHz frequency-modulated radio-frequency radiation, or to 848 MHz radio-frequency radiation with CDMA modulation (the latter two exposure regimens simulate protocols used by mobile phones in the U.S.). Malyapa et al. [106,107] found no evidence of DNA damage in the cells that were exposed to radio-frequency radiation.

Balcer-Kubiczek and Harrison [110,111] reported that radio-frequency radiation did not cause cell transformation unless TPA, a known epigenetic agent, was present. Cain et al. [112], however, found no effects of radio-frequency radiation on cell transformation in the presence of TPA.

When chromosome aberrations and micronucleus formation are used as assays for genotoxicity, the results of radio-frequency radiation exposure are very mixed, with some studies reporting genotoxic effects [102,113-117] and others not [40,94,97-99,104,109,118,119]. Some of the studies showing enhanced chromosome aberrations and micronucleus formation were done at very high power levels [102,113,117]. The study by Maes et al. [102], for example, was conducted at an SAR of 75 W/kg; but a confirmation study done by Vijayalaxmi et al. [104] found no evidence for this effect at 1.7-6.5 W/kg.

### 7.2) Studies of the epigenetic potential of radio-frequency radiation

Radio-frequency radiation does not enhance mutations induced in cells by chemical carcinogens [95,96,119], does not inhibit repair of DNA damage [92,105], and does not enhance cell transformation induced by ionizing radiation [110,120] or chemical carcinogens [120]. In two studies [100,101], radiofrequency radiation did not enhance chromosome injury induced by chemical carcinogens, but in a third study [117] radio-frequency radiation at an SAR of 70 W/kg enhanced micronucleus formation induced by a chemical carcinogen.

Balcer-Kubiczek and Harrison reported that radio-frequency radiation did not enhance cell transformation induced by ionizing radiation [110,111,120] or chemical carcinogens [120] unless TPA, a known epigenetic agent, was present.

Pakhomova et al. [121] reported that while exposure to 61 GHz radio-frequency radiation did not enhance UV-induced mutagenesis, it did enhance UV-induced recombinations. They noted that the recombination effect was “much weaker than could be produced by traditional chemical and radiation mutagens” and that it could be “merely a result of microwave heating”.

7.3) Summary of in vitro assessment of the carcinogenic potential of radio-frequency radiation

There are over 40 published in vitro studies of radio-frequency radiation and carcinogenic potential that include over 80 separate tests for genotoxic and epigenetic activity<sup>4</sup>. These assays largely show the absence of evidence for both genotoxic and epigenetic activity. The positive studies are dominated by tests reporting increased frequencies of chromosome aberrations and micronuclei, tests whose false positive rates are in the 10-20% range [122,123]. Some of the positive results may also be a result of hyperthermia, rather than a direct result of exposure to radio-frequency radiation.

Overall, exposure of cells to radio-frequency radiation with an intensity that does not significantly raise cell temperature does not produce any consistent evidence for genotoxic or epigenetic potential. Exposures to radio-frequency radiation at intensities sufficient to cause substantial increases in cell temperature may produce both genotoxic and epigenetic activity; this is not unexpected, as there is independent evidence that hyperthermia may have both genotoxic [85,86,90,124,125] and epigenetic [126,127] activity.

## **8) Overall Cancer Risk Assessment**

An evaluation of the evidence for a causal association between exposure to radio-frequency radiation and cancer requires evaluation of all of the epidemiological, animal, cellular and biophysical evidence (Table I). The epidemiological studies of radio-frequency radiation and cancer do not suggest a causal association. The long-term animal exposure studies present no compelling evidence

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<sup>4</sup>In a report issued 20 October 1999, the U.S. Food and Drug Administration (FDA) provided the following summary of an additional as-yet unpublished genotoxicity study of radio-frequency radiation.

"Researchers conducted a large battery of laboratory tests to assess the effects of exposure to mobile phone RF on genetic material. These included tests for several kinds of abnormalities, including mutations, chromosomal aberrations, DNA strand breaks, and structural changes in the genetic material of blood cells called lymphocytes. None of the tests showed any effect of the RF except for the micronucleus assay, which detects structural effects on the genetic material. The cells in this assay showed changes after exposure to simulated cell phone radiation, but only after 24 hours of exposure. It is possible that exposing the test cells to radiation for this long resulted in heating. Since this assay is known to be sensitive to heating, heat alone could have caused the abnormalities to occur. The data already in the literature on the response of the micronucleus assay to RF are conflicting. Thus, follow-up research is necessary [Tice et al: Tests of mobile phone signals for activity in genotoxicity and other laboratory assays. In: Annual Meeting of the Environmental Mutagen Society; March 29, 1999, Washington, D.C.; and personal communication, unpublished results.]"

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that long-term exposure to radio-frequency radiation is genotoxic in animals. However, some of the long-term animal exposure studies suggest the possibility that radio-frequency radiation might have epigenetic activity at high (possibly thermal) exposure levels. Cellular studies of genotoxicity have been extensive, and although a few of these studies have suggested the possibility of genotoxicity, the weight of evidence is that radio-frequency radiation is not genotoxic. Assessment of the epigenetic potential of radio-frequency radiation in cell culture has been less extensive and the results are equivocal. Finally, biophysical evaluation indicates that it is implausible to expect that radio-frequency radiation would have biological activity at the sub-thermal power levels characteristic of residential and most occupational exposures.

An overall weight-of-evidence evaluation (Table II) indicates that the evidence for a causal association between exposure to radio-frequency radiation and cancer is weak to non-existent.

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**Table I: Assessing Evidence for Carcinogenicity**

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**Epidemiology**

- Are there multiple independent studies showing an association between exposure and cancer?
  - Is there a strong association between exposure and cancer?
  - Is the evidence for the association with cancer internally and externally consistent (i.e., do different studies show similar risks for the same types of cancer)?
  - Does the incidence of cancer increase with increased exposure (i.e., are there exposure-response trends)?
  - Have possible sources of bias and confounding been eliminated?
  - Does human exposure cause chromosome damage?
- 

**Animal (in vivo) studies**

- Does long-term exposure of rodents cause cancer?
  - Does exposure of rodents or insects cause mutations?
  - Does exposure of rodents, insects or plants cause chromosome damage?
  - Does exposure of rodents increase the probability that animals exposed to a known carcinogen will develop cancer (i.e., is the agent a “promoter”)?
- 

**Cellular (in vitro) studies**

- Does exposure of bacteria, yeast, plant or mammalian cells cause mutations?
  - Does exposure of mammalian cells cause chromosome damage?
  - Does exposure of mammalian cells cause neoplastic cell transformation?
  - Does exposure of bacteria, yeast, plant or mammalian cells cause inhibition of DNA repair?
  - Does exposure of mammalian cells increase the probability that cells exposed to a known carcinogen will show enhanced chromosome damage, mutation or cell transformation?
- 

**Biophysical/biochemical studies**

- Are there biophysical and/or biochemical mechanisms that could explain how the agent could cause effects in biological systems?
-

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**Table II: Weight-of-Evidence Assessment of Radio-Frequency Radiation and Cancer Risk**

<b>Criteria</b>	<b>Assessment for Radio-frequency (RF) Radiation</b>
Number and quality of epidemiological studies	<ul style="list-style-type: none"> <li>• Small number of studies of poor-to-fair overall quality</li> </ul>
Strength of association in the epidemiological studies	<ul style="list-style-type: none"> <li>• The association is weak to non-existent</li> </ul>
Consistency of the epidemiological studies	<ul style="list-style-type: none"> <li>• No consistent associations have been reported between exposure and either overall cancer or any specific types of cancer</li> </ul>
Exposure-response relationships in the epidemiological studies	<ul style="list-style-type: none"> <li>• There is little or no evidence for an exposure-response relationship</li> </ul>
Amount of laboratory evidence relevant to assessment of genotoxicity	<ul style="list-style-type: none"> <li>• Extensive studies in cell culture</li> <li>• A small number of whole-animal studies</li> </ul>
Strength of laboratory evidence for genotoxicity	<ul style="list-style-type: none"> <li>• Cellular studies strongly unresponsive of genotoxic activity</li> <li>• Animals studies moderately unresponsive of genotoxic activity</li> </ul>
Amount of laboratory evidence relevant to assessment of epigenetic activity	<ul style="list-style-type: none"> <li>• Relatively few cellular studies</li> <li>• Some whole-animal studies</li> </ul>
Strength of laboratory evidence for epigenetic activity	<ul style="list-style-type: none"> <li>• Some unreplicated evidence for epigenetic activity at high (possibly thermal) exposure levels</li> </ul>
Coherence of the association with biophysics and physics	<ul style="list-style-type: none"> <li>• Significant biological effects are implausible at sub-thermal power levels</li> </ul>
<b>Overall Evidence</b>	<ul style="list-style-type: none"> <li>• Nothing suggests a causal association, but there is no strong epidemiology and there are few strong animal studies</li> </ul>

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