

REVIEW

Cell Phones and Cancer: What Is the Evidence for a Connection?¹

J. E. Moulder,^a L. S. Erdreich,^b R. S. Malyapa,^c J. Merritt,^d W. F. Pickard^e and Vijayalaxmi^f

^a *Radiation Oncology, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, Wisconsin 53226;* ^b *Bailey Research Associates, 292 Madison Avenue, New York, New York 10017;* ^c *Radiation Oncology, Washington University, 4511 Forest Park Boulevard, St. Louis, Missouri 63108;* ^d *Radio-Frequency Radiation Branch, Air Force Research Laboratory, Brooks Air Force Base, Texas 78235;* ^e *Electrical Engineering, Washington University, One Brookings Drive, St. Louis, Missouri 63130;* and ^f *Radiation Oncology, University of Texas at San Antonio, 7703 Floyd Curl Drive, San Antonio, Texas 78284*

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There have been allegations in the media and in the courts that cell phones and other types of hand-held transceivers are a cause of cancer. There have also been numerous public objections to the siting of TV, radio and cell phone transmission facilities because of a fear of cancer induction. A recent publication in *Radiation Research* by Repacholi *et al.* (147, 631–640, 1997) which suggests that exposure to radiofrequency (RF) radiation may increase lymphoma incidence in mice has contributed to this controversy. The goal of this review is to provide biomedical researchers a brief overview of the existing RF radiation–cancer studies. This article begins with a brief review of the physics and technology of cell phones. It then reviews the existing epidemiological studies of RF radiation, identifying gaps in our knowledge. Finally, the review discusses the cytogenetics literature on RF radiation and the whole-animal RF-radiation carcinogenesis studies. The epidemiological evidence for an association between RF radiation and cancer is found to be weak and inconsistent, the laboratory studies generally do not suggest that cell phone RF radiation has genotoxic or epigenetic activity, and a cell phone RF radiation–cancer connection is found to be physically implausible. Overall, the existing evidence for a causal relationship between RF radiation from cell phones and cancer is found to be weak to nonexistent. © 1999 by Radiation Research Society

INTRODUCTION

There were approximately 50 million cellular phone users in the United States at the start of 1998, and the number of users worldwide is expected to increase to at least 200 million by the year 2000. Widespread use of cell phones

and other types of hand-held transceivers has led to increased concerns about possible health hazards, particularly concerns about brain cancer, as the antennas for these phones lie along the head during use (1). The issue first came to widespread public attention in 1993, when a Florida man appeared on a popular TV talk show to claim that his wife's brain cancer had been caused by radiofrequency (RF) radiation from her cell phone. The resulting lawsuit was dismissed in 1995 because of the lack of scientific and medical support for the claim, but the issue had entered the public arena. Since 1993, there have been numerous allegations in the media and in the courts that cell phones and other types of hand-held transceivers are a cause of cancer. There have also been numerous public and legal objections to the siting of TV, radio and cell phone transmission facilities because of a fear of cancer induction and/or promotion. These allegations have led to an increase in interest in the biology, physics and epidemiology of RF radiation. A recent publication in *Radiation Research* by Repacholi *et al.* (2) which suggests that exposure to RF radiation may increase the incidence of lymphoma in mice has further raised the profile of this issue, as has a series of papers by Lai and Singh (3, 4) that suggest that relatively low-level exposure to RF radiation can cause DNA strand breaks in rat brain cells.

The goal of this review is to provide biomedical researchers a brief overview of RF radiation–cancer studies. The review follows a risk assessment format. It begins with a brief review of the physics and technology of cell phones, followed by a discussion of the dosimetry of RF radiation, exposure standards, typical exposure levels, and possible mechanisms for biological effects. It then reviews the existing epidemiological studies of RF radiation, with an emphasis on identifying gaps in our knowledge. Next, the review discusses the cytogenetics literature on RF radiation, some controversial new studies that suggest that low-level exposure to RF radiation might cause DNA strand breaks, and the studies of long-term animal exposure. Finally, the

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TABLE 1
Triage of the Electromagnetic Spectrum

Realm	Frequency	Wavelength	Characteristics
Network	0 Hz–3 MHz	∞ m–100 m	Powerline and static fields Analyzed by Kirchhoff's and Ohm's laws Wavelength determines biological effects
Wave	3 MHz–300 THz	100 m–1 μ m	Radio- and microwaves Analyzed by Maxwell's equations Both wavelength and energy/photon determine biological effects
Photon	300 THz– ∞ THz	1 μ m–0 μ m	Visible light and ionizing radiation Energy/photon determines biological effects

review presents a weight-of-evidence evaluation of the human, animal, cellular and biophysical evidence relevant to assessing whether cell phone RF radiation might pose a carcinogenic risk to humans.

THE PHYSICS AND DOSIMETRY OF RF RADIATION FOR WIRELESS COMMUNICATIONS

The electromagnetic (EM) spectrum extends from d.c. (direct current) up to and into the realm of ionizing radiation. This spectrum is divided by scientists into ill-bounded subregions according to the state of technology, and the precise phenomena under consideration. One of many such *ad hoc* divisions is given in Table 1. Cellular and personal communication systems (PCS) reside in the “wave” realm, specifically in the ultra high frequency (UHF) region from 300 to 3000 MHz. Here classical mathematical analysis with Maxwell's equations is usually appropriate, and there are few, if any, biological effects that cannot be attributed directly or indirectly to the heating of tissue (5–8).

Channel Capacity and Modulation

By itself, a continuous wave of UHF radiation carries no information and communicates nothing. To make it useful, information is imposed upon it by a process known as modulation. Modulation takes the original wave (the carrier) and alters it at a rate somewhat slower than its nominal frequency by pulsing (digital modulation), by varying its amplitude (amplitude modulation, AM), or by varying its phase (phase modulation, FM).

The capacity of a given section of spectrum to carry information is distinctly limited (as is attested to, for example, by the great monetary value of VHF television channels). By the Shannon theorem (9), the limiting capacity, C (in bits/s), of a communication channel of bandwidth W (in Hz) is

$$C = W \cdot \log_2 \left(1 + \frac{S}{N} \right), \quad (1)$$

where S/N is the signal-to-noise ratio. Because the logarithm of a quantity is so strongly sublinear, C/W grows very slowly with S/N . Note that, although the Shannon limit establishes an upper limit to the transfer of information within

a channel, it does not tell one how to reach that limit in practice.

In “wired” communication, channel capacity is presently increased by adding optical fibers in parallel, with each fiber optically isolated from its neighbors. In personal wireless communication, it is increased by transmitting weak signals which attenuate rapidly near the transmitter, thereby enabling a given slice of the EM spectrum to be reused repeatedly in the same metropolitan area by geographically separated and isolated “cells” (hence the term “cellular” phones).

The manner in which a given section of EM spectrum is allocated among users affects the degree to which the Shannon limit can be approached when a section of spectrum is reused by geographically neighboring cells. In turn, the degree of reuse depends in part on how the information is encoded; in consequence, coding strategies have proliferated (9). The three basic ones are:

1. Frequency division multiple access (FDMA). The section of EM spectrum is subdivided into narrow slices (commonly 30 kHz wide) and one cellular subscriber at a time is permitted access to each slice. Within a slice, the carrier has information imprinted on it by either amplitude modulation, frequency modulation, or a digital modulation scheme. With the FDMA option, the time-domain signal from a cellular telephone looks much like a continuous carrier wave of constant amplitude.
2. Time division multiple access (TDMA). Again the section of EM spectrum is divided into slices, but not necessarily as narrow as those used in FDMA. Each frequency slice is then divided into short sets of time frames (e.g. a few ms), and each user is constrained to just one time frame of each set. With TDMA, the time-domain signal from a cellular telephone can look much like a continuous carrier wave, pulse-modulated at a fixed frequency.
3. Code division multiple access (CDMA). The section of EM spectrum is divided into a relatively few wide slices. A number of users use all of a slice all of the time, with the users of a slice distinguished by the way that their inputs are digitally encoded. With CDMA, the time-domain signal from a cellular telephone looks like an irregular train of 1.25-ms-wide pulses of carrier wave,

with the amplitude of each pulse varying in seemingly chaotic fashion about a fixed mean.

RF-Radiation Dose and Its Measurement

Neglecting the finer details, the energy flux (in W/m^2), also called the power density, across a surface is given by the relationship (10):

$$\text{power density} = \text{Re}(\hat{\mathbf{n}} \cdot \mathbf{S}) = \text{Re}[\hat{\mathbf{n}} \cdot (\mathbf{E} \times \mathbf{H}^*)], \quad (2)$$

where Re is the real part of the expression in brackets, \mathbf{S} is the complex (i.e. frequency domain) Poynting vector in W/m , $\hat{\mathbf{n}}$ is a unit vector perpendicular to the surface in question, \mathbf{E} is the complex electric field strength in V/m , and \mathbf{H}^* is the complex conjugate of the complex magnetic field strength in A/m . Power density measures the strength of an incident EM wave and is the favored metric of *external exposure* to a UHF field, in part because it is relatively easy to measure. The most stringent (for “uncontrolled environments”) of the ANSI/IEEE C95.1 (11) recommendations for average external exposure to UHF is

$$\begin{aligned} \text{power density (in } \text{W}/\text{m}^2) &= \frac{f(\text{in Hz})}{1.5 \times 10^8} = 2 \text{ to } 20 \text{ W}/\text{m}^2 \\ &= 0.2 \text{ to } 2.0 \text{ mW}/\text{cm}^2. \end{aligned} \quad (3)$$

The International Commission on Non-Ionizing Radiation Protection (ICNIRP) (12) has recently recommended similar power-density guidelines for limiting exposure of the general public to RF radiation. These limits keep humans from being overheated by restricting exposures to levels that are relatively weak (compared, for example, to summer sunshine, which peaks at roughly $1000 \text{ W}/\text{m}^2$).

Unfortunately, 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 W/kg). The SAR is generally used as the dose metric in laboratory experiments, although this would be a problematic concept if nonthermal effects of UHF radiation actually exist. For typical biological tissue, the SAR is given by

$$\text{SAR} = (\mathbf{E}_{\text{local}})^2 \times \frac{\sigma_{\text{eff}}}{\rho}, \quad (4)$$

where $\mathbf{E}_{\text{local}}$ is the r.m.s. electric field (in V/m) in the organism at the point of interest, σ_{eff} is the effective conductivity in S/m , and ρ is the local mass density in kg/m^3 . In “uncontrolled environments” ANSI/IEEE (11) limits the spatial-average SAR to $0.08 \text{ W}/\text{kg}$ whole-body, and to $1.6 \text{ W}/\text{kg}$ as averaged over any 1 g of tissue; under ANSI/IEEE it is permissible to average both power density and SAR over 30-min intervals. The 1998 ICNIRP (12) “basic restrictions” on SAR are similar to the ANSI/IEEE (11) limits.

To bring the possible consequences of external exposure into perspective, suppose the power density is $\sim 1 \text{ W}/\text{m}^2$. If this influx is absorbed, entirely and uniformly, in a tissue

layer $1000 \times 1000 \times 1 \text{ mm}$, it corresponds to an SAR of $\sim 1 \text{ W}/\text{kg}$. Further, at 1000 MHz , it corresponds to ~ 1 photon/s deposited in each $1 \times 1 \times 1\text{-nm}$ cube of tissue. It is difficult to see how weak UHF photons arriving at this rate can deposit energy fast enough to have a measurable effect on chemical bonds or biological systems.

SAR is estimated in three ways:

1. Micro-antennas. Small antennas can be used to determine the local electric field in tissue, and if σ_{eff} is known, the SAR can be computed using Eq. (4). Sometimes, however, it is daunting to place the antenna where it is needed, and technology has yet to develop suitable antennas with sub-millimeter characteristic dimensions. In addition, σ_{eff} may not be known for the tissue and frequency of interest.
2. Miniature thermal probes. RF radiation causes heating of tissue which can be detected and used to infer the SAR in the neighborhood of a temperature probe. In a medium with spatially homogeneous SAR,

$$\text{SAR} = c_p \frac{\delta T}{\delta t}, \quad (5)$$

where c_p is the specific heat at constant pressure in $\text{J}/(\text{kg} \cdot \text{K})$, and δT is the change in tissue temperature over a time δt . In principle, SAR determination is as simple as turning on the RF-radiation source and measuring the temperature change as a function of time. Unfortunately, heat diffuses, and spatially nonuniform SAR can, over the time needed to produce a measurable temperature offset, be significantly confounded by thermal diffusion. Moreover, the “nonperturbing” 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. Numerical modeling. Fortunately, the numerical modeling of macroscopic bodies 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 actually work when tested (13). However, FDTD modeling can be time consuming and expensive.

Human Exposure

The meaning of the $1.6 \text{ W}/\text{kg}$ local SAR limit in the IEEE/ANSI standard (11), and the similar $2\text{--}4\text{-W}/\text{kg}$ local SAR restrictions in the ICNIRP guidelines (12), can be judged by noting that this closely matches the human whole-body resting metabolic rate, and is of the order of one-eighth of the brain’s resting metabolic rate. In the United States, a typical cellular telephone has a time-averaged power output of 600 mW or less and yields numerically

modeled brain SARs which may sometimes exceed the 1.6-W/kg limit, but which generally lie within the ANSI/IEEE (11) "controlled environment" limit of 8 W/kg averaged over 6 min (1, 14). This 600 mW is less than 1% of the body's normal resting metabolic output and under 4% of the brain's normal resting metabolic output. The telecommunications industry is interested in reducing brain SAR as much as possible, not only to guard against any possible biological consequences, but also to achieve a more mundane engineering goal: UHF energy deposited in the brain depletes the battery without any useful communication function, and short battery life is a major customer complaint.

Possible Mechanisms for Biological Effects

To effect a change in biological material through which it is passing, an EM wave must deposit enough energy to alter some structure significantly. But every material particle within the body already possesses an average thermal kinetic energy (in joules, J) of the order of kT , where k (1.38×10^{-23} J/K) is the Boltzmann constant and T is the absolute temperature (in kelvin, K), and these particles continually collide with other particles of similar energy. For a change to occur in biological material, the EM wave seemingly should transfer energy considerably above kT to selected particles, and at 310 K (37°C, body temperature), kT is 4.3×10^{-21} J. Another standard of comparison is the chemical bond, because to be effective in promoting change the field should be able to deposit packets of energy larger than the bond energy, and bonds are typically within an order of magnitude of an electron volt (1.6×10^{-19} J) (6). The energy carried by an EM photon is precisely hf , where h (6.625×10^{-34} J s⁻¹) is the Planck constant and f is the frequency of the wave in Hz (cycles/s); and thus in the UHF realm (300 to 3000 MHz) the energy of one photon ($<2 \times 10^{-24}$ J) is less than 0.1% of either kT (4×10^{-21} J) or the bond energy (1.6×10^{-19} J).

Alternatively, one might imagine that biological material could be altered by the translation of a charged particle within it. In condensed matter (e.g. tissue), where ballistic ion motion is not possible, such translation is collision-dominated and particle velocity obeys the mobility equation

$$\mathbf{v} = \text{sgn}(q)\mu\mathbf{E}, \quad (6)$$

where \mathbf{v} is the vector ion velocity in m/s, $\text{sgn}(q)$ is the sign of the ionic charge, \mathbf{E} is the vector time-domain electric field in V/m, and μ is the ionic mobility in m²/(V s). In an aqueous solution at body temperature, even an atypically mobile ion such as chloride will possess a mobility of the order of only 1×10^{-7} m²/(V s) (6). Even at an extremely high field strength such as 100 V/m, this implies a net displacement (over a half cycle of an applied UHF field) of the order of 10^{-14} m, a distance comparable to the diameter of an atomic nucleus.

Because the photon energy within the UHF realm is far

less than either kT or the bond energy, many observers would argue that there is little prospect of UHF irradiation having biological activity (let alone carcinogenic sequelae) at subthermal power levels.

EPIDEMIOLOGICAL STUDIES OF RF-RADIATION EXPOSURE AND CANCER

Epidemiological studies of RF radiation present a striking contrast to those of ionizing radiation. The dose-response curve for induction of cancer by ionizing radiation has been determined primarily from one high-dose event (Hiroshima-Nagasaki) and verified in numerous studies of occupationally exposed and medically treated populations. Many studies now strive to characterize the shape of the dose-response curve at low doses. Although RF-radiation energy has been part of our society for at least as long as ionizing radiation, and several occupations have exposure potential, no epidemiological study has clearly shown RF radiation to be carcinogenic. Existing exposure limits (11, 12), and the thermal hazard, keep population exposures relatively low, and there are unlikely to be any long-term population exposures at high doses. At present, occupational exposures either are below the limits, or if higher are so only intermittently and/or they are higher only in small groups of workers. In addition, although sophisticated instruments have been developed to measure levels of RF radiation, no completely satisfactory methods exist to continuously monitor individual exposures or to estimate exposures to RF radiation 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 putative carcinogenic effects of exposure to RF radiation remains a challenge for epidemiology. Despite these limitations, some information regarding the question of cancer can be obtained from existing epidemiological studies.

Criteria for Selection of Epidemiological Studies of RF Radiation

In reviewing the literature, all reports with exposures to RF radiation were included, so that the database was not limited to the frequencies used by cellular and PCS systems. Studies that considered only power-frequency (50 or 60 Hz) exposures were not considered pertinent. Many post-1979 studies address "electrical workers"; these were not considered if RF radiation was not specifically and appropriately identified. Standard criteria were used to evaluate the studies (15, 16). The assessment criteria included proper selection and characterization of exposed and control groups, adequate characterization of exposure, length of follow-up adequate to assess cancer development, consideration of bias and confounding, adequacy of sample size, and appropriateness of methods and statistical analysis.

The epidemiology of cancer and RF radiation includes studies of cancer mortality or incidence in cohorts of people exposed to RF fields, case-control studies of individuals who have had specific types of cancer, geographic correlation studies that compare cancer rates among areas with different potential exposures to RF radiation, and "cancer cluster" studies. Geographic correlation studies (e.g. 17–19) estimate the presence of RF radiation in geographic areas and correlate these estimates with disease rates in those areas. Even when the design of geographic correlation studies is optimal, they are considered exploratory and cannot be used for determining causality. Therefore, geographic correlation studies are not included in this review.

Reports of isolated cases, or even clusters of disease cases, provide limited and potentially misleading information. The major steps in evaluating reports of "cancer clusters" are: (1) define a logical (as opposed to arbitrary) boundary in space and time, (2) determine whether an excess of a specific type of cancer has actually occurred, and (3) identify common exposures and characteristics (20). The above steps have not generally been followed in studies of RF radiation, and reports of such cancer clusters (e.g. 21, 22) are not included in this review. Another study of RF radiation omitted from review is a recent mortality study of cellular and mobile telephone users that did not include information on cancer (23).

Studies of Workers with Exposure to RF Radiation

1. Radar laboratory workers

Hill² studied the long-term health, including cancer, of employees of the laboratory at the Massachusetts Institute of Technology who worked on research and development of radar applications between 1940 and 1946 (the "Rad Lab"). The results are unpublished but are available in a dissertation.² Exposure was estimated for each individual based on the work history, predominant job, and characteristics of the contemporary (1943) radar systems. The maximum near-field power density was estimated to be 2–5 mW/cm².

The cohort included 1456 subjects and had a long period of follow-up (to 1975). Exposure was assessed by linking job descriptions to the characteristics of the workplace, a method that should provide a better surrogate of exposure to RF radiation than a single job title. Mortality rates in the workers were compared to the U.S. male general population as well as to a group of physician specialists. The physicians were selected as a control because their socioeconomic status was similar to the college-educated Rad Lab workers. To limit confounding, the physicians were from specialties which were considered unlikely to have had occupational exposure to ionizing radiation.

² D. A. Hill, *Longitudinal study of a cohort with past exposure to radar: the MIT Radiation Laboratory follow-up study*. University of Michigan Dissertation Service, Ann Arbor, MI, 1988.

Based on life-table models, the risks for cancers of the brain and central nervous system, leukemia, lymphoma or Hodgkin's disease were not significantly elevated in the Rad Lab workers compared to the physicians (Table 2). Compared to the U.S. white male population, overall cancer in the Rad Lab cohort was significantly less than expected, and cancers of the brain and central nervous system were slightly less (but not significantly so) than expected. Cancer of the gallbladder and bile ducts was much more frequent in the Rad Lab workers, as was cirrhosis of the liver. When cancer rates in the Rad Lab workers were examined by exposure level, there was no evidence of increased risk with higher exposures; that is, there was no evidence for an exposure-response trend.

2. Foreign Service workers

From 1953 to 1976, low-intensity microwaves were aimed at the American Embassy building in Moscow. Lilienfeld *et al.* (24) performed a comprehensive survey of the health experience of 1800 foreign service employees who had been assigned to work at the embassy. Their health experience was compared to 2500 foreign service workers assigned to other East European embassies. Measurements of several different exposed areas of the Moscow embassy in three periods indicated the maximum exposure was at 0.015 mW/cm² (at 0.5 to 9 GHz) for 18 h/day. For most of the exposure period, the maximum level was lower. The embassies of the comparison population were said to be at background levels.

Lilienfeld *et al.* (24) found no evidence that individuals in the Moscow group experienced higher mortality for any cause, or higher mortality from cancer in general or from any cancer subtype (Table 2). Although this study was well-designed, the relatively small cohort size and short follow-up time limited its power. The power of this study is also limited by the extremely low levels of RF radiation, although it should be noted that the levels are similar to those found near cell phone base station antennas.

3. U.S. Naval personnel

Robinette *et al.* (25) studied the cancer mortality of 20,000 U.S. Navy personnel who were likely to have encountered RF radiation in their occupations during the Korean War. The follow up was about 20 years (early 1950s through 1974). The surrogate for exposure was occupation, grouped for high and low potential exposure, based on ship-board monitoring and documented accidental exposures. Although exposures in the high-exposure group were assumed to average less than 1 mW/cm², the three high-exposure categories included opportunity for exposure in excess of 10 mW/cm². For a subset of the personnel, exposures were assessed based on the power rating of the radar on the ships to which they were assigned and by duration of the assignment; this assessment was used to assign a "hazard number" to each occupation. This analysis iden-

TABLE 2
Epidemiological Studies of RF-Radiation Exposure and Cancer^a

Source	Cohort size ^c	Risk estimates ^b			
		All cancer	Leukemia	Hematopoietic plus lymphatic	Brain cancer
Hill (footnote 2)	1,456	0.6 (0.5–0.7)	0.8 (0.3–1.9)	—	0.7 (0.1–1.9)
Lilienfeld <i>et al.</i> (24)	4,179	0.9 (0.5–1.4)	2.5 (0.3–9.0)	—	0.0 ^{d,e}
Robinette <i>et al.</i> (25)	40,890	1.4 ^e	—	1.6 ^e	—
Milham (28)	67,829	0.9 (0.8–1.0)	1.2 (0.9–1.7)	1.2 (1.0–1.5)	1.4 (0.9–2.0)
Tynes <i>et al.</i> (28)	37,945	—	2.8 ^f (1.3–5.4)	—	0.6 ^f (0.1–1.8)
Szmigielski (30)	(3,017 RF-exposed) 127,800 ^g	2.1 ^h (1.1–3.6)	—	6.3 ^h (3.1–14)	1.9 ^h (1.1–3.5)
Lagorio <i>et al.</i> (31)	(3% exposed) 302 (females)	2.0 (0.7–4.3)	—	—	—
Muhm (32)	304	0.3 (0.04–1.2)	4.4 (0.1–24)	3.3 (0.4–12)	—
Grayson (33)	230 ⁱ	—	—	—	1.5 ^j (0.9–2.5)

^a Overall cancer, brain cancer, hematopoietic cancer and lymphatic cancer were the most common cancer types studied. Some authors assessed other types of cancer as well, including lung cancer (25, 28) and gastrointestinal cancer (25, 30).

^b Standardized mortality ratio unless noted (with 95% confidence intervals where available).

^c Males unless otherwise noted.

^d No brain cancers in the exposed cohort; not unexpected, given the cohort size and follow-up time.

^e Not statistically significant ($P > 0.05$) according to the authors.

^f Standardized incidence ratio.

^g Annual mean population; rates not adjusted for age, entry or withdrawal.

^h Incidence rate ratio, not standardized.

ⁱ Number of cancer cases, as this is a case-control study.

^j Risk estimate as odds ratio.

tified an increasing trend for potential for higher exposures within the exposed occupations.

In the high-exposure occupations, the age-standardized mortality ratios were higher for cancer in general and for cancers of the lymphatic and hematopoietic system (Table 2) and respiratory tract; however, only the increase in respiratory tract cancer was statistically significant. No exposure–response trends were apparent either by occupation or by hazard number. This study provides little indication of a link between exposure and cancer; however, some power may have been lost because the high-exposure group was compared to the total group rather than just to the low-exposure group.

Garland *et al.* (26, 27) studied the relationship between occupation and non-Hodgkin's lymphoma and leukemia in a cohort of U.S. Navy personnel. Although RF radiation was not specifically studied, the Naval occupations studied were comparable to those in the study of Robinette *et al.* (25). The occupations that Robinette *et al.* had identified as the high-exposure group (electronics technician, aviation electronics technician and fire control technician) had lower rates of non-Hodgkin's lymphoma and leukemia than the general male population.

4. Amateur radio operators

The hypothesis that exposure to RF radiation is related to cancer was tested in a cohort study of amateur radio operators by Milham (28). Milham considered possession of an amateur operator's license to be a surrogate for ex-

posure to both RF and power-frequency fields. No information was provided on the frequencies emitted, the power density levels at the operator's position, or the hours of use for individuals; and the author notes that amateur operators may be exposed to possible cancer-causing substances in soldering fumes and solvents when they maintain their equipment. The cohort was relatively large, but limitations in exposure assessment and the incomplete ascertainment of deaths limit the value of the results.

Mortality from all causes, as well as overall cancer mortality, was lower than in the general population; this decrease was statistically significant (Table 2). The risk for acute myelogenous leukemia was increased and reached statistical significance. Cancer of the respiratory system was significantly decreased. The report states that no other causes of death had significant excess risks.

5. Norwegian electrical workers

Tynes *et al.* (29) classified "electrical occupations" into five categories of exposure based on discussions with workers and technical experts; one of the categories specified exposure to RF fields. Although no field measurements were taken, the exposure assessment and study design provide more reliable information on exposure to RF radiation than most other occupational "EMF" studies. Particular strengths were the use of national occupation and cancer registries and the use of cancer incidence rather than mortality. Use of occupation registries to identify all electric workers in the cohort and use of the national cancer registry

to identify incident cases are methods that should reduce bias by limiting loss to follow-up. The assessment of occupation for the workers' lifetime is an improvement on the death certificate data that have been used in previous studies. Incidence is a more reliable indicator of cancer occurrence over time than mortality, since not all cancers lead to death. Nevertheless, occupation was evaluated at one time, so the number of years in the job was not known, and exposure was not measured at any workplace. The group whose jobs were assumed to result in exposure to RF radiation (radio/telegraph operators plus radio/TV repairman) did not have an elevated risk of brain cancer, but did have an increased risk of leukemia (Table 2).

6. Polish military radar workers

Szmigielski *et al.* (30) studied cancer in a cohort of about 120,000 Polish military personnel, of whom 3% had worked with heat sealers that used RF radiation. Exposure was determined from assessments of field levels at various service posts, of which 80–85% were said to have levels below 0.2 mW/cm². No consideration was given to the length of time at the post or to the job at the post. Life-table methods suitable for studying a cohort over time were not used, there are no data on person-years, and there is no evidence of age adjustment (needed to prevent bias from age differences between the exposed and comparison groups).

Results were presented only as rates of cancer incidence, so that neither the actual number of cases nor the total number of the personnel at risk is known, and the author states that some of the rates were highly unstable. Nearly all of the reported average annual rates are low, as would be expected from the relatively short follow-up. Cancer of all types, brain cancer, cancer of the alimentary canal, and cancer of the lymphatic and hematopoietic organs were reported to be greater in exposed personnel (Table 2). The methods of data collection and analysis are described inadequately or are unsuitable, and this limits the credibility of the data. 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 criteria for acceptability.

7. Female heat sealer operators

Lagorio *et al.* (31) compared the cancer mortality of female plastics workers who used heat sealers that used RF radiation to the cancer mortality of the general population of the area. Exposure assessment was based on the time assigned to jobs using RF-radiation heaters. Estimates of exposure to RF radiation were based on a survey carried out in the past, which indicated that the standard (1 mW/cm²) had been exceeded. The data from this survey were not provided.

Among heat sealer operators in this small cohort, there was a higher than expected overall rate of cancer deaths

(based on six cases). However, neither chance, other work site exposures, nor other confounding factors could be ruled out. In addition, 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 work area also included exposure to chemicals associated with cancer (solvents and vinyl chloride) that may have confounded the results.

8. Electromagnetic pulse test program

Prompted by the report of a case of leukemia, Muhm (32) examined the cancer mortality over a period of 11 years in a cohort of 304 workers in a military electromagnetic pulse test program. These workers were exposed to high-intensity electromagnetic pulses that included RF fields at 10 kHz to 100 MHz. The excess cancer risk (Table 2) is uninformative because of the limited size of the cohort and inclusion of the index case.

9. U.S. Air Force

Grayson (33) assessed the occurrence of brain tumors in a cohort of male Air Force personnel who had served at least 1 year in an 18-year study period. The categories of RF-field exposure intensity of "probable" and "possible" or "no exposure" were based on overexposure reports; few details are provided except that jobs involving maintenance and repair of emitters were likely to be in the "probable" category. Potential exposure scores were combined with duration to summarize exposure. This system is very crude because incidents of overexposure cannot reliably be assumed to reflect opportunities for daily or repeated exposure of other workers in the job class. Brain tumor risks, adjusted for age, race and socioeconomic status (i.e. rank), were elevated for "probable" and "possible" exposure categories combined, but no exposure–response trend was seen.

Summary of Epidemiological Studies of RF-Radiation Exposure

The majority of the epidemiological studies of RF radiation (Table 2) have deficiencies in exposure assessments because occupation or job title was used as a surrogate measure of exposure. Although some of the studies provided some information on the opportunity for exposure at the job site, others did not, and none included systematic measurements of exposures for individuals. For studies of reasonable design, the higher the quality of the exposure assessment, the greater the confidence that can be placed in the results.

Based on the criteria described above, more weight can be given to the three epidemiological studies with acceptable design and analysis, larger sample size and longer follow-up time² (25, 28). These three studies do not show statistically significant associations between RF-radiation

exposure and either cancer in general or any specific type of cancer. The other studies using acceptable designs (24, 31, 32) have more significant limitations in exposure assessment, case ascertainment or follow-up time; these three studies also do not suggest that RF-radiation exposure increases the risk of cancer. The lack of associations with total cancer, or with any specific type of cancer, suggests that RF radiation is unlikely to have a strong causal influence on cancer; however, these studies have less power to detect changes in less common cancers, including brain and leukemia. Case-control studies in progress regarding brain cancers and cellular telephone use may provide additional information.

A set of criteria, commonly called the Hill criteria (34), are used to guide evaluation of epidemiological data for evidence of causality. The more firmly the Hill criteria are met, the more convincing is the evidence that observed associations imply cause and effect. Strong associations in epidemiological studies (i.e. high relative risks), consistent results across different study populations, increase in disease incidence with an increase in the level or likelihood of exposure (i.e. exposure-response trends), correct temporal sequence, and consistent evidence for a specific disease are considered in the context of coherence with the biological evidence. To support a cause and effect relationship, the data must present a logically coherent and consistent picture. Clearly, the epidemiology of RF radiation does not fare well when viewed in the context of the Hill criteria (34): The associations are not strong, consistent, or specific for any type of cancer, and exposure-response trends are not obvious.

In a case such as this, where epidemiological evidence for a link between an agent and a disease is weak and the effect is biophysically implausible, laboratory studies become critical for risk evaluation (16, 34, 35). If there were strong cell or animal evidence that RF-field exposure was carcinogenic, it might make the few associations reported in these epidemiology studies more believable. Conversely, if appropriate cell and animal studies were done and these studies consistently failed to show any evidence for carcinogenicity of RF radiation, then we would tend to discount such weak epidemiological evidence, particularly in view of the biophysical implausibility.

EVALUATION OF THE GENOTOXIC POTENTIAL OF RF RADIATION

Investigation of the genotoxicity of an agent is a standard method for assessing its carcinogenic potential (15, 16). Genotoxicity assays can be done after exposure of cells in cell culture or with cells harvested from animals that have been exposed to the agent being tested. A number of investigators have examined the genotoxic potential of RF radiation using human and rodent cells (for recent reviews, see refs. 7 and 8). While the majority of the studies have not revealed significant genotoxicity (34-44), some have

reported positive effects (3, 4, 45, 46). The positive reports by Maes *et al.* (46) and Lai and Singh (3, 4) are of particular interest.

Maes *et al.* (46) exposed human lymphocytes *in vitro* to 2450 MHz RF fields for 30-120 min at an SAR of 75 W/kg and reported a significant increase in chromosomal aberrations. These data are difficult to interpret because of uncertainties concerning the dosimetry of the RF radiation and the temperature measurements. Of particular concern is the possibility that the temperature probe (a metallic thermistor which was fed through a hypodermic needle placed in the exposure vessel) might have been heated by the RF radiation, resulting in heat damage to those cells touching the needle. There is also uncertainty concerning the SAR measurements, which were done during a separate experiment.

Lai and Singh (3, 4) reported that a 2-h exposure of rats to 2450 MHz RF radiation at SARs of 0.6 or 1.2 W/kg caused DNA strand breaks in brain cells. They observed DNA strand breaks both immediately and 4 h after RF irradiation. Their observation of increased DNA damage after a 4-h interval is inconsistent with known mechanisms of repair of DNA damage produced by other types of radiation (47). In addition, previous work by Meltz *et al.* (41) had not found excess strand breaks after *in vitro* exposure of mammalian cells to RF radiation.

In view of the continuing debate about the possible genotoxic potential of RF radiation and previous negative studies, these studies by Maes *et al.* (46) and Lai and Singh (3, 4) need independent replication. Vijayalaxmi *et al.* (48-50) and Malyapa *et al.* (51-53) have attempted such studies.

Cytogenetic Damage in Mice Chronically Exposed to RF Radiation

Vijayalaxmi *et al.* (48, 49) assessed cytogenetic damage in blood and bone marrow cells of cancer-prone mice that were chronically exposed to 2450 MHz RF radiation. The study was part of a larger investigation designed to determine whether chronic exposure of mammary tumor-prone mice to RF radiation would result in a higher incidence of mammary tumors (54, 55).

Two hundred female mice were randomly divided into two groups. One group was exposed to 2450 MHz RF radiation at an SAR of 1.0 W/kg (20 h/day, 7 days/week, 18 months) and the other group was sham-exposed. The exposure system and dosimetry have been described in detail by Vijayalaxmi *et al.* (48). An additional 75 mice were maintained as sentinel animals and used for periodic examinations of health status. Seven of the sentinel mice which survived through the full 18-month study period were used as positive controls; they were injected with mitomycin C (1 mg/kg) and sacrificed 24 h later. Peripheral blood and bone marrow smears were made from all mice that were alive at the end of the 18-month study period.

TABLE 3
Micronucleus Frequencies in Peripheral Blood and Bone Marrow of Cancer-Prone Mice Chronically Exposed to RF Radiation^a

Group	Number of mice	Micronuclei/1000 PCEs ^b	
		Peripheral blood	Bone marrow
All surviving mice:			
Sham-exposed	58	4.0 ± 0.5	5.7 ± 0.8
RF-radiation-exposed ^c	62	4.5 ± 0.6	6.1 ± 0.9
Positive control ^d	7	50.9 ± 3.1	55.2 ± 2.4
Mammary tumor-bearing mice:			
Sham-exposed	8	4.1 ± 0.4	5.5 ± 0.8
RF-radiation-exposed ^c	12	4.6 ± 0.5	6.1 ± 0.9

^a Data from Vijayalaxmi *et al.* (48, 49).

^b For each mouse, 2000 consecutive polychromatic erythrocytes (PCEs) were measured, and the micronucleus frequency is shown with its standard deviation.

^c 2450 MHz, 20 h/day, 7 days/week for 18 months at a SAR of 1.0 W/kg.

^d Mitomycin C (1 mg/kg) 24 h prior to sacrifice.

For each mouse, the incidence of micronuclei was determined from the examination of 2000 polychromatic erythrocytes in peripheral blood and in the bone marrow.

At the end of the 18-month exposure period, the study group consisted of 62 mice exposed to RF radiation and 58 sham-exposed controls. The mean number of micronuclei per 1000 polychromatic erythrocytes in the exposed mice was 4.5 (range: 3.5–6.0) in peripheral blood and 6.1 (range: 4.5–7.5) in bone marrow (Table 3). The corresponding micronucleus frequency in sham-exposed control mice was 4.0 (range: 3.0–6.0) in peripheral blood and 5.7 (range: 4.0–7.0) in bone marrow (Table 3). The difference between chronically exposed and sham-exposed mice was statistically significant for both peripheral blood ($P < 0.001$) and bone marrow ($P = 0.011$).

Although the difference between RF-radiation-exposed and sham-exposed mice was statistically significant, the biological relevance must be put in perspective. The increase in the frequency of micronuclei in the mice exposed to RF radiation (compared to the frequency in the sham-exposed mice) was only 1 additional micronucleus per 2000 cells. Biologically, this is a very small change, in a large number of animals, exposed to RF radiation over a very long period. Based on this evidence alone, it is premature to conclude that the RF-radiation exposure acted as a mutagen. Furthermore, the statistical increase in the frequency of micronuclei in the erythrocytes was not correlated with a carcinogenic outcome, as there was no evidence that this exposure was carcinogenic [see discussion of refs. (54, 55) in the next section]. Furthermore, comparison of mice exposed to RF radiation and sham-exposed control mice which had developed mammary tumors indicated no significant differences in the incidence of micronuclei in their

peripheral blood or in bone marrow (both $P > 0.05$) (Table 3).

Cytogenetic Damage in Human Lymphocytes Exposed to RF Radiation

Vijayalaxmi *et al.* (50) also designed studies to investigate cytogenetic damage in human blood lymphocytes after exposure to 2450 MHz RF radiation. Blood samples were exposed *in vitro* to continuous-wave 2450 MHz RF radiation; exposure was either continuous or intermittent (30 min on and 30 min off) for a total exposure period of 90 min. The intermittent exposure was intended to investigate any possible effect of turning the RF field on and off repeatedly and was not meant to mimic any technology in current use.

The exposure system and dosimetry have been described in detail by Vijayalaxmi *et al.* (48). The mean power density measured at the distance of the cells from the antenna was 5.0 mW/cm². The SAR was calculated using FDTD analysis (Arthur W. Guy, personal communication); more than 75% of the cells were exposed to SARs greater than 1.72 W/kg, and more than 50% of the cells were exposed to SARs greater than 6.53 W/kg. Sham-exposed blood samples were used as negative controls. Positive controls were exposed to 1.5 Gy ¹³⁷Cs γ radiation.

Immediately after the RF-radiation exposure, the lymphocytes were cultured to determine the incidence of chromosomal aberrations and micronuclei. The incidences of chromosomal damage, exchange aberrations and acentric fragments in the lymphocytes exposed to RF radiation (continuous or intermittent) were not significantly different from those in sham-exposed cells (Table 4). Similarly, the frequency of micronuclei in the lymphocytes exposed to RF radiation was not significantly different from that in the sham-exposed cells. When the continuous and intermittent exposures were compared, there were no significant differences in any of the cytogenetic parameters investigated.

Under the RF-radiation exposure conditions used in these studies, there were no significant differences between RF-radiation-exposed and sham-exposed human lymphocytes with respect to proliferation kinetics (50), chromosomal aberrations (Table 4) or micronucleus frequency (Table 4). These results do not support those of Maes *et al.* (46), but it should be noted that Maes *et al.* used a much higher SAR (75 W/kg).

DNA Damage after In Vitro Exposure to RF Radiation

Malyapa *et al.* designed *in vitro* (51, 52) and *in vivo* studies (53) to replicate and extend the studies of Lai and Singh (3, 4) which had reported that exposure of animals to RF radiation could cause DNA strand breaks in brain cells. Although the results reported by Lai and Singh were based on *in vivo* exposures, *in vitro* studies are valuable because the *in vitro* systems allow careful monitoring and control of cell growth, temperature (to avoid thermal artifacts), dosimetry and other experimental conditions. DNA

TABLE 4
Chromosome Damage in Cultured Human Blood Lymphocytes Exposed to RF Radiation^a

Group	Chromosome damage ^b	Exchange aberrations ^b	Acentric fragments ^b	Micronuclei ^c
Continuous RF-radiation exposure:				
Blood donor 1				
Sham-exposed	2.0 ± 0.0	0.0	2.0 ± 0.0	20 ± 1
RF-radiation-exposed ^d	3.0 ± 1.0	0.3 ± 0.6	2.7 ± 1.1	22 ± 2
Positive control ^e	64.7 ± 5.5	54.7 ± 4.0	31.7 ± 2.5	333 ± 26
Blood donor 2				
Sham-exposed	3.3 ± 0.6	0.0	3.3 ± 0.6	23 ± 1
RF-radiation-exposed ^d	4.3 ± 0.6	0.3 ± 0.6	4.0 ± 1.0	25 ± 1
Positive control ^e	66.3 ± 1.5	48.0 ± 7.0	36.3 ± 8.3	341 ± 32
Intermittent RF-radiation exposure:				
Blood donor 1				
Sham-exposed	2.7 ± 1.1	0.0	2.7 ± 1.1	26 ± 3
RF-radiation-exposed ^f	4.0 ± 1.0	0.3 ± 0.6	3.7 ± 0.6	28 ± 4
Positive control ^e	61.3 ± 2.5	47.0 ± 3.0	43.3 ± 11.1	304 ± 30
Blood donor 2				
Sham-exposed	3.3 ± 0.6	0.0	3.3 ± 0.6	24 ± 2
RF-radiation-exposed ^f	4.0 ± 1.0	0.3 ± 0.6	3.7 ± 1.2	28 ± 1
Positive control ^e	65.0 ± 11.8	49.7 ± 7.1	42.0 ± 6.1	290 ± 15

^a Data from Vijayalaxmi *et al.* (50).

^b Per 200 metaphases, with standard deviation.

^c Per 2000 binucleate cells, with standard deviation.

^d 2450 MHz, continuous for 90 min at 5 mW/cm² (SAR of 1.7–6.5 W/kg).

^e 1.5 Gy ¹³⁷Cs γ rays.

^f 2450 MHz, 90 min at 5 mW/cm² (SAR of 1.7–6.5 W/kg) in an intermittent (30 min on/off) schedule.

damage was measured by the version of the alkaline comet assay used by Olive *et al.* (56), after demonstrating (51, 57) that the sensitivity of this assay was comparable to the version developed by Singh *et al.* (58).

Cells were exposed *in vitro* to 2450 MHz continuous-wave RF radiation, to 836 MHz frequency-modulated RF radiation, or to 848 MHz RF radiation with CDMA modulation; the latter two exposure regimens simulate protocols used by cell phones in the U.S. Exposures were carried out in an exposure system that is described in detail in Moros *et al.* (59). SARs were 0.7 and 1.9 W/kg for the 2450 MHz study and 0.6 W/kg for the 836 and 848 MHz studies (59). Exposures were done at 37°C for 2, 4 or 24 h, and analysis of DNA strand breaks was done immediately after irradiation, except for the 2-h exposure, where analysis was done both immediately and after 4 additional hours at 37°C [to simulate one of the protocols of Lai and Singh (3)].

The alkaline comet assay did not reveal any evidence of DNA damage in cells exposed to RF radiation (Fig. 1). No DNA damage was observed even when cells treated with 10 μ M bromodeoxyuridine (BrdU) were exposed at 836 or 848 MHz for 2–24 h, although when cells labeled with BrdU were exposed to fluorescent light, gross DNA damage was detected (52). Therefore, no evidence of DNA damage was observed when cells were exposed *in vitro* to the frequencies tested.

DNA Damage after *In Vivo* Exposure to RF Radiation

The *in vivo* studies of Malyapa *et al.* (53) were designed to be a replication of those of Lai and Singh (3) with three exceptions: The method of Olive *et al.* for the alkaline comet assay was used (56, 57), computerized image analysis was used to measure comet parameters, and additional methods of euthanasia were assessed.

Rats were either sham-exposed or exposed for 2 h to 2450 MHz RF radiation at an SAR of 1.2 W/kg. After exposure, rats were euthanized simultaneously by CO₂ asphyxia, and the brains were dissected out sequentially. Irrespective of RF irradiation, the order in which rats were dissected determined the amount of DNA damage (Fig. 2). It appears that the DNA damage determined by this technique is largely the result of the delay between death and the removal of the brain, and the level of damage produced by this delay exceeded that seen after exposure to 2 Gy (53). The degree of damage is not surprising, as hypoxia of even a 2–3-min duration causes irreversible damage to brain cells, leading to death by apoptosis (60). When rats were euthanized with CO₂ asphyxia, and brain removal was carried out immediately, no difference between the sham-exposed and RF-radiation-exposed groups was observed (Fig. 3A). However, the rat-to-rat variability in the time to death by asphyxia led to high mean values of comet parameters and high standard deviations.

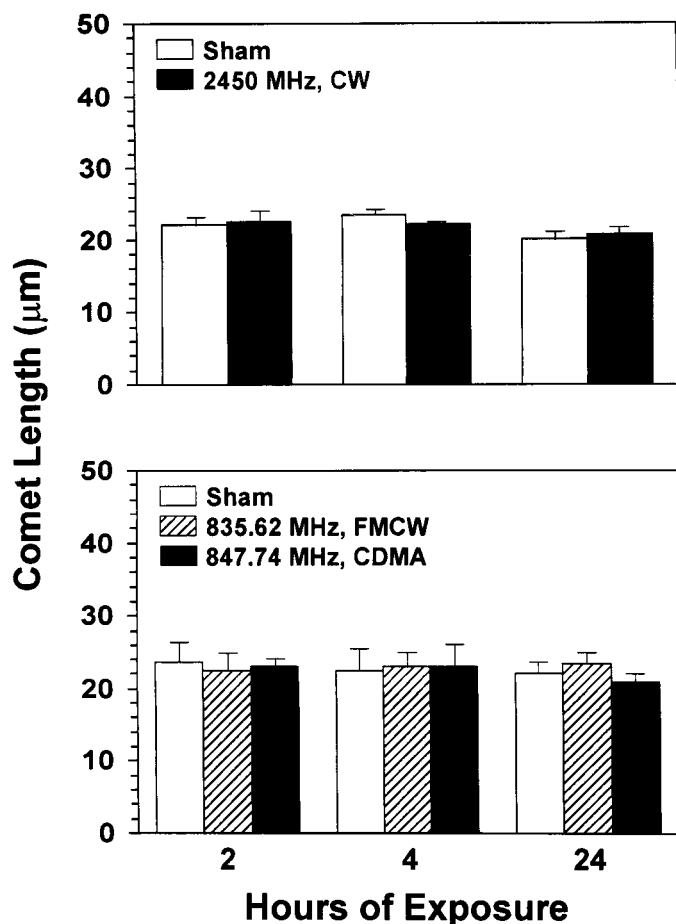


FIG. 1. Effect on comet length of exposure of mouse fibroblasts to 2450 MHz RF radiation (SAR = 1.9 W/kg), 835.62 MHz frequency-modulated RF radiation (SAR = 0.6 W/kg), and 847.74 MHz CDMA RF radiation (SAR = 0.6 W/kg). Each bar represents the mean of three independent experiments, and the error bar shows the standard error. Data from Malyapa *et al.* (51, 52).

Because CO₂ asphyxia caused DNA damage in rat brain cells that could be detected by the alkaline comet assay, additional studies were carried out using guillotine euthanasia immediately after 2 h of exposure to 2450 MHz RF radiation at 1.2 W/kg. Not only was there no difference between RF-radiation-exposed and sham-exposed groups with this method, there was also very little experimental variability in the comet assay (Fig. 3B). The experiment was repeated using a 4-h interval after 2 h of RF-radiation exposure [as done in one of the protocols of Lai and Singh (3)]. Again, no evidence of DNA damage was observed in rat brain cells isolated from the exposed group (Fig. 3C).

These results are in contrast to those reported by Lai and Singh (3, 4), who found excess DNA strand breaks both immediately and 4 h after exposure to RF radiation. There is one other report (61) in which the alkaline comet assay was used to study DNA damage after *in vivo* exposure to RF radiation. In that study (61), increases in comet length were reported for both RF-radiation-exposed and sham-exposed animals, possibly due to the stress of transportation

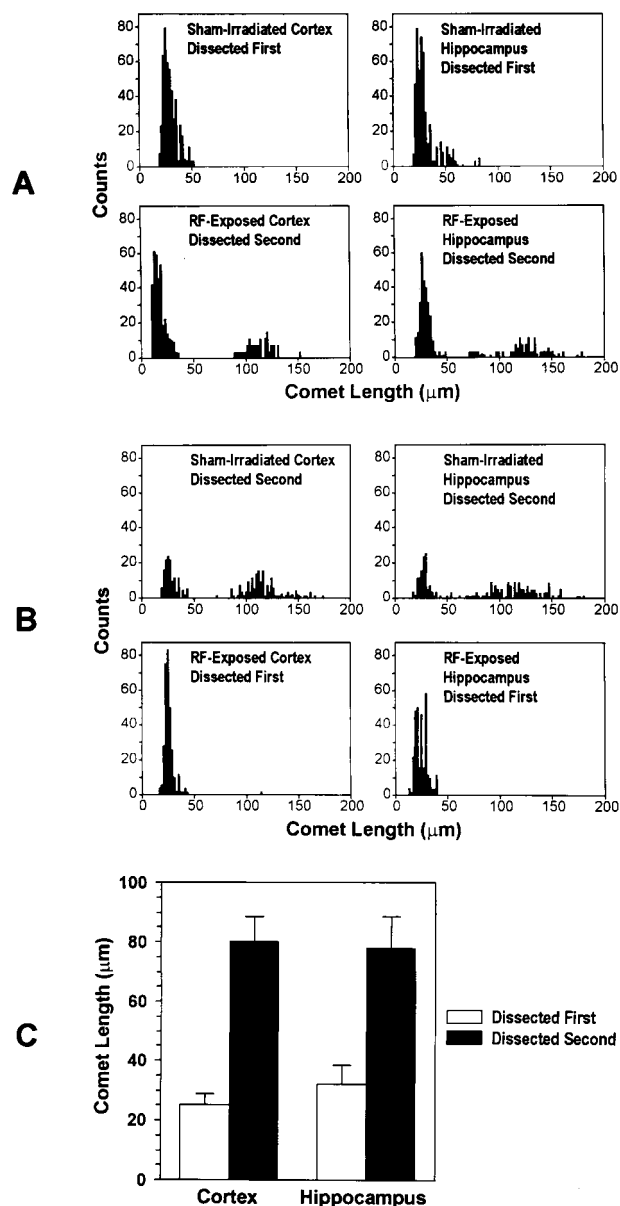


FIG. 2. Effect of delay between CO₂ euthanasia and brain dissection on comet length. Each frequency distribution is for two animals that were sham-exposed or exposed to 2450 MHz RF radiation (SAR = 1.2 W/kg) for 2 h. Panel A: Comet lengths when sham-exposed rats were dissected first. Panel B: Comet lengths when RF-radiation-exposed rats were dissected first. Panel C: Mean comet length (with standard error) for animals that were dissected first (open bars) or second (closed bars), irrespective of whether the animals were sham-exposed or exposed to RF radiation. Reproduced (and modified) with permission from Malyapa *et al.* (53).

to and from the exposure site. It appears likely that the effects observed by Lai and Singh were confounded by the euthanasia procedure or by some as yet unknown aspect of the animal handling or of the comet assay they used.

Summary of Genotoxicity Studies with RF Radiation

Tests of the potential genotoxic activity of RF radiation have been extensive (7, 8). The majority of the studies have

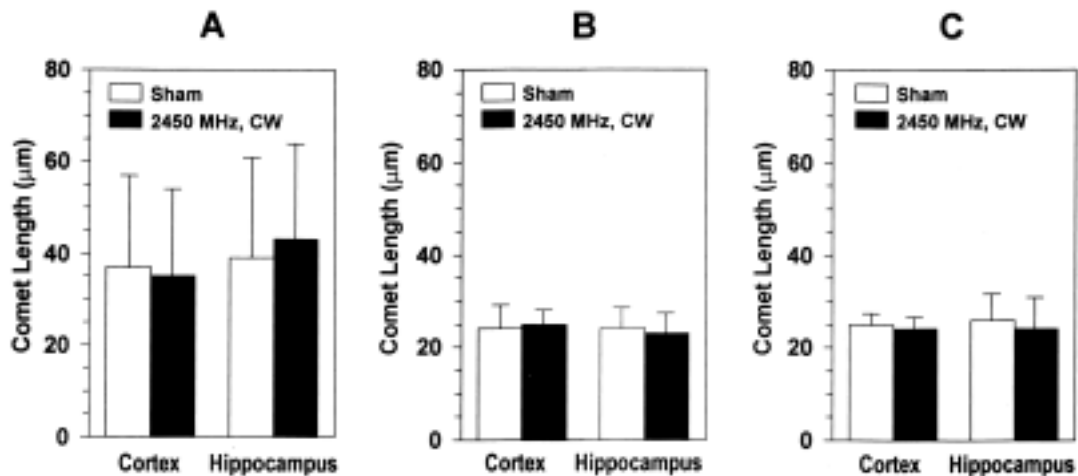


FIG. 3. Effect of method of euthanasia on comet length in cells isolated from rat brain. Each bar is for two animals that were sham-exposed or exposed to 2450 MHz RF radiation (SAR = 1.2 W/kg) for 2 h. Panel A: Sequential CO₂ asphyxia and dissection immediately after the end of exposure. Panel B: Sequential guillotine euthanasia and dissection immediately after the end of exposure. Panel C: Sequential guillotine euthanasia and dissection 4 h after the end of a 2-h exposure. Reproduced (and modified) with permission from Malyapa *et al.* (53).

indicated no significant genotoxicity (36–44, 48–53). Among the studies that have reported some evidence of genotoxicity, several (3, 4, 46), as discussed here, have failed attempts at replication. While it is impossible to prove a negative, it appears unlikely that RF radiation poses a genotoxic risk at subthermal exposure levels. The issue of whether RF radiation might contribute to the development of cancer without being directly genotoxic, that is that it might have epigenetic activity (16), has not been explored in as much detail.

LONG-TERM ANIMAL EXPOSURE STUDIES WITH RF RADIATION

The standard laboratory assay for assessing the carcinogenic potential of an agent is a long-term (usually lifetime) exposure study in normal animals. The fact that exposure in these studies lasts for a substantial fraction of the life span of the animals means that these assays are capable of detecting epigenetic as well as genotoxic carcinogens (16). Such assays usually use multiple doses of the agent, with the highest dose consisting of the maximum dose that the animals can tolerate without acute effects. There have been no long-term animal studies using RF-radiation exposure that meet all the above conditions (i.e. normal animals, multiple exposure levels and lifetime exposure), but a number of studies have been published that bear on the issue of whether RF radiation has carcinogenic potential. These studies should have been able to detect pronounced carcinogenic effects of RF exposure, had any existed.

Long-term animal exposure studies are difficult to accomplish and are expensive. Ideally, constant environmental conditions should be maintained throughout the experimental period, the handling of test animals should be rigidly controlled, and standard operating procedures should

be developed and followed. This requires the long-term dedication of significant resources and the commitment of management if the effort is to be successful. Special and separate exposure facilities are generally required for studies of RF radiation, further adding to the expense and complicating experimentation. Nevertheless, a number of such studies have been undertaken over the years.

Most studies of exposure to RF radiation have been of less than 1 year's duration. Some of these studies have not measured cancer incidence; rather they have assessed life span or have assessed multiple end points related to the overall health of the animals. In some cases, there have been large numbers of end points with multiple comparisons. A few studies have focused on the epigenetic potential of RF radiation, that is, whether exposure to RF radiation would increase ("promote") cancer incidence in animals that were already at high risk for cancer because of their genetic make-up, or because they had been deliberately exposed to a carcinogenic virus or chemical.

Early (1962–1982) Long-term Exposure Studies with Mice

1. Prausnitz and Susskind, 1962 (62)

In this study, which is included for its historical interest, mice were exposed to 9.27 GHz RF radiation at 100 mW/cm² (4.5 min/day, 5 days/week, for 59 weeks). The SAR was later estimated to be 40–50 W/kg, equivalent to about half the lethal SAR for a mouse (63). The exposure to RF radiation caused the rectal temperatures to increase by 2–5°C. The mice were followed for up to 83 weeks after the start of exposure. The authors described the presence of a leukocyte neoplasm, which they termed "leucosis", as well as testicular degeneration, in the exposed animals.

Numerous flaws in this study, as pointed out by Roberts

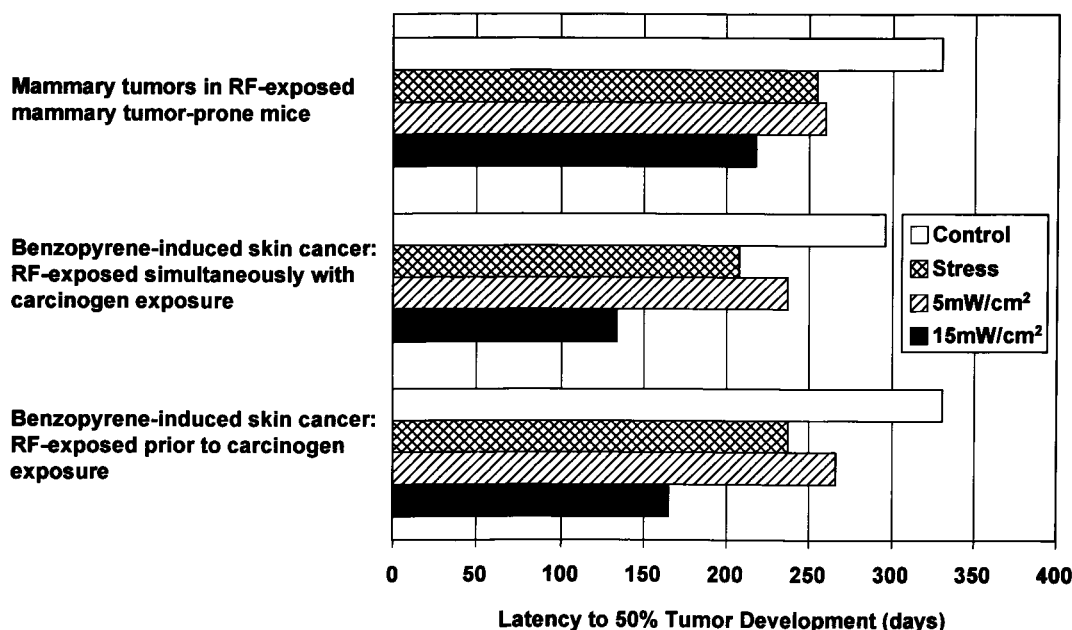


FIG. 4. Effect of RF-radiation exposure on development of mammary tumors in mammary tumor-prone mice, and on benzopyrene-induced skin cancer in mice. Mice were exposed to 2450 MHz RF radiation for 2 h/day, 6 days/week, for up to 6 months. Exposures were at either 5 or 15 mW/cm² (SAR roughly estimated at 2–3 and 6–8 W/kg, respectively). Controls included both normal animals and animals subject to “confinement stress”. Data from Szmigielski *et al.* (65).

and Michaelson (63), greatly diminish its contribution to an assessment of the risk of exposure to RF 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. However, it should also be noted that the animals exposed to RF radiation had a longer mean life span than the control group, so that, as stated by Roberts and Michaelson (63), “an equally plausible case could be made for the concept that the study . . . demonstrated microwave-induced beneficial, rather than detrimental effects.”

2. Spalding *et al.*, 1971 (64)

This study exposed mice to 800 MHz RF radiation for 2 h/day, 5 days/week, for 35 weeks. The power density was 43 mW/cm² (estimated SAR of 13 W/kg). End points included erythrocyte and leukocyte count, hemoglobin level, hematocrit, activity level, body weight and life span. No significant differences between the RF-radiation-exposed and sham-exposed groups were seen for any of these measures. The mean life span of the exposed group (664 days) was slightly but not significantly longer than that of the sham-exposed group (645 days).

3. Szmigielski *et al.*, 1982 (65)

This study used mice to examine whether RF radiation could “promote” various types of cancer. Animals were exposed to 2450 MHz RF radiation for 2 h/day, 6 days/

week, for up to 6 months. Exposures were at 5 or 15 mW/cm² (SAR roughly estimated at 2–3 and 6–8 W/kg, respectively). Controls included both normal animals, and animals subject to “confinement stress”.

In a study of skin tumor promotion, benzopyrene (a skin tumor carcinogen) was painted on the backs of the mice, and the animals were exposed to RF radiation either prior to or during exposure to the carcinogen (Fig. 4). The animals were observed for 12 months. Both exposure to RF radiation and confinement stress significantly accelerated the appearance of the chemically induced skin tumors (Fig. 4). In a study of mammary tumor promotion, the authors studied the appearance of tumors in mammary tumor-prone mice (Fig. 4). In this C3H mouse model, mammary tumors normally develop in about 80% of the animals; presumably these tumors are induced by mouse mammary tumor virus (MTV), although this is not explicitly stated by the authors. Again, both RF-radiation exposure and confinement stress significantly accelerated the appearance of tumors (Fig. 4). Finally, the investigators transplanted sarcoma cells into mice and looked for lung metastases. Both RF-radiation exposure and confinement stress significantly increased the number of lung metastases, with the 15-mW/cm² group having the greatest frequency.

The implications of these findings are difficult to assess, and the studies of mammary cancer promotion are contradicted by other recent studies [see Toler *et al.* (66) and Frei *et al.* (54, 55) later in this section]. The similarities between the 5-mW/cm² 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 RF-radiation exposure; and stress has been shown by others to both decrease the latency for development of MTV-induced mammary tumors in C3H mice (67, 68), and to increase the rate of lung metastases (69). The dosimetry in this study is also questionable, because it is based upon one carcass exposed at high power densities for a short time and extrapolated to long-term exposure of living animals at lower power densities. In addition, the authors reported that no rectal temperature increase occurred in the animals exposed to RF radiation, yet indicated that the absorbed energy "markedly exceeded" the basal metabolic rate of the mouse (the metabolic rate for a mouse is about 9 W/kg). The authors also suggest the existence of "hot spots" due to nonuniform absorption. It seems likely that the mice exposed at 15 mW/cm² were highly stressed and subject to at least localized heating.

Long-term Exposure Studies with Rats

1. Toler et al., 1988 (70)

This study examined the effects of RF-radiation exposure on multiple end points in rats. The animals were exposed for 22 h/day, 7 days/week, for 6 months to 435 MHz RF radiation at 1 mW/cm², resulting in an SAR of approximately 0.3 W/kg. Blood samples were assayed for corticosterone, prolactin and catecholamines. Erythrocyte and leukocyte counts, hematocrit, heart rate and mean arterial blood pressure were also measured. There were no significant differences, for any of the end points measured, in the RF-radiation-exposed group compared to the sham-exposed group. Although this study lasted only 6 months, it indicated that chronic exposure to low-level RF radiation had no effect on overall health or physiological status.

2. Chou et al., 1992 (71)

This study examined the effects of long-term pulsed RF-radiation exposure on the longevity and general health of the rats. The rats were exposed to 2450 MHz RF radiation pulsed at 800 pulses/s (10- μ s pulse width square waves modulated at 8 Hz). The average SAR decreased as the animals grew in size and ranged from 0.15 to 0.4 W/kg. The rats were exposed for 21.5 h/day, 7 days/week, for 25 months beginning at 8 weeks of age. At intervals during the exposure period, blood samples were collected for analysis of serum chemistries, corticosterone levels, blood cell counts, and plasma protein fractions. Body mass, food intake, and water intake were measured daily; oxygen consumption, CO₂ production, and immunological competence were assayed in a subset of the animals. At the end of 25 months, the survivors were sacrificed and examined histopathologically.

There were 155 comparisons in the entire study. The authors concluded that exposure to RF radiation had no biologically significant effects on the general health of the

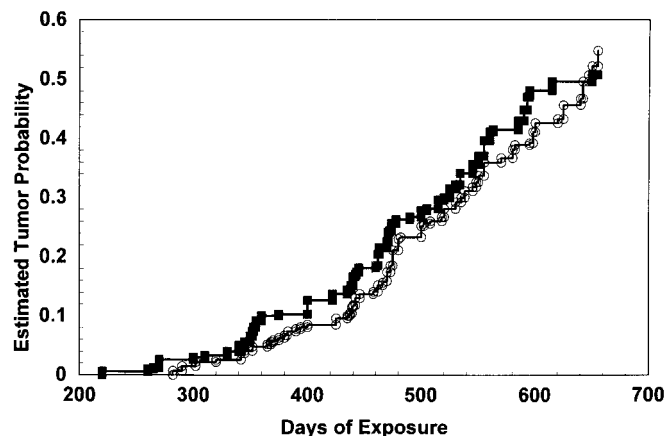


FIG. 5. Effect of RF-radiation exposure on survival in rats, RF-radiation-exposed (■) compared to sham-exposed (○). Rats were exposed to pulsed 2450 MHz RF radiation for 25 months (from 8 weeks of age) for 21.5 h/day, 7 days/week. The average SAR ranged from 0.15 to 0.4 W/kg. Data from Chou et al. (71).

animals. Figure 5 shows that there were no significant differences in survival between the two groups. There were statistically significant differences in corticosterone levels and immunological competence between the sham-exposed animals and those exposed to RF radiation at 13 months into the study, but these findings were not confirmed (71). An excess of primary malignancies was found in the exposed animals when all malignant tumor types were considered together; but there were no differences between the two groups for any specific type of malignant tumors, or when benign tumors were added to the count.

Later (1994) Long-term Exposure Studies with Normal Mice

1. Liddle et al., 1994 (72)

This study examined the effects of lifetime 2450 MHz RF-radiation exposure in mice. Mice were exposed throughout their life for 1 h/day, 5 days/week at either 3 or 10 mW/cm² (SARs were 2 and 6.8 W/kg, respectively). Overall animal survival was assessed, but actual causes of death were not determined. Life span was significantly shortened in mice exposed at 10 mW/cm² (median of 572 days compared to 706 days in the sham-exposed group). However, at 3 mW/cm², the animals exposed to RF radiation lived slightly, but not significantly, longer (median of 738 days) than the sham-exposed group. The authors suggested that the heating from exposure at 10 mW/cm² was stressful enough to decrease life span.

2. Wu et al., 1994 (73)

This study investigated the possibility that exposure to RF radiation could promote chemically induced colon tumors in mice. The animals were injected with dimethylhydrazine (DMH, a chemical carcinogen) alone, or before and during exposure to 2450 MHz RF radiation. The ex-

TABLE 5
Effect of RF Radiation on Promotion of Colon Tumors Induced by a Chemical Carcinogen^a

	Carcinogen ^b alone	Carcinogen ^b + RF radiation ^c	Carcinogen ^b + positive control ^d
Number of tumors per mouse	2.8	3.3	7.2 ^e
Fraction of mice with more than three tumors	23	30	59 ^e
Fraction of mice with total tumor area greater than 5 mm ²	31	31	71 ^e

^a Data from Wu *et al.* (73).

^b Dimethylhydrazine.

^c 2450 MHz, 3 h/day, 6 days/week, for 5 months at a power density of 10 mW/cm² (SAR of 10–12 W/kg).

^d 12-*O*-tetradecanoylphorbol-13-acetate (TPA).

^e Significantly greater ($P < 0.05$) than for carcinogen alone or carcinogen plus RF radiation.

posure to RF radiation was for 3 h/day, 6 days/week, for 5 months at 10 mW/cm² (SAR estimated to be 10–12 W/kg). One group treated with DMH was also treated with the tumor promoter 12-*O*-tetradecanoylphorbol-13-acetate (TPA) as a positive control. The study found no differences in the number or size of tumors in the DMH-treated group compared to the DMH plus RF-radiation group (Table 5). The DMH plus TPA group (the positive control) had significantly greater number and size of tumors than either the DMH-alone or the DMH plus RF-radiation group (Table 5).

Long-term Exposure Studies with Tumor-Prone Mice

1. Toler *et al.*, 1997 (66)

This study examined the effect of long-term exposure to RF radiation on mammary tumor-prone mice. In this model, MTV-induced mammary tumors normally develop in about 50% of the animals. The mice were exposed for 22 h/day, 7 days/week, for 20 months to horizontally polarized 435 MHz pulsed RF radiation (10,000 pulses/s, 1- μ s pulse width). The power density was 1 mW/cm², which yielded

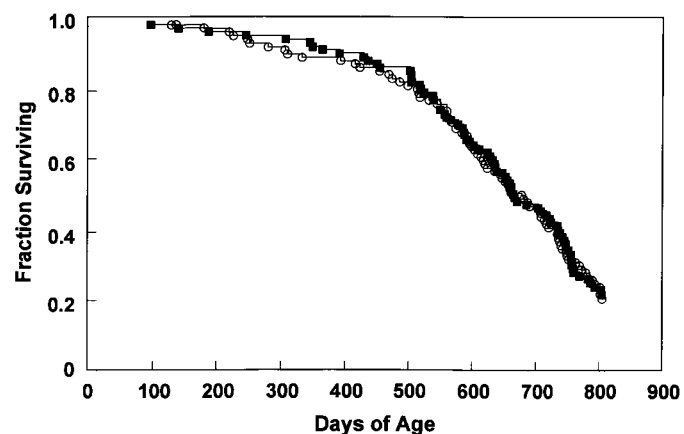


FIG. 6. Effect of RF-radiation exposure on mammary tumor development in mammary tumor-prone mice, RF-radiation-exposed (■) compared to sham-exposed (○). The mice were exposed for 22 h/day, 7 days/week, for 20 months to pulsed 435 MHz RF radiation at 1 mW/cm² (SAR of 0.32 W/kg). Reproduced with permission from Toler *et al.* (66).

an SAR of 0.32 W/kg. Control mice were sham-exposed under identical conditions. The mice were examined weekly, and animals found dead or moribund were necropsied immediately. At the end of 21 months, survivors were sacrificed and terminal necropsies performed.

There were no differences between the RF-radiation-exposed and sham-exposed groups with respect to time of mammary tumor detection, mammary tumor growth rate, or mammary tumor incidence (Fig. 6), nor were there differences in the numbers of malignant, metastatic or benign tumors. There was no difference in survival between the two groups.

2. Frei *et al.*, 1998 (54, 55)

These studies used a design similar to that of Toler *et al.* (66), except that the mammary tumor-prone mice were exposed at 2450 MHz. The mice were sham-exposed or exposed to RF radiation at 2450 MHz for 20 h/day, 7 day/week, for 18 months. The measured SAR was 0.3 W/kg (54) or 1.0 W/kg (55). No significant differences were noted in mammary tumor incidence, latency to mammary tumor onset, or rate of mammary tumor growth. Similarly, there were no differences in the numbers of malignant, metastatic or benign tumors. Of particular interest [in view of the results of Repacholi *et al.* (2), discussed below], there was no increase in lymphoma incidence in the mice exposed to RF radiation. Analysis of survival also revealed no difference between the two groups.

3. Repacholi *et al.*, 1997 (2)

This study examined the possibility that long-term exposure to pulse-modulated RF radiation (similar to that used in digital cell telephone communication) would enhance the incidence of lymphoblastic lymphomas in a transgenic mouse model. These transgenic mice are moderately predisposed to develop lymphoblastic lymphomas. The animals were exposed to two 30-min episodes per day of 900 MHz RF radiation (217 pulses/s, 0.6-ms pulse width) for 18 months. Depending on the size of the mice and their

TABLE 6
Effect of Pulsed RF Radiation on Development of Lymphomas and Other Diseases in Lymphoma-Prone Mice^a

Group	Lymphoma ^b			Unknown ^d
	Lympho- blastic	Non- lympho- blastic	Renal disease ^c	
Sham-exposed	0.03	0.19	0.11	0.07
RF-radiation-exposed ^e	0.06	0.37 ^f	0.10	0.07

^a Data from Repacholi *et al.* (2); some were animals alive and well at the end of the study, so numbers do not add to 1.00.

^b Fraction of animals diagnosed with lymphoma.

^c Fraction of animals with severe renal disease (alone or in addition to lymphoma).

^d Fraction of animals dying of undiagnosed causes.

^e 900 MHz, two 30-min sessions per day for 18 months (SAR of 0.01–4.2 W/kg).

^f Significantly different ($P < 0.05$) than in sham-exposed animals.

orientation in the field, incident power ranged from 0.26 to 1.3 mW/cm², and SARs ranged from 0.008 to 4.2 W/kg.

The authors reported an increase in the incidence of all lymphoma types in the mice exposed to RF radiation compared to the controls (43% compared to 22%, Table 6); the incidence of lymphoblastic lymphoma was not significantly different (3% compared to 6%, Table 6). A multivariate analysis of the data indicated that the risk for developing lymphoma was significantly higher in the mice exposed to RF radiation than in the sham-exposed group. The authors did not interpret their results as an indication that exposure to RF radiation could induce lymphoma in normal mice, and it should be noted that an excess incidence of lymphoma has not been noted in the other studies of long-term exposure of animals (54, 55, 66, 71).

Summary of Long-term Animal Exposure

Taken together, these studies present no compelling evidence that long-term exposure to RF radiation has a negative impact on the general health of animals. In particular, there is no consistent evidence that exposure to RF radiation initiates carcinogenesis; that is, there is no evidence for genotoxicity. There is contradictory evidence with regard to the possibility that exposure to RF radiation has epigenetic activity, that is that it “promotes” tumor formation. Repacholi *et al.* (2) reported promotion of lymphoma in lymphoma-prone transgenic mice, and Szmigielski *et al.* (65) reported promotion of skin and mammary tumors. In contrast, the studies by Toler *et al.* (66) and Frei *et al.* (54, 55) show that long-term exposure to RF radiation is not associated with promotion of mammary tumors, the study by Wu *et al.* (74) indicates that long-term exposure to RF radiation is not associated with promotion of chemically induced colon tumors, and recent studies by Imaida *et al.* (74, 75) indicate that medium-term exposure to RF radiation is not associated with promotion of chemically

induced liver cancer. Certainly, no specific disease state, cancer or otherwise, has been associated with long-term exposure to RF radiation in rodents.

CONCLUSIONS

The biophysics, epidemiology and laboratory studies relevant to the carcinogenic potential of cell phone RF radiation are summarized in Table 7. A biophysical evaluation indicates that it is implausible to expect that cell phone RF radiation would have biological activity at the subthermal power levels characteristic of the current generation of cell phones. The published epidemiological studies of RF radiation and cancer do not suggest a causal association, but the studies are few and all suffer from deficiencies in exposure assessment. Cellular studies have largely been limited to genotoxicity testing. Although a few of these studies have suggested the possibility of genotoxicity (e.g. 3, 4, 45, 46), the weight of evidence is that RF radiation is not genotoxic. Assessment of the epigenetic potential of RF radiation in cell culture has been minimal, and the results are equivocal at best (e.g. 43, 45). The studies of long-term exposure of animals present no compelling evidence that long-term exposure has a negative impact on overall health and show no convincing evidence that RF radiation is genotoxic in animals. However, some of the studies of long-term exposure suggest the possibility that RF radiation may have epigenetic activity, particularly at high exposure levels.

A weight-of-evidence evaluation (Table 7) indicates that the evidence for a causal association between exposure to RF radiation and cancer is weak. However, relevant data in some areas are sparse. In particular, the epidemiological evidence is limited, and there is little immediate prospect for improvement, since highly exposed populations are relatively small and assessment of exposure remains a serious problem. The studies of long-term exposure of animals are also relatively weak. Although four large studies have recently been published (2, 54, 55, 66), all were of tumor-prone animals, and all used only a single exposure protocol. Large lifetime exposure studies of normal (as opposed to cancer-prone) animals with multiple exposure levels and high-quality dosimetry would be of great value, but such studies are expensive and technically challenging. In addition, two of the long-term animal exposure studies reviewed here (2, 71) urgently require replication. Further evaluation of the possibility that RF radiation has epigenetic activity at subthermal power levels would also be useful, although there is little biological rationale to guide the design of such studies.

It is often stated that the risks from exposure to RF radiation, even if real, are too low to be of significance to public health. However, if the cancer risks suggested by some of the studies were real, then RF radiation could conceivably be a significant environmental cause of cancer. If an exposure affects many people, and the outcome is ex-

TABLE 7
Weight-of-Evidence Criteria for RF Radiation and Cancer

Criteria	Current state of evidence
Amount and quality of epidemiological evidence	Limited data of poor to fair overall quality
Strength of association in the epidemiology	None to weak—relative risks of 0.6–2.5
Consistency of the epidemiology	Studies show no consistent associations between exposure and any specific types of cancer; and consistently show no associations between exposure and overall cancer
Exposure–response relationship	Even studies which show an association show little or no evidence for an exposure–response relationship
Amount of laboratory evidence relevant to assessment of genotoxicity	Extensive genotoxicity studies in cell culture, but only limited whole-animal exposure studies
Strength of laboratory evidence for genotoxicity	Cellular studies strongly unresponsive, animal studies moderately unresponsive
Amount of laboratory evidence relevant to assessment of epigenetic activity	Few relevant cellular studies, some animal studies
Strength of laboratory evidence for epigenetic activity	Some unreplicated evidence for epigenetic activity at high (possibly thermal) exposure levels
Coherence with the physics of RF radiation	Significant biological effects are implausible at the sub-thermal power levels
Overall	Nothing in the epidemiology, biology or biophysics suggests an association; but few standard long-term animal exposure studies, and no strong epidemiology

tremely adverse (as cancer can be), even a small increase in incidence can be a serious risk to public health. On the other hand, a small increase in risk for a rare disease has little consequence for the general population, which faces much larger risks in everyday life.

Only if it is demonstrated that RF radiation is carcinogenic, and if there is some understanding of the conditions under which this cancer risk occurs, can effective measures be taken to protect public health. The issue, then, is one of hazard identification; that is, does RF radiation cause or contribute to cancer under exposure conditions that are relevant to human health? Even after decades of study, we have not identified RF radiation as a carcinogen. On the other hand, it is also clear that we can never prove that health hazards from exposure to cell phone RF radiation are impossible. The very nature of risk research, and of the scientific method, means that there will always be loose ends and unexpected findings. Additional epidemiological and laboratory investigations could address some of these uncertainties, but it is not plausible to expect that they would be able to address all of them.

In part, the endless controversy about electromagnetic fields and cancer reflects the intrinsic difficulties inherent in cancer risk assessment. It is relatively easy to prove that exposure to an agent is not associated with a statistically significant increase in the incidence of a specific type of cancer under specific exposure conditions. It is impossible, however, to prove that exposure has no association with any type of cancer under all possible exposure conditions. The controversy also reflects the fact that there is no simple cause of cancer, and thus that the unambiguous identification of carcinogens is often impossible. The scientific issue is not “Does cell phone RF radiation cause cancer?” as that question can never be answered in the negative. Rather the questions are: “How strong is the evidence linking cell

phone RF radiation and cancer?” and “How hard have we looked for evidence that RF radiation causes cancer?”

As this review has tried to illustrate, answering the above questions requires examination of a diverse body of evidence in disciplines ranging from biophysics to epidemiology, and no single piece of this evidence is likely to be definitive. In addition, because there are no precise rules for deciding how much research is “enough”, the answers will always be matters of judgment. In fact, it has been argued that risk assessment is not science at all, but a form of policy analysis that requires a high level of scientific input (16). In such an arena, disputes about subtle risks may be settled by political accommodation, rather than by scientific consensus. If such is the case for cell phone RF radiation and cancer, risk communication and risk management will be very complex issues.

The controversy about cell phones and cancer is likely to continue either until clear-cut evidence of a hazard is established or until the public (including politicians, businessmen, lawyers and journalists) concludes that there is little likelihood of a real and significant hazard. Perhaps the greatest contribution that scientists can make to this debate is to help educate the public (and other scientists) about the uncertain nature of risk assessment, and about the breadth of disciplines and rigor of analysis that must be brought to bear if high-quality risk assessment is to be accomplished.

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