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EXECUTIVE SUMMARY

The use of wireless telecommunications devices in Canada has increased dramatically over the past decade. With the increased use has come a greater visibility of the technology and a concurrent rise in public concern over its safety.

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Guidelines for safe exposure limits to radiofrequency (RF) fields are laid out in Health Canada's Safety Code 6. The Royal Society of Canada Expert Panel on radiofrequency fields was brought together to examine potential biological and health effects from RF fields resulting from the use of wireless telecommunications technology in order to review the adequacy of Safety Code 6.

Surveys conducted in proximity to base stations operating in Canada indicate that the public is exposed to extremely low intensity RF fields in this environment. These exposures are typically thousands of times lower than the recommended maximum exposure levels in Safety Code 6. Workers who maintain base-station antennas may experience somewhat higher exposures, although these exposures can be controlled by careful work practices. Exposures from commercial cellular telephones and wireless communication devices are below the limits given in Safety Code 6, although exposures near these limits can occur.

In preparing this review, the panel primarily used information obtained from published peer-reviewed scientific papers. The panel met with representatives from the two sponsoring agencies (Health Canada and Industry Canada). The Canadian Wireless Telecommunications Association (CWTA) was consulted regarding the use of wireless telecommunications devices in Canada and for engineering and technical information. The panel also took note of research that is currently underway, communicating with scientists involved in major studies in this field. Finally, interested parties were invited to send written submissions to the panel. Approximately 30 submissions were received from both organizations and individuals, and were circulated to all panel members so that they could be taken into account in preparing this report.

The terms of reference for the panel were specified in the form of a series of questions about the potential health effects of exposure to RF fields. These questions, and the panel's responses, follow.

Do the Provisions of Safety Code 6 Protect Both RF Workers and the General Population From the Thermal Effects Associated With Exposure to Radiofrequency Fields?

Thermal effects involve the direct heating of an organism, tissue, or cell by RF fields. Safety Code 6 was explicitly designed to protect workers and the public from thermal exposures with recommended exposure levels set at levels far below those at which such thermal effects could occur for whole-body exposures at a distance from the radiating source. Specifically, the panel found no evidence that thermal effects can occur at or below the whole-body exposure limits of 0.4 W/kg (workers) or 0.08 W/kg (general public).

The panel noted that the local limits for partial body exposure are set at much higher levels, with the local limits for workers being 8 W/kg in the head, neck, and trunk, and 20 W/kg in the extremities. The strong

intensities permitted by such exposures, although local in nature, and the fact that Safety Code 6 has no time limits on such exposures, creates a situation where thermal effects could occur even within the limits of Safety Code 6. Local exposures at the thermal levels of these limits may, in some cases, lead to adverse health effects. The panel recognizes that there are only limited data on which to define the biological limits of local energy deposition. In the absence of adequate data, the panel concluded that the local exposure limits may not fully protect workers from the thermal effects associated with exposure to RF. Additional research is needed to determine if it is necessary to establish limits on the duration of local exposures, particularly for workers, in addition to the intensity of exposures.

It should be noted that various diagnostic applications of RF radiation such as magnetic resonance imaging devices and new therapies for treating or ablating benign and malignant tumors may involve exposing patients to RF field in excess of the limits outlined in Safety Code 6. However, the panel noted that regulations for such procedures (such as those in Safety Code 6 that address patient exposure in magnetic resonance imaging) limit these more intense exposures to short periods of time. For example, in patients, the U.S. Food and Drug Administration limits exposure to the head to 8 W/kg, but only if the exposures are less than 5 min in duration, and 12 W/kg to the extremities for at most 5 min. It is important to ensure that personnel operating these devices are properly protected from overexposures.

What Are the Biological and/or Potential Adverse Health Effects Associated With Exposure to Radiofrequency Fields?

A number of laboratory studies have been conducted on potential biological and adverse health effects of RF fields. Biological effects are measurable changes in biological systems that may or may not be associated with adverse health effects. A number of biological effects have been observed at nonthermal RF field intensities that do not produce measurable heating. At this time, however, these biological effects are not known to cause adverse health effects in exposed humans or animals. The following biological effects were investigated by the panel.

Biological Effects

Cell proliferation Various findings have been reported on the effects of RF on cell proliferation. There is evidence that cell proliferation (specifically LN71 glioma cells) may be increased through exposure to high-intensity RF fields under rigid thermal control conditions. Alterations in cell-cycle kinetics under similar exposure conditions have been observed using Chinese hamster ovary cells. However, other studies have not demonstrated increased cell growth. A decrease in cell growth was seen only after 30 min of cell exposure or less. At low-intensity, nonthermal levels, RF fields do not appear to alter cellular proliferation rates.

Calcium efflux Although RF fields that are not extremely low frequency (ELF) modulated do not appear to effect Ca^{2+} efflux from brain tissue, low-frequency modulation of RF and microwave carriers at intensities below the limits set out in Safety Code 6 alters Ca^{2+} efflux. Low power density exposures were not tested to provide evidence for a calcium efflux effect at frequencies above 1 GHz. It is not clear that RF field exposures from wireless communications devices would affect calcium regulation in the brain, or that effects of this type would have any health consequences.

Ornithine decarboxylase (ODC) activity Increases in CDC activity have been observed in experiments using RF fields in the frequency range of standard wireless telecommunications devices at exposure levels below those recommended in Safety Code 6. This increased activity occurs only when the amplitude of the radiofrequency field is modulated by ELF. Pulsed digital telephone fields with a low-frequency component also are capable of increasing ODC activity. ODC activity has been shown to increase with increasing RF field strength. The panel noted that while nearly all factors capable of causing cancer lead to elevated ODC activity, not all stimuli capable of increasing ODC activity promote cancer.

Melatonin The effect of extremely low frequency electric and magnetic fields on melatonin has been widely studied in animals and humans. It has been hypothesized that ELF fields could alter human disease processes through changes in melatonin. Because melatonin levels are strongly affected by exposure to light, and may be affected by exposure to ELF fields, it is reasonable to consider whether melatonin might be affected by exposure to RF fields. However, there has been very little research on the effects of RF on melatonin, and the few existing studies do not provide clear information about such effects.

Cell membrane effects Various studies have identified influences of microwave (MW) exposure on Ca^{2+} release from cell membranes. These studies have documented increased release of Ca^{2+}. However, other studies have shown no effect on Ca^{2+} release. Effects of radiofrequency/microwave fields on transport of cations such as Na^{+} and K^{+} across cell membranes have also been documented. It is possible that these effects may occur without measured changes in temperature.

Although it appears that RF fields affect membrane channels, the specific biophysical interaction mechanism responsible for this effect has not been elucidated. The manner by which radiofrequency/microwave fields interact with proteins and membrane lipids altering cellular function needs to be investigated in more detail.

Blood–brain barrier Several studies have shown that exposure to RF radiation below the exposure limits in Safety Code 6 does increase blood–brain permeability. However, not all studies have demonstrated this effect. These inconsistencies may indicate that effects at low-level RF exposure are not significant, or that the changes in permeability may be related to

the specific RF frequency or to the ELF modulation of the RF carrier frequency.

Behavior In some studies, rats exposed to RF fields have performed less well in spatial memory tasks. The investigators have suggested that these behavioral effects could possibly be related to some effect of RF fields on the endogenous opioid system.

Mechanistic considerations As yet, there is little understanding of the mechanism behind the observed nonthermal effects of exposure to RF fields and the influence of low-frequency modulation of RF fields. It is important to understand the underlying biophysical mechanisms of the interactions between RF fields and cells and tissues in order to better clarify possible relationships between biological and adverse health effects.

Health Effects A number of toxicological, epidemiological, and clinical studies have also been conducted to investigate potential adverse health effects of exposure to RF fields. The panel's review of the currently available scientific literature on potential adverse health effects is summarized next.

Toxicological studies Both in vitro and in vivo studies of the effects of RF field exposure on DNA have produced conflicting results. While some studies have shown that exposed cells and animals experience significantly more DNA damage than unexposed cells do, others have found no significant difference. Still further studies have shown significantly less DNA damage in cells exposed to wireless telecommunications signals. Because DNA damage can result in serious health consequences, the possibility that low-energy nonthermal RF field exposures can cause DNA damage remains a concern. Further research is needed to clarify this possibility.

A number of toxicological studies have focused on the ability of RF fields to induce tumors in laboratory animals. Although a few studies have demonstrated elevated tumor rates in animals exposed to RF fields, most studies have found no significant difference in tumor occurrence rates between animals that have been exposed to RF fields and unexposed controls. There is little evidence that exposure to RF fields at nonthermal levels enhances tumorigenesis in animals.

There is also little evidence that exposure to RF fields at nonthermal levels promotes the growth of tumors in animals. Although a few studies have shown a significant increase in tumor promotion in the exposed groups, the significance of these findings is unclear pending replication of the results by other investigators. The majority of studies to date have found no significant differences between unexposed and exposed animals, and no clear evidence of an exposure-response relationship.

The committee identified only two published studies that examined the relationship between RF exposure and tumor progression. Neither of these studies found any significant difference in tumor progression between exposed and unexposed animals.

Though decreased life span has been observed in some animal studies of RF fields, it seems likely that these effects are related to thermal effects from particular exposure regimens. Sporadic reports of increased longevity in animals exposed to RF fields may be a result of the reduction in caloric intake, which has been noted in exposed animals.

Epidemiological studies The epidemiological studies examining the health effects of radiofrequency fields that have been published so far are of limited value, mostly because of the difficulty in adequately assessing exposure. Of those studies that were of adequate design with respect to exposure assessment, potential confounding, and outcome ascertainment, no consistent significant increases in health risk due to exposure to RF fields were seen. However, epidemiological studies have demonstrated that the use of cellular telephones while driving is associated with an increased risk of having an automobile accident.

Clinical studies Some clinical studies have been done on the relationship between RF fields and brain function and neurological health in humans. These studies, which have looked at epileptic seizures, sleep disorders, and "RFR (radiofrequency radiation) syndrome" have failed to show adverse health effects from RF exposure. However, contrary to animal studies, certain RF field exposures appear to shorten the sleep onset latency in humans, an interesting biological effect, but not a clinically relevant result.

Overall, the results of the currently available clinical and epidemiological studies are inconsistent and provide no clear pattern of adverse health effects related to RF exposure. Due to the designs of the published studies, the information needed to describe temporal relationships between exposure and outcome is not available. Current epidemiological evidence does not support an association between exposure to RF fields and risk of cancer, reproductive problems, congenital anomalies, epilepsy, headache, or suicide. At the same time, this evidence is inadequate to permit a comprehensive assessment of potential health risks. Additional epidemiological studies with adequate information on exposure to RF fields are therefore needed.

What Are the Nonthermal Biological Effects and/or Potential Adverse Health Effects Associated With Exposure to Radiofrequency Fields Emitted From Wireless Telecommunications Devices Such as Wireless Phones and Base-Station Transmitters?

Because of the low field strengths associated with public exposure to RF fields from wireless telecommunications base-station transmitters, neither biological nor adverse health effects are likely to occur. Although RF fields from cellular telephones could be of sufficient intensity to cause the type of biological effects described previously, such biological effects are not known to be associated with adverse health effects. The panel noted that the characteristics of the RF fields emitted from cellular telephones, including low-frequency modulation of the RF carrier wave, may be im-

portant in defining the nature of biological effects caused by RF fields from wireless telecommunications devices.

Particular concerns have been expressed about the potential for exposure to RF fields from cellular telephones to increase cancer risk. While the toxicological and epidemiological studies conducted to date are not definitive in this regard, the weight of evidence does not support the conclusion that exposure to RF fields of the type and intensity produced by wireless telecommunications devices contributes to the production or growth of tumors in animals or humans. Although some investigations have suggested that RF fields may damage DNA (notably studies of DNA strand breaks using the Comet assay), most genotoxicity studies conducted to date have been negative. More research should be done in this area to clarify the genotoxic potential of RF fields.

Clinical studies have examined the potential effect of RF fields on brain function and neurological health in humans. These studies, which have looked at epileptic seizures, sleep disorders, and RFR syndrome, have also failed to show consistent adverse health effects. RF field exposures may shorten the time to sleep onset in humans, although this biological effect is not considered to be an adverse effect.

Is There Evidence That Such Nonthermal Effects, If Any, Could Be Greater for Children or Other Population Subgroups?

There is ample evidence that children or other subpopulations (such as pregnant women or the elderly) can be more susceptible to the effects of exposure to chemical and radiological hazards than healthy, young adults. The issue of susceptible subpopulations has received very little study with respect to RF field exposure. Future studies of the potential risks of RF exposure should therefore address the possibility of uniquely susceptible individuals.

The epidemiological studies that have focused on children have been ecological in design, lacking any individual-level data for either exposure or potential confounders. Consequently, these studies are not particularly informative about potential RF health risks.

Eight clinical studies have been conducted to explore the existence of an RF sickness syndrome. None found any effect at all of RF fields on the symptoms linked to this syndrome. However, it does appear that some people are able to sense if they are exposed to RF fields.

What Are the Implications for Safety Code 6 of the Panel's Scientific Review of the Currently Available Data on Biological Effects and the Potential Adverse Health Effects of Exposure to Radiofrequency Fields? In Particular, Should the Phenomenon of Nonthermal Effects Be Considered in Safety Code 6?

Based on its review of the currently available scientific data, the panel concluded that Safety Code 6 generally protects both workers and the

general public from adverse health effects associated with thermal exposures to RF fields. However, although the whole-body exposure limits given in Safety Code 6 appear protective against thermal effects, the panel noted that protracted worker exposures at the local limits of 8 W/kg for the head, neck and trunk and 20 W/kg for the limbs could lead to thermal effects. The panel therefore recommends that these local exposure limits for workers be reviewed, in terms of both the intensity and duration of exposure. The establishment of the need for updated localized exposure limits to protect workers will require additional studies to define the joint effects of intensity and duration of exposure.

Because of the unique physiological characteristics of the eye, including its limited ability to dissipate heat, the panel is not satisfied that the local exposure limit of 8 W/kg for worker exposures to the head, neck, and trunk is adequately protective of the eye. (Safety Code 6 recognizes this concern by suggesting that even lower exposures are desirable.) Although the available data are insufficient to define a precise limit of localized exposure for the eye, the panel suggests that the exposure limit of 1.6 W/kg given in Safety Code 6 for the head, neck, and trunk (including the eye) of the general public be considered as an interim exposure guideline for the eyes of RF workers. The panel identified the generation of the data needed to clarify exposure limits for the eye as a high priority.

The panel noted that biological effects may occur at nonthermal exposure levels, including levels below the limits for RF field exposure established in Safety Code 6. Although such biological effects could conceivably lead to adverse health effects, there is insufficient information to conclude that adverse health effects are associated with biological effects caused by nonthermal exposures to RF fields. The potential health significance of biological effects of RF fields observed at nonthermal exposure levels requires clarification before nonthermal biological effects are considered for inclusion in Safety Code 6. The panel recommends that additional research on the biological effects of RF fields, including the mechanism by which such effects occur, be undertaken.

What Research Is Needed to Better Understand the Potential Health Consequences for Nonthermal Effects?

The committee has identified four distinct experimental approaches that are required to further our knowledge of RF fields. These are in vivo and in vitro animal and cell experiments, to provide basic information with which to assess any potential health effects; molecular approaches that examine mechanisms of biological effects; clinical studies, particularly to assess subgroup effects in humans; and epidemiological approaches that will monitor the potential impact of RF exposure on human health. A more detailed research agenda is included in a later section of the report.

Further research will be required as new technologies emerge that use frequencies and modulations that have been inadequately studied

previously. A major gap in knowledge that the panel identified is the lack of information on the role of the effect of modulation of RF at ELF frequencies.

Continued epidemiological studies are essential as they provide the primary means of directly identifying and characterizing the potential effects of RF fields on human health in the environment. Cellular telephones and similar devices have not been in general use for a sufficient period of time to permit a thorough investigation of all potential health effects. Moreover, not only is the use of this mode of communication expanding, but future systems will use different radiofrequencies and use protocols with diverse characteristics. In the future, it is anticipated that exposure to RF fields will be reduced as a consequence of the current trend toward reduced power emissions from wireless telecommunications devices. However, it is likely that the range of radiofrequencies and transmission characteristics of future communications systems will be different from those currently in use, and will require further evaluation to assure safety.

To date, no rigorous epidemiological studies on the potential adverse health effects of cellular telephone use have been reported. The panel recommends that the results of ongoing studies be carefully examined as they become available, including any implications for Safety Code 6. The panel noted that epidemiological studies of populations living near base stations are also lacking, but considers such studies to be of lower priority because of the very low field strengths in the vicinity of base-station transmitters.

INTRODUCTION

Background

Over the last 10 years there has been a remarkable growth in the wireless telecommunications industry in Canada. Between 1987 and 1996, the number of subscribers to cellular telephones has increased from 98,364 to 3,420,318 (Statistics Canada, 1998). This growth in subscribers—the rate of which has fluctuated between 30% and 40% annually since 1990 (Statistics Canada, 1998)—has resulted in an increased presence of cellular phones and base stations in people's lives and neighborhoods. With this increased visibility has come public concern over the possible health effects associated with this relatively new technology. The expert panel on potential health risks of radiofrequency fields from wireless telecommunications devices was brought together to address this growing public concern.

In 1991, Health Canada established Safety Code 6 in order to protect workers and the public from radiofrequency (RF) and microwave radiation in the frequency range of 3 kHz to 300 GHz. Radiofrequency radia-

tion is that part of the electromagnetic spectrum below the frequencies of visible light and ionizing radiation (see Figure 1). Ionizing radiation (at higher frequencies than visible light), which has enough energy to break chemical bonds, is treated separately from nonionizing radiation, which does not have sufficient energy to break chemical bonds.

Wireless telecommunications technologies operate at frequencies slightly higher than television and FM radio signals, both of which have boon present in our environment for many decades. They operate at similar frequencies, but different strengths, as some forms of radar used in air traffic control and in remote sensing, and as microwave ovens (2450 MHz).

Current and Emerging Wireless Technologies All current and emerging wireless telecommunications devices operate at nonionizing frequencies within the range covered by Safety Code 6 (SC6). SC6 is, therefore, the primary source of information on the safety requirements for these devices. The frequencies used by wireless telecommunications technologies currently in operation and in development are as follows:

Cellular phones (analog): 824–849 MHz.
Time division multiple access cellular phones (digital): 824–849 MHz.
Cellular base stations (analog and digital): 869–894 MHz.
Personal communications services (PCS—digital): 1850–1990 MHz.
Mobile satellite service (emerging technology): over 1990 MHz.
Fixed wireless access systems (soon to be implemented): 3400–3700 MHz.
Low modular cellular service (soon to be implemented): 24 and 38 GHz.

Thermal and Nonthermal Effects The exposure limits outlined in SC6 (which was published in 1991, reprinted in 1994, and is currently being revised) have been set below the point at which significant thermal effects are anticipated. However, public concern has been expressed over the possibility that RF fields can cause "nonthermal" biological and health effects* at levels below those causing thermal effects. Terms such as "thermal" "nonthermal," and "athermal," as applied to the biological effects of RF exposure, are relative and it is not possible to identify specific zones of exposure dose at which effects belong in one or another of these categories. The level of energy deposition that would cause a thermal effect varies depending on a number of exposure factors, including the biological specimen exposed (e.g., cell culture, small animal, large animal, human), the frequency of the RF field, the polarization of the field, and the control of ambient temperature around the specimen. Nevertheless, some general features related to these descriptive terms can be defined. In this report, the following interpretations of these terms are used:

*Biological effects are physiological, biochemical, or behavioral changes induced in an organism, tissue, or cell. Health effects are biological changes induced in an organism that may be detrimental to that organism.

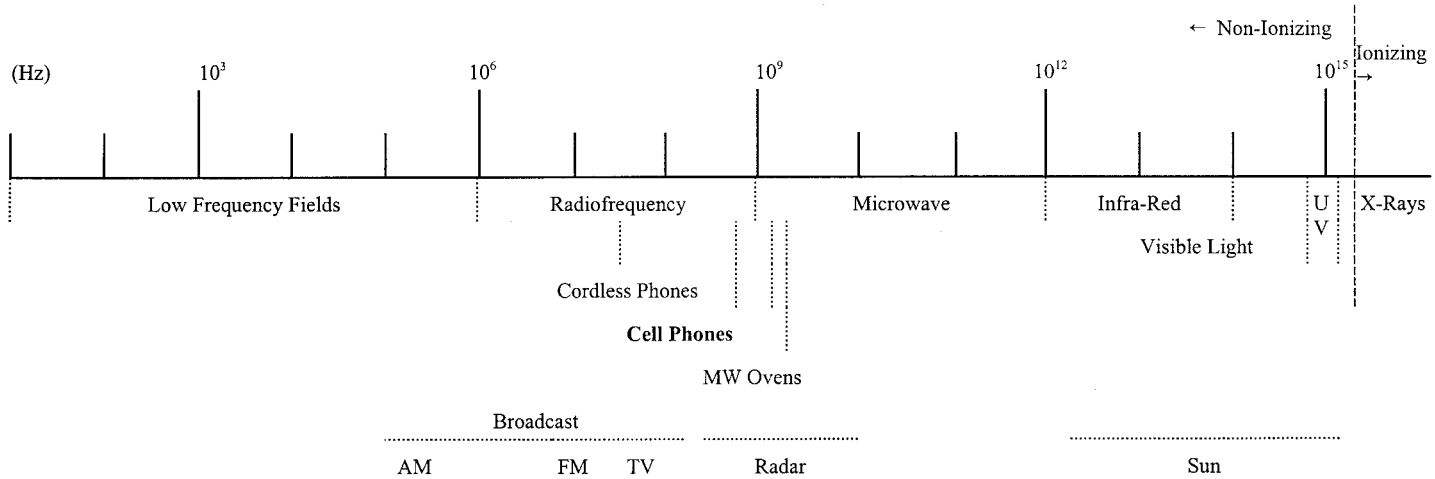

FIGURE 1. The electromagnetic spectrum. Source: Royal Society of New Zealand (1998).

- *Thermal effects* often occur when sufficient RF energy is deposited to cause a measurable increase in the temperature of the sample in question (e.g., more than 0.1°C).
- *Athermal effects* are those occurring when sufficient energy is deposited to nominally cause an increase in the temperature of the sample, but no change in temperature is observed due to endogenous temperature regulation or exogenous temperature control.
- *Nonthermal effects* are those occurring when the energy deposited in the sample is less than that associated with normal temperature fluctuations of the biological system being studied.

When considering the amount of energy deposited in a biological system, the preferred unit of measure, and of comparison for different exposures, is the specific absorption rate, or SAR. Different metrics for defining RF exposure are discussed later, but SAR is the unit that is used as the basis of virtually all RF exposure guidelines (including SC6). The SAR is defined in watts per kilogram (W/kg), and is the rate of absorption of RF energy in a unit mass of tissue—or tissue equivalent material in the case of phantom models. The critical point is that the SAR represents the energy actually absorbed and as such is a "bottom line" indicator of the measure of the dose of RF energy. The SAR cannot be readily measured in routine exposure assessment, but requires special techniques to determine it, either in the laboratory or with computer estimations. A large volume of data on the estimation of SAR from computer modeling has been compiled in a handbook to aid researchers (Durney et al., 1986). When SAR is not known, characteristics of the RF field (e.g., power density, electric field strength, magnetic field strength, polarization) are used to estimate exposure. SC6 uses these field characteristics—electric field strength, magnetic field strength, power density, and induced body current—as surrogates for SAR in defining exposure limits. In comparing research studies with various in vitro and in vivo laboratory specimens, it is essential to compare exposures based on SAR, since direct estimates of SAR from exposure parameters in these situations is problematic due to the other factors involved in the system.

Issues Addressed by the Panel

The Expert Panel is charged with examining the adequacy of SC6 in protecting workers and the public from potential health effects in light of published research into thermal and nonthermal effects from the RF fields produced by existing and emerging wireless telecommunications devices. With regard to wireless telecommunication devices and Health Canada's November 1998 Draft Version of Safety Code 6, the Expert Panel will address the following specific questions:

- What are the biological effects and/or potential adverse human health effects associated with exposure to radiofrequency fields emitted from wireless telecommunication devices such as wireless phones and base station transmitters?
- Do the provisions of Safety Code 6 protect both RF workers and the general population from the "thermal" effects associated with the exposure to radiofrequency fields?
- What "nonthermal" biological effects and/or potential adverse health effects have been reported in the literature?
  - Is there evidence that such "nonthermal" effects, if any, could be greater for children or other population sub-groups?
  - What are the implications for Safety Code 6 of the panel's scientific review of the currently available data on biological effects and the potential adverse health effects of exposure to radiofrequency fields? In particular, should the phenomenon of "nonthermal" effects be considered in Safety Code 6?
  - What research is needed to better understand the potential health consequences for "nonthermal" effects?

The approach of evaluating the available research literature on a scientific basis (excluding anecdotal or unpublished reports, and requiring replication of scientific findings for confirmation of effects) to determine recommendations for guidelines or established levels of health effects has limitations. It may, in fact, be at odds with public concern to keep all exposure below the levels at which any biological effect has been observed. Nevertheless, this panel is convinced that the scientific approach is the best way to determine guidelines for public health recommendations.

In preparing this review, the panel used only information obtained from published, peer-reviewed, scientific papers. The panel met with representatives from the two sponsoring agencies (Health Canada and Industry Canada). The Canadian Wireless Telecommunications Association (CWTA) was consulted regarding the use of wireless telecommunications devices in Canada and for engineering and technical information. The panel also took note of research that is currently underway, communicating with scientists involved in major studies in this field. Finally, interested parties were invited to send written submissions to the panel. Approximately 30 submissions were received from both organizations and individuals and were circulated to all panel members so that they could be taken into account in preparing this report.

Summary of Safety Code 6

Background to Safety Code 6 Health Canada and Industry Canada recently reaffirmed the November 1988 Memorandum of Understanding (MOU) between the then Department of Communications and the Depart-

ment of National Health and Welfare that assigns to Health Canada the role of principal advisor to Industry Canada regarding radiation hazards to human health. In order to fulfill its role of protecting the health of Canadians from the potential health hazards of nonionizing radiation, Health Canada has developed, and revised, Safety Code 6 (SC6). The panel based its review on the most recent revision, received in November 1998. The guidelines contained in this document are brought into effect through Industry Canada's licensing procedures.

The latest proposed revision of SC6 has been developed by the Radiation Protection Bureau of the Environmental Health Directorate of the Health Protection Branch of Health Canada. It recommends limits for human exposure to radiofrequency electromagnetic fields in the frequency range from 3 kHz to 300 GHz. SC6 is specifically designed to protect people from the heating (thermal) effects of RF fields. SC6 pertains directly to individuals employed by the federal government and its agencies, or individuals who fall under the Canada Labour Code. However, because Industry Canada requires that any installation of, modification to, or operation of any radio transmitter meet the guidelines in SC6, these limits have also become the de facto standard for industry and the public.

The purposes of SC6 are:

1. To specify maximum levels and durations of exposure to RF fields of frequencies between 3 kHz and 300 GHz to prevent human health effects.
2. To specify maximum allowable RF contact and induced body currents to prevent the physical perception of RF fields by the general public and RF shock or burns to RF and microwave exposed workers.
3. To recommend general procedures for ensuring that exposure of the general public and of personnel working in the vicinity of RF and microwave devices is not greater than the levels specified in this code.
4. To recommend working conditions that will lead to high standards of safety for all personnel engaged in the manufacture, operation, and maintenance of RF devices.

The limits in SC6 are given in terms of the body's specific absorption rate (SAR) of electromagnetic energy from RF fields. However, as it is difficult to measure SAR outside the laboratory, exposure limits are also given with regard to the maximum electric and magnetic field strengths and power densities, which would generate an SAR in accordance with the specified limit.

An approximate safety factor of 10 was used to derive exposure limits for RF workers that are 10 times below the scientific-consensus threshold for adverse health effects. An additional safety factor of 2 to 5 is used to derive even lower exposure limits for the general public. A lower limit for public exposure is used for two reasons: The public may be exposed for

longer periods of time; and it may include people who are particularly susceptible, such as the elderly, children, and the chronically ill.

Biological effects of RF fields at nonthermal levels were reviewed in revising SC6. However, because it was felt at that time that these effects and their implications for human health were not well established, they were not considered in SC6 as a relevant basis for establishing exposure guidelines for low-intensity RF fields. This issue is one that the panel has been asked to address.

Exposure Limits SC6 covers a broad range of frequencies and devices (Figure 1). For purposes of this report, we focus on guidelines given in SC6 for exposure to radiofrequency fields associated with wireless telecommunications devices.

The nature of radiofrequency fields changes with the distance from the source of the field. Fields far from the source, called the far field, can be described in terms of the electric field strength, magnetic field strength, and power density. The characteristics of such fields are orderly and predictable, and can be measured with commercially available instruments. SC6 defines limits for far-field exposures in terms of electric field strength, magnetic field strength, and power density as a function of the frequency of the source. Except for special work situations, exposures to fields from base station transmitters would normally occur in the far field zone. Table 1 summarizes exposure limits given in SC6 for the frequency ranges associated with base station transmitters used with both analogue and digital cellular telephones. Although SC6 specifies such limits in terms of electric and magnetic field strengths, as well as power density, such fields are normally assessed in terms of power density. (Power density is sufficient to characterize far field strength at these frequencies, and is easily measured with standard instrumentation.) Note that exposure limits for the general public are five times lower than those for workers. It is important to remember that all limits of SC6, including those applicable to base-station transmitters, are based on an underlying limit in absorbed energy, the SAR. The fundamental SAR limit for all far-field, whole-body exposures is 0.4 W/kg for workers, and 0.08 W/kg (one-fifth) for the general public. However, since it is not possible to measure SAR in the environment, the other parameters, primarily power density, are used as exposure guidelines.

TABLE 1. SC6 Exposure Limits for Radiofrequency Fields Applicable to Base-Station Transmitters

	Power density limit (W/m^2)	
Frequency (f) (MHz)	Workers	Public
300–1500	f/30	f/150
1500–15,000	50	10

Fields very near to the source, called the near field, require special consideration. In the near field, relationships among electric and magnetic field strengths and power density are more complex. In the case of cellular telephones, the proximity of the antenna to the body further complicates the assessment of radiofrequency field exposure. Consequently, exposure limits for cellular telephones are expressed in terms of the SAR (Table 2). SC6 specifies different limits for the whole body as distinct from local exposures to the head, neck, and trunk, or to the limbs. For cellular telephones, the SAR limits for the head and neck region specified in Table 2 for the general public are the most relevant. Although the most recent revision of SC6 does not include a separate SAR limit for the eye, the code suggests that organ-averaged SAR for the eye should not exceed 0.2 W/kg.

Not only does SC6 provide exposure limits, it also makes recommendations for the prevention of the overexposure of both RF workers and the public.

Measuring Exposure All means to protect the public and RF workers from overexposure to RF fields are predicated on proper measurement. SC6 provides a comprehensive account of how and when surveys of RF devices and installations should be measured and compliance evaluated. Surveys should be conducted as often as possible around devices and installations which are capable of exceeding exposure limits. Otherwise, a survey should be conducted after any installation, repair, change in working conditions, or suspected relevant malfunction.

SC6 stipulates that only competent persons using appropriate instrumentation should undertake an RF survey and outlines the preferred methods of measuring, calculating, and assessing exposure in order to ensure, among other things, that the values have been properly averaged over space and time. Formulas are provided for calculating the time-averaged values of a field exposure if the field changes significantly (by more than 20%) within a period of 0.1 h. Detailed instructions are given for the placement of sensors within a sampling area so that the average values for a RF field can be accurately calculated if the field changes significantly over space (by more than 25%). It even provides an outline of the proper procedures for measuring SARs. SARs can only be accurately measured in a laboratory using models of the human body. SC6 specifies that SARs shall be determined with an uncertainty level of no greater than ±20%.

TABLE 2. SC6 Exposure Limits for Radiofrequency Fields Applicable to Cellular Phones

	SAR limit (W/kg)	
Exposure condition	Workers	General public
Whole body (averaged over the whole body mass)	0.4	0.08
Head, neck, and trunk (averaged over any 1 g of tissue)	8.0	1.60
Limbs (averaged over any 10 g of tissue)	20.0	4.00

Beyond measuring the RF fields, a survey should include an assessment of the location with regards to controlled and uncontrolled areas and an inspection of warning signs, interlocks and "on–off" switches.

Siting and Installation Depending upon the levels of RF fields, different areas must be designated as controlled or uncontrolled. In controlled areas, limits for RF workers apply, field levels must be known, and the maximum time a worker may remain in the area must be posted. Measures must be taken to prevent unqualified individuals from entering controlled areas. These measures include signs, fencing, and interlock systems. In uncontrolled areas, limits for the exposure of the general public must not be exceeded. Overall, the siting of RF generators must take into account the presence of any other RF sources and metallic objects in the area.

Safety Procedures for Operators and Maintenance Personnel of RF Devices SC6 first specifies that workers must be made aware of the potential hazards of RF fields. Instructions for operating, maintaining and repairing RF devices must be accessible to and followed by RF workers. Only qualified personnel may repair or replace RF devices or components, or even specify instructions and procedures regarding RF devices. Testing may only take place when all RF components are in their proper places, all personnel are out of any direct RF beam, and no RF energy will be allowed into occupied areas.

Protection of the General Public In addition to protecting workers, SC6 also outlines the means by which the public shall be protected from overexposure. First, the general public is not to be given access to any area where the limits are exceeded. Second, if it is physically possible for a member of the general public to gain access to an area where RF field limits may be exceeded, warning signs must be posted at the entrances. Finally, devices that are capable of producing an RF leakage that would exceed the limits set out for the general public, and to which public access is allowed, must be inspected after installation, whenever a malfunction is suspected, and after any modification or repair that could result in a leakage.

How Safety Code 6 Recommendations Are Implemented The guidelines in SC6 apply to federal departments and agencies. (The department of National Defense may be exempted from the code in cases when compliance would have a detrimental effect on activities in support of training and operating the Canadian Forces.) However, the guidelines in SC6 are used by Industry Canada in the development of its licensing requirements for wireless telecommunications devices including both hand-held units and base stations. Since SC6 is only a guideline, Industry Canada cannot make the code a requirement for licensing. However, Industry Canada uses the guidelines set out in the code to develop licensing requirements that manufacturers of wireless communication equipment and service providers must meet.

Industry Canada does not do routine inspections of wireless telecommunications devices and installations. The onus is on industry members to verify that they comply with the license agreement. Licensing requirements for base stations are now in place (Client Procedures Circular CPC-2-0-03). However, the radio specification standard (RSS) for mobile and hand-held units is still in draft form, as consultations with the industry are ongoing. Until the RSS is finalized, the industry is required to comply with the U.S. Federal Communications Commission (FCC) standards, which are similar to, but not as rigorous as, the proposed Canadian standards. The proposed RSS includes exposure criteria for the eye and does not accept compliance by computations, but only by measurement. Both of these elements are absent from the FCC certification process.

EXPOSURE CHARACTERIZATION

Background

Although Safety Code 6 applies to all sources of radiofrequency (RF) fields, and is designed to address as broad a range of RF exposures as possible, this report is primarily concerned with sources of RF fields related to wireless telecommunications devices. As such, this discussion does not cover all RF sources, and, specifically, does not address industrial sources such as RF heat sealers, induction heaters, and microwave ovens. The frequency range of consideration is also more limited, since wireless communications sources operate at a more narrow range of frequencies than those covered by SC6. Other sources (such as speed-detecting radar for traffic law enforcement or sport uses) are not specifically considered, although principles presented here may be applicable when those devices operate with RF frequencies in the same range as the wireless sources under consideration.

Historically, mobile or cellular telephone systems were developed in the 1970s, and were widely introduced in North America in the early 1980s. These systems operated in a relatively narrow range of frequencies between 800 and 900 MHz. Newer mobile phone systems, operating with pulsed characteristics or digital modulation, operate at higher frequencies as well, usually between 1800 and 2000 MHz. These mobile phone systems utilize both individual handsets and a series of RF-transmitting towers, or base stations, that transmit the wireless communications throughout the system. As a general category, wireless communications also include paging systems, two-way radios, wireless computer networks, some data transmission systems, and other devices for sending information from one location to another by RF transmissions without fixed wire connections.

Cellular telephones, also known as mobile telephones, continuously transmit RF signals to base-station antennas when their power is turned on, whether or not they are being used for a call. Thus, cellular phones

are always in active communication with a base-station antenna. Unlike cellular phones, paging systems establish only one-way communication from the base-station antennas to the pager. Mobile (two-way) radio systems represent more limited communication networks, serving just one specific geographic area, and transmitting only when specifically activated by the user. Paging systems and mobile radio systems operate in several different frequency ranges, in the vicinity of either 150, 450, or 850 MHz. Although wireless telecommunications systems are under development that will utilize frequencies as high as 60 GHz, the predominant systems for potential exposure at this time are those with frequencies between 800 MHz and 2000 MHz.

One of the characteristics of the growth of wireless communications systems is that RF fields are now ubiquitous in our society. Prior to the widespread employment of wireless systems, RF field exposure was primarily a phenomenon that affected only limited population subgroups, such as military personnel, industrial workers using RF devices, and medical personnel using treatment devices like diathermy applicators. Base-station antennas are currently found in most urban areas in Canada, and millions of people now use personal wireless devices.

Environmental Exposure

Environmental RF field exposures from wireless system (base-station) tower antennas have become a source of public concern, in large part due to the appearance of the towers. These towers are 75 to 250 feet tall, and include self-supported steel structures, monopole towers, and guyed towers. Roof-top antennas and antennas mounted on water towers and other existing tall structures are also common, but less conspicuous. Ground-level RF fields near cellular phone base stations have been measured and documented in the scientific literature and in government reports (Petersen & Testagrossa, 1992; IEEE-USA, 1992; Conover et al., 1997; Gadja et al., 1997). Without exception, the exposures on the ground in the vicinity of a single wireless base station antenna have been found to be very low, in the neighborhood of 10 mW/m^2 or less, with most measurements showing exposures many orders of magnitude below that level. These measurements also indicate that the strongest exposures are not directly beneath the antenna, but rather at distances of 30 to 250 m from the base of the tower, depending on the characteristics of the antenna transmitting beam, the angle of declination of the beam, and the topography of the land or other buildings around that site.

Of particular interest are measurements made of exposures in Canada. In a survey done at an elementary school across from a PCS antenna mounted on a church steeple (Gadja et al., 1998b); the maximum power density was found to be 170 $\mu W/m^2$ indoors (59,000 times below the SC6 limit) and 1620 $\mu W/m^2$ outdoors (6200 times less). Observations made at another school with a roof-mounted tower found that the exposure was

highest on the roof, 10 m away from the antenna (25 times below SC6). Measurements on the ground outside this school found exposures 230 times below SC6, while indoors the maximum exposure was less than 4900 times below SC6. Observations made at a school one block away from a cellular antenna found maximum power densities did not exceed 8800 times less than SC6.

Other studies done at the request of concerned citizens have found even lower power densities (10 $\mu W/m^2$) from an analog cellular base station in a neighborhood in Corbyville, Ontario (Gadja et al., 1998a), and at a southern Ontario farm (0.2 $\mu W/m^2$) (Gadja et al., 1998b). The measurements in all of these Canadian studies are consistent with those observed elsewhere (discussed earlier) and show very-low-level exposure in areas accessible to the general population.

One situation in which such reported measurements may not accurately reflect the actual exposure occurs where a number of towers are colocated at the same site, or where more than one antenna system is placed on the same tower. If a few cellular phone transmitters are placed at the same site, the worst-case scenario may be estimated by a sum of the individual contributions of the individual transmitters. In cases where there are many antennas, or even multiple towers with multiple antennas on each, all colocated at a given site, field characterization is more complex, and exposure intensities can be considerably stronger than from a single installation.

The situation is further complicated when these multiantenna sites include large broadcast towers for radio or television transmissions. Radio and TV broadcast antennas typically transmit hundreds or even thousands of times more RF power than do cellular telephone systems. Broadcast antenna systems also operate over different frequency ranges than cellular phone systems. Radio stations operate either in the AM frequency band (53.5 to 1605 kHz) or the FM band (88 to 108 MHz), while TV stations operate at several different higher frequency bands in the ranges of 54 to 108 MHz, 176 to 216 MHz, or 470 to 806 MHz. Overall, except in rare cases where an unusually large number of antennas of various types are colocated, environmental exposures to RF transmissions from wireless telecommunications base stations are expected to be orders of magnitude below the limits specified by Safety Code 6 (and other similar guidelines), based on the reported measurements referenced earlier.

The potential exposure to RF fields is markedly different, however, for workers who need to conduct maintenance work on the tower structures, on rooftops, or on other structures where these antennas are located. In these situations, overexposure to RF fields may be possible, or even unavoidable unless exposure control measures are implemented. Exposure assessment in these cases can range from a simple preliminary evaluation of the number and types of transmitters present at the site, to the use of sophisticated instruments to measure and identify the exposure contribu-

tions of different transmitters. Control measures may involve limiting the time spent in certain locations around the antenna, or having the power transmitted reduced or turned off altogether for a period of time, or, in extreme cases, using protective clothing to shield the worker from RF fields. When workers have to be in the vicinity of such antennas, prior assessment of potential exposure is essential, whether the worker actually has to deal with the antenna or tower itself, or is engaged in work on other equipment nearby such as rooftop-mounted air conditioners.

Factors That Affect Exposure

Many factors influence the RF exposure an individual may receive, whether environmental or occupational. These factors include:

- The power output, frequency, and type of RF transmitter.
- The distance the person is from that transmitter.
- The location of the person with respect to the transmitted beam.
- The type of antenna and the direction of the transmitted beam.
- The presence of other structures near the person that may shield them or reflect the RF signals toward them.
- The time spent in a particular area of the RF field.

In the case of environmental exposures, many of these factors (such as relative location with respect to the antenna, presence of other structures, and time spent in that location) may be nearly constant. For workers, these factors may be much more variable, leading to greater fluctuations in exposure intensity.

There are two basic types of RF signals, continuous wave (CW) and pulsed. Continuous-wave signals are those that are constantly transmitted whenever the transmitter is on, although the amplitude or total power transmitted may change. In contrast, pulsed signals are emitted in bursts while the transmitter is on. These bursts, or pulses, are usually transmitted at regular intervals, in very rapid succession, with a momentary break in the transmission between pulses. The time intervals involved in pulsed transmission are very short, typically a few millionths of a second or a microsecond. The pulse may be described by its maximum strength (the peak power or power density), the pulse width, and the pulse repetition rate. In the case of wireless telecommunications, the pulse pattern is used as an essential part of the information transmission, and the pulse parameters can be very complex. For the purposes of measuring exposure, the average power or power density is normally used to describe pulsed RF radiation as well as continuous wave RF radiation. In the case of RF fields from wireless telecommunications, this approach for measuring exposures should be subject to review on a frequent basis, because laboratory reports exist of biological effects that are dependent on the particular modulation of the RF field exposure.

Wireless communications antennas come in many types. Often cellular telephone base-station towers have multiple antennas that transmit the signals in certain directions. Each area or sector around that tower may be subject to different RF field power intensities. Some systems use antennas that look like long rods, or whips, that are more omnidirectional in their transmissions and therefore would present a different exposure profile than the more directional antennas.

It is also important to note that cellular telephone antennas do not transmit the same irradiated power on a continuous basis. These systems have channels that are automatically turned on and off as the demand for the number of phone calls to be handled by a given base station fluctuates. A single base station may have 20 to 50 channels, with a power output usually expressed as the number of watts irradiated power per channel. The total power transmitted by a given antenna at a particular time would depend on the power output per channel and the number of channels transmitting. The maximum output possible for a given base station would be the total number of channels multiplied by the power per channel, although the base station would not usually have all channels activated at one time. An estimate of the maximum field strength might be obtained by making exposure measurements at that time of day when the base station is likely to be operating closest to capacity.

One of the critical factors in evaluating exposure is the relative location of the person with respect to both the antenna and the resulting RF field, in particular, ascertaining whether the area in question is within the near field zone of the antenna or the far field zone. The wavelength of the emitted RF signal can be described mathematically as the ratio of the velocity of light to the frequency of the RF signal. In general, the higher the frequency of the RF source, the shorter the wavelength. Without delving into the mathematics of these definitions, the area very close to an RF antenna is referred to as the "near field." The area farther away from the antenna is referred to as the "far field." Safety Code 6 defines the "near field" as a three-dimensional space, generally close to an antenna or other radiating structure, in which the electric and magnetic fields do not exhibit substantially plane-wave characteristics, but vary considerably from point to point. From a practical standpoint, this means that determining exposure in the near-field zone is far more complex and variable, and only special techniques or extensive measurements can reliably determine what that exposure will be. In contrast, the far-field zone is an area in which the field characteristics are more orderly and the field has a predominantly plane-wave character. Most RF field exposure measurement instruments are designed to work in the far-field zone where measurements are more predictable and consistent. Nearly all environmental exposures are in the far field zone. In occupational situations, near-field exposure is common and presents greater challenges in exposure assessment.

Measurement of RF Exposure

There are a number of different metrics that can be measured to characterize RF field exposure. Definitions of these metrics can be found in the glossary of terms in Safety Code 6. The most common means of measuring RF exposure is through power density, expressed as watts per meter squared (W/m^2). Power density is a measure of the power passing through a unit area, and indicates the strength of the RF field in air. Commercially available RF survey instruments usually measure power density as a reading of the field strength at a given point in time. However, recent advances in technology have resulted in commercially available measurement instruments capable of averaging RF power density over a period of time, usually up to 6 min. Dosimeters that record exposure over longer periods of time, spanning many hours, are not yet commonly available. For frequencies of interest in wireless telecommunications, the instruments normally provide readings of power density based on measurement of the electric field strength. Below 300 MHz (radio station broadcasts and lower frequency TV bands) the measurements and guidelines deal directly with both the electric (E) and magnetic (H) fields rather than with power density.

A common unit for describing exposure to many agents, both physical and chemical, is the time-weighted average (TWA). The TWA is a simple average of the exposure intensity measured over a period of time, such as a normal 8-h workday, or a 24 h period. Since instrumentation to determine TWA for RF fields is not readily available, a determination of TWA exposures to RF fields requires estimation based on a series of spot measurements of power density and a calculation of the average of those measurements over time, based on reasonable assumptions about how constant the power density was between those measurements. For many agents, the relevant exposure guidelines are defined in terms of the TWA, as well as a peak exposure limit. For RF fields, Safety Code 6 limits are defined in terms of 6-min (0.1-h) averages, which is a form of TWA. A TWA for periods longer than 6 min is not provided. Since power density is a measure of the RF intensity at a given point in time, it cannot be used to define cumulative exposure to RF fields, other than in a TWA. As noted later in this report, there is reason to reconsider this approach toward RF exposure assessment. Possible areas of reconsideration include the modulation characteristics of the RF signal, and duration of exposure beyond the 6-min average now used in Safety Code 6.

It is important to realize that power density (field strength) measurements do not provide an indication of how much RF energy is absorbed by the body of a person exposed. Power density merely reflects the amount of energy present in an area that is or might be occupied by a person. For this reason, SC6 and other RF field safety guidelines are also defined on the basis of another metric, the specific absorption rate, or SAR, which measures the rate of energy absorption by the body. The SAR

is not actually determined on the basis of personal exposures, but is experimentally determined in the laboratory using phantom models or computed using mathematical models. By considering the SAR over a period of time it is possible to derive a cumulative dose estimate expressed as the specific absorption (SA) in joules per kilogram, calculated as the product of the SAR and the time of exposure (in seconds). However, exposure guidelines have not been expressed in cumulative dose, but rather are defined in terms of power density and SAR.

Another unit of exposure to RF radiation is induced current. At lower RF frequencies, particularly those of broadcast radio (AM and FM) transmissions, RF exposure causes the flow of low-level electrical currents within the body. The current induced by the RF field will attempt to flow out of the body where there is contact with the ground or with electrically grounded objects, usually through the hands or the feet. Induced body currents are normally measured in milliamperes (mA). If the field is strong enough, the induced current can cause heating of body tissues, particularly at the narrowest regions of the body extremities—notably the wrist and the ankle—where the current flow is greatest due to the restricted area through which it must pass. Safety Code 6 and other RF exposure guidelines now set limits for induced current for RF exposure below 100 MHz. Due to recent technological advances, instruments to measure induced currents in various situations have greatly improved.

For wireless or cellular telephones, the radiating antenna is too close to the body to make meaningful power density measurements. The only way to assess exposure from these devices is to estimate the SAR in tissues near the antenna, particularly the ear, head, and face. Such estimates have been made by a number of laboratories. The results have indicated that while exposures from cellular phones are limited to a small part of the body (primarily just the hand and the side of the head on which the phone is held), the local SAR from these exposures can approach the local SAR limits defined in Safety Code 6 (Kuster et al., 1997). In some cases, local SAR deposition from RF exposure to fields from mobile radio handsets may also exceed the local SAR limits (Kuster & Balzano, 1992; Anderson & Joyner, 1995).

The SAR is dependent not only on the strength of the field, or power density, but also on the frequency of the RF source, since the rate of absorption of RF energy by the body varies with frequency. Due to the changing relationship of the body size with respect to the wavelength, the whole-body absorption has a "resonance," or maximum, for adult humans between 30 and 100 MHz and is less at the higher frequencies associated with wireless communications (Durney et al., 1986). This aspect of RF absorption is different from the molecular resonances well known in spectroscopy for microwave frequencies, but the body characteristics of absorption are more important for determining the internal distribution of energy and the overall biologic effect of exposure of the whole organism. Generally, lower fre-

quencies penetrate the body more and deposit RF energy deeper in body tissues than do higher frequencies with shorter wavelengths. For the purposes of this report, the differences between the whole-body absorption characteristics over the range of frequencies of concern for wireless communications sources (800 to 2000 MHz) are not large, and the biological effect of equivalent SARs is likely to be similar over that frequency range.

Extremely Low Frequency Modulation

There is one additional factor to be considered in evaluating the potential biological effect of RF exposure from wireless telecommunication sources. This factor is the modulation, or variation, of RF signals that occurs as a result of certain digital pulsing characteristics of some systems, where the modulation frequency has particular characteristics at extremely low frequencies below 300 Hz (ELF). These modulations are a component of the signal that is superimposed on the basic RF carrier signal that operates at frequencies in the millions of hertz (MHz). Some research suggests that the ELF characteristics of the signal may be important in altering biological systems. However, the role of ELF modulation of wireless communications RF transmissions in possible bioeffects is unclear and is discussed further later in this report. On a related note, there is actually a measurable ELF magnetic field as well as the RF field associated with the pulse modulation of digital phones. This ELF magnetic field is not the same phenomenon, however, as the low-frequency modulation imposed on the RF signal. The biological significance of these different ELF components of the electromagnetic exposure from mobile phones has yet to be determined.

Summary

In summary, RF field exposures from wireless communications sources depend upon a number of variables. Environmental RF field exposures from wireless systems base-station antennas are very weak. However, local partial body exposures resulting from the use of cellular phones themselves are stronger and at times approach the recommended limits of Safety Code 6. Furthermore, occupational exposure of workers who must work near the base-station antennas may be strong enough to require control measures to limit exposure, particularly when many antennas are colocated on a particular site.

EFFECTS OF THERMAL EXPOSURE LEVELS

Thermal Exposure Levels

A substantial database exists to evaluate the biological effects of RF exposures strong enough to be thermal in nature (i.e., exposures that deposit enough RF energy into the body to alter body temperature, or

stimulate thermoregulatory responses). Most of this literature deals with laboratory experiments in which animals were subjected to controlled RF exposures for short times of less than 8 h. This literature has been the basis upon which various exposure guidelines have been recommended, including those by the International Electrical and Electronic Engineers (IEEE C95.1-1991), the International Radiation Protection Association (IRPA, 1988), the World Health Organization (WHO, 1993), the U.S. National Council on Radiation Protection and Measurement (NCRP, 1986), and the Canadian Safety Code 6. Biological endpoints of many types, from in vitro studies of molecules and subcellular components to in vivo studies of intact organisms, have been investigated. Relatively few of the studies have been conducted at frequencies directly related to those used by wireless telecommunications systems. Nevertheless, many of these studies are relevant to the question of biological effects from the RF signals emitted by wireless systems.

From the published reports of laboratory studies we know that when the intensity is sufficient to cause heating of the biological system, a response of that system can be measured. These reports have led a number of reviewers to the conclusion that genetic changes have been observed in microwave studies only in the presence of a substantial temperature rise (Elder, 1987; Michaelson & Lin, 1987; Blackman, 1984). These observations are consistent with the interpretation that RF fields, because they involve only low-energy photons at these frequencies, do not cause direct damage to the DNA. Experimental studies of cells and molecules exposed, in vitro, to microwaves also support the interpretation that changes are only associated with a significant rise in temperature (U.S. EPA, 1984; Cleary, 1990a; Liburdy, 1992).

In general, the effects on in vitro systems—whether they are intact cells in culture, subcellular components, or tissue cultures—are difficult to relate to potential adverse health effects on intact organisms. In addition, many of the in vitro experiments have been conducted with high specific absorption rates (SAR), such that some of the changes reported would not occur with exposures less than those allowed by SC6.

In the case of animal studies, the observed responses to RF radiation exposure have been quite varied and include changes in temperature regulation, endocrine function, cardiovascular function, immune response, nervous system activity, and behavior (Elder, 1987; Roberts et al., 1986; Cleary, 1990b). However, when the intensity of exposure is low enough that overt heating of tissue does not occur, the nature of the biological response is much less clear. Of these various observed effects, the behavioral responses have been considered to be among the most sensitive in the whole organism, and thus of the greatest importance in setting guidelines for human exposure (IEEE, 1991; NCRP, 1986; WHO, 1993).

A threshold exposure level of 4 W/kg for potentially adverse effects, based predominantly on short-term behavioral studies in several species

(D'Andrea, 1991), has been used in developing these guidelines. While the 4-W/kg threshold has achieved a broad consensus, it is not an unequivocal demarcation since some responses to thermalizing RF exposure at levels in the 1–2 W/kg range have been noted that are similar to those observed at or above 4 W/kg (DeLorge, 1984; Lotz, 1985; Adair & Adams, 1980). The uncertainty in the threshold level of responses related to increases in body temperature results from variations in frequency of RF field, body size of the subject animal, ambient conditions during exposure, and thermoregulatory capacity of the animal. Other experimental factors that affect either the biophysical deposition of energy, the thermal balance of the subject, or simply the biological variability among individual subjects are also influential. A few effects, particularly those associated with very intense exposures (greater than 10 W/kg), may be irreversible, including developmental effects in offspring, cataractogenesis, burns, or even the thermal effects on wound healing. At moderate thermal exposures, those that would occur with exposure levels about 1 to 4 W/kg, these irreversible effects would not be expected to occur, and other changes, including circulatory, endocrinological, hematological, immunological, biochemical, and behavioral changes, have been reported. In general, these physiological and behavioral effects of moderate thermal exposure to RF are reversible upon cessation of exposure.

For occupational exposures, where workers may be in contact with metal objects, such as guy wires or structures around towers, there is a risk of shocks and burns at RF frequencies below 100 MHz (Gandhi, 1990). This would not normally involve wireless telecommunications frequencies, but might be relevant in situations where radio broadcast antennas are in close proximity to wireless base station antennas. Safety Code 6 considers the induced and contact currents associated with shock and burn hazards, and provides guidelines to eliminate such hazards.

Exposures to Humans from Diagnostic and Therapeutic Devices

Interstitial thermal therapies, which use electromagnetic energy, are being designed to treat or ablate benign and malignant lesions. Some of these therapies use RF fields similar to those used in wireless telecommunications (e.g., 344 MHz, 915 MHz) via an interstitial antenna (Couglin et al., 1983) or external applicator arrays (Diederich et al., 1991), while others use lower radiofrequency radiation (e.g. 27 MHz) (Delannoy et al., 1990; Hall et al., 1990). In the application of RF energy for therapeutic use, the local SAR (1000 W/kg) usually exceeds limits set by SC6. More importantly, if this future form of therapy becomes widespread, the exposure of operational personnel must not be allowed to exceed the occupational exposure limits specified in SC6.

Another form of RF therapy, ELF modulation of a 27-MHz carrier wave, which has recently been awarded FDA approval for the treatment of chronic psychophysiological insomnia, uses a device that has a maxi-

mum output power of 100 mW. As shown by clinical evidence, this therapy is effective even though the maximum SAR claimed is below safety limits variously defined for the general public by the American National Standards Institute, the Institute of Electric and Electronic Engineers, and the International Radiation Protection Association, as well as that of Safety Code 6 (ANSI, 1982; IEEE–USA, 1992; IRPA, 1988; Pasche et al., 1996). This therapy provides strong evidence that RF fields can elicit biological effects below SC6 limits.

Currently, the greatest source of exposure to patients from RF comes from magnetic resonance imaging (MRI) devices (primarily around 60 MHz, but varying from 4 to 80 MHz). This year, approximately 250,000 patients in Canada will undergo an MRI exam and hence be exposed to RF fields. In Canada, *Safety Code 26* (SC26, *Guidelines on Exposure to Electromagnetic Fields from Magnetic Resonance Clinical Systems;* Health and Welfare Canada, 1987) limits RF exposure to patients. Specifically, RF exposure should not be higher than that which could cause an increase in body temperature of more than 0.5°C and of any part of the body of more than 1°C. It is expected that these limits will be satisfied if the SAR does not exceed 1 W/kg as averaged over 25% of the whole-body mass for exposures of longer than 15 min duration and 2 W/kg as averaged over any 25% of the whole-body mass for exposures of up to 15 min duration. More recently, the U.S. FDA revised its guidelines (Food & Drug Administration: *Guidance for Magnetic Resonance Diagnostic Devices—Criteria for Significant Risk Investigations;* http://www.fda.gov/gov/cdrh/ode/magdev.html, 1997). It recommends the following SAR limits: 4 W/kg averaged over the whole body for any period of 15 min, 3 W/kg averaged over the head for any period of 10 min, and 8 W/kg in any gram of tissue in the head or torso or 12 W/kg in any gram of tissue in the extremities for any period of 5 min. Other countries have similar guidelines. A recurring theme, however, is that SAR limits are tied to the length of exposure. This seems reasonable and is especially important for target tissues having limited capacity for heat dissipation due to limited blood flow such as the eye. It should be noted that MRI operators are generally well protected from RF exposure, as the RF field drops off extremely quickly as one moves away from the RF transmit coil. Also, the patient and operator are usually separated by an efficient RF screen.

BIOLOGICAL EFFECTS (NONTHERMAL)

Radiofrequency Exposure Effects on Cell Proliferation

One of the key research priorities for in vitro studies, identified by a World Health Organization program (Repacholi, 1997), is to "determine RF field thresholds for altering the cell-cycle kinetics and proliferation of normal and transformed cells." The influence of RF exposure on cell proliferation in vitro has been studied by a number of investigators with mixed findings.

Cleary et al. conducted numerous studies of cell proliferation and cell-cycle kinetics in different cell lines with continuous wave RF exposures at either 2450 MHz or 27 MHz. They have reported increased proliferation of a glioma cell line (LN71) at 1, 3, and 5 days after a single 2-h RF exposure to either of these frequencies (Cleary et al., 1990a). This increased proliferation, as indicated by increased uptake of radiolabeled nucleic acids in DNA synthesis, was observed at SARs of 5 to 50 W/kg. The exposure system was designed to provide rigid thermal control conditions (i.e., changes in measured temperature were <0.1°C) even in the presence of strong RF exposure. No threshold for the effect was found since statistically significant differences were observed at even the lowest SAR tested (5 W/kg). Similar effects were seen in human peripheral lymphocytes exposed using the same system and RF conditions (Cleary et al., 1990b). This research group has also reported alterations in cell-cycle kinetics under similar exposure conditions with another cell culture: Chinese hamster ovary cells (Cleary et al., 1995).

Stagg et al. (1997) exposed both a glioma cell line (C6) and primary rat glial cells to RF signals identical to certain cellular telephone signals (836.55 MHz, time domain multiple access, TDMA) for a longer period (24 h) but at much lower exposure levels than those used by Cleary et al. In these experiments, increases in radiolabeled nucleic acid uptake in DNA synthesis were observed in one subset of log-phase C6 glioma experiments at an SAR of 5.9 mW/kg, but not at 0.59 or 59 mW/kg. These investigators also assessed proliferation by direct cell counts after exposure for up to 12 days. The growth curves of both cell types were not altered by any of the RF exposures they used.

In a study using RF exposures similar to cellular telephone signals from the global system for mobile communications (GSM), Kwee and Raskmark (1998) evaluated cell proliferation in cultures of transformed human epithelial amnion cells (AMA) exposed to 960 MHz at SARs of 0.021, 0.21, and 2.1 mW/kg for exposure times of 20, 30, or 40 min. The GSM signals include a modulation of the RF carrier at 217 Hz. Proliferation was assessed 24 h after exposure using colorimetric assay. A decrease in cell growth was seen at all three SAR levels tested, but only for exposures lasting 30 min or longer.

Some additional information is available on the effects of RF exposure on cell proliferation in recent reports by Antonopoulos et al. (1997), Donnellan et al. (1997), and French et al. (1997). However, it is not clear from the available data if, or under what conditions, RF exposure alters cell proliferation, and what the nature and dose-response characteristics of that alteration may be.

Radiofrequency Effects on Ca^{2+}

In 1975, Bawin et al. published a seminal paper indicating that exposure to an extremely low frequency-modulated 147-MHz radiofrequency carrier increased $^{45}Ca^{2+}$ efflux from neonatal chick neural tissue in vitro.

When the tissue was exposed to the carrier frequency alone, no effect was observed. Rather, the effect peaked around 11–16 Hz modulation. The incident power density used was 10–20 W/m^2, which is higher than the Safety Code 6 limit of 2 W/m^2. This effect is not directly dependent on power density. However, in follow-up experiments using a 450-MHz RF carrier modulated at 16 Hz, a 1-W/m^2 power density increased $^{45}Ca^{2+}$ as well as an exposure of 10 W/m^2, whereas 0.05-W/m^2 and 20-W/m^2 exposures were not effective in showing any increase (Bawin et al., 1978) (SC6 gives a limit of 3 W/m^2 at 450 MHz).

When a biological effect occurs between two extremes of an exposure metric, but not at the extremes, then it is common to refer to this as a window phenomenon. Therefore, the results just described are referred to in the literature as a power density window.

This modulation frequency dependence was replicated by Blackman et al. (1979, 1980a) at 147 MHz (7.5 W/m^2). These studies also showed power density window effects at 7.5 W/m^2, but not at 5 W/m^2 or 10 W/m^2. A further study by Blackman et al. found an effect dependent on a frequency modulation window at 16 Hz for a 50-MHz carrier with a power density window around 17 W/m^2 (1980b). In cultured nerve cells in a 915-MHz field, increased calcium efflux occurred at SARs of 0.05 and 1.0 W/kg but not at higher, lower, or intermediate rates (Dutta et al., 1984). The response at 0.05 W/kg, but not 1.0 W/kg, was dependent on 16 Hz modulation. Adey et al. published consistent data in awake cat cerebral cortex (1982) (30 W/m^2, 450 MHz, 16 Hz modulation).

However, experiments conducted by Shelton and Merritt (1981) (1000 MHz carrier modulated at 16 Hz with 5, 10, 20, 150 W/m^2 and 32 Hz at 10, 20 W/m^2) in rat brain tissue did not show any effects. Merritt et al. (1982) also observed no effects in microwave irradiated rat brain tissue loaded with $^{45}Ca^{2+}$ by intraventricular injection (1000 MHz, 0.29 or 2.9 W/kg; 2450 MHz, 3 W/kg; 2060 MHz, 0.12 or 2.4 W/kg), although low power densities were not tested in these two studies. The work of Bawin et al. (1978) and Blackman et al. (1979, 1980a) indicates that the power density window might be lower as the carrier frequency increases. This is indirectly supported by measurements of Bawin and Adey (1976) and Blackman et al. (1991) in which it has been shown that $^{45}Ca^{2+}$ efflux from chick brains can be altered by exposure only to ELF at power densities many orders of magnitude lower. Conceptually, these experiments correspond to exposure to an ELF-modulated electromagnetic wave with a carrier of infinite frequency. If the mechanisms associated with effects from ELF-modulated RF and ELF alone are similar, it would be important to consider the ambient static field during RF exposures (Prato et al., 1996).

In summary, power density windows have been observed for extremely low frequency modulation of RF and microwave carriers. Evidence that this does not occur at frequencies above 1000 MHz is inconclusive since low SAR and low power density exposures were not tested. Therefore,

this body of data suggests that ELF-modulated RF radiation may effect Ca^{2+} efflux from brain tissue.

Ornithine Decarboxylase and Polyamines Following Exposure to Electromagnetic Fields and Potential Relationship to Cancer

ODC and Polyamines Relationship to Cancer and Cell Proliferation

There is extensive evidence to indicate that the polyamines putrescine (P), spermidine (SD), and spermine (SP) are critically involved in the growth and differentiation of both normal and neoplastic cells (Pegg & McCann, 1982; Seiler, 1988; Janne et al., 1991; Pegg et al., 1995). Ornithine decarboxylase (ODC) is the initial and normally rate-limiting enzyme in the polyamine biosynthetic pathway catalyzing the decarboxylation of ornithine into putrescine. ODC activity must increase to provide polyamines in order for a cell to grow and proceed through the cell cycle in response to growth factors, hormones, or lymphokines. Suppression of ODC activity by the highly selective inhibitor α-difluoromethyl ornithine (DFMO) leads to the inhibition of both normal and neoplastic cell growth, with some greater effect in tumors, and seems to be an integral part of the reversal of tumor promotion in particular (Pegg, 1988; Marton & Pegg, 1995). The large changes in ODC activity observed in stimulated cells and tissues are caused by alterations in the amount of ODC protein. ODC turns over very rapidly, reaching a new steady state of enzyme protein quickly after alterations in the rate of ODC synthesis or breakdown, a hallmark characteristic of a growth-associated gene.

The regulations of ODC activity and polyamine metabolism have also been studied extensively in relation to the cancer phenotype. A high level of ODC (and elevated putrescine and polyamines) has been found in a number of premalignant conditions. Many chemical carcinogens have been shown to increase ODC levels, and increased ODC activity is a common phenomenon related to the exposure of cells and tissues to various chemical tumor-promoting agents (Pegg, 1988; McCann & Pegg, 1992; Marton & Pegg, 1995; Gilmour et al., 1992; DiGiovanni, 1992; Kim et al., 1994). In this regard, elevation and inhibition of ODC activity have been used as part of a screen for naturally occurring and synthetic tumor-promoting compounds and chemopreventative agents (Kim et al., 1994; Kitchin et al., 1994). The activity of ODC is known to be elevated in preneoplastic and neoplastic lesions of the skin (DiGiovanni, 1992), liver (Reeben et al., 1996), and other tissues (Blackshear et al., 1989; Mori et al., 1996). For example, liver nodules and carcinomas, in a rat model of carcinogenesis, exhibited high ODC activity and DNA synthesis (Pascale et al., 1993). This observation suggested that overexpression of the ODC gene and alterations in regulatory mechanisms of ODC activity, including gene expression, may be implicated in the progression of preneoplastic liver lesions to malignancy. In surgical specimens of human gastric carcinoma, ODC mRNA in the tumors was expressed to a significantly greater extent than

in the normal mucosa (Mori et al., 1996). Those cases of tumors with high vascular vessel invasion also showed a significantly higher ODC mRNA expression. These observations led the authors to conclude that overexpression of ODC mRNA in tumor tissue may correlate with aggressive biological behaviors such as vascular vessel invasion. In this and other studies a strong correlation exists between ODC and c-myc overexpression.

Several known oncogenes such as c-myc, Ki-ras, and Ha-ras (via TGF-β) increase ODC activity apparently by enhancing transcription of the ODC gene (Bell-Fernandez et al., 1993; Wagner et al., 1993; Hurta et al., 1993; Wrighton & Busslinger, 1993; Tabib & Bachrach, 1994). In a recent study, transformation by activated ras was accompanied by an induction of ODC in part through a Raf pathway (Shantz & Pegg, 1998). The results further strongly suggested that ODC induction was required for transformation by the oncogenic H-Ras. O'Brien, Boutwell, and Verma (Kim et al., 1994; O'Brien et al., 1994; O'Brien, 1976; Gilmour et al., 1991) have shown that ODC regulation and polyamine metabolism is strongly correlated with the process of tumor promotion in the epidermal model of initiation–promotion. These investigators were the first to report a constitutively high level of ODC and polyamines in both skin papillomas and carcinomas and proposed that this constitutively high ODC/polyamine expression in tumor tissue of epithelial origin offered a growth advantage to these cells.

Most of the studies regarding the association of ODC activity and polyamines in relation to the cancer phenotype are correlative in nature. It has long been considered, in polyamine research, that increased ODC activity and polyamine accumulation was essential for tumorigenesis but not sufficient for this process. However, in recent years a number of investigators have shown that ODC itself may function as an oncogenic protein if expressed at sufficiently high levels. Constitutively high levels of ODC overexpression in normal cells do not occur because this process is very highly regulated by a variety of mechanisms, including changes in the rate of ODC gene transcription, translation of ODC mRNA, and degradation of the ODC protein (Janne et al., 1991; Holm et al., 1989; Kumar & Butler, 1997). The level of ODC is highly regulated by the cellular polyamine content. Elevated cellular polyamines lead to a reduction in ODC activity and protein, both by inhibiting the translation of the ODC mRNA and by increasing production of a protein called the antizyme that stimulates the degradation of ODC by the 26S proteasome (Pegg et al., 1994; Cannellakis et al., 1993; Suzuki et al., 1994; Ichiba et al., 1994; Murakami et al., 1992; Rom & Kahana, 1994).

However, ODC constructs can be designed to produce a protein of full enzymatic activity, yet unable to interact with the antizyme (a truncated ODC lacking the carboxyl end 37 amino acids) (Ghoda et al., 1989). Cell lines and transgenic animals can be engineered, using these constructs with various promoters, to maintain constitutively high levels of ODC activity, ODC protein, and intracellular and extracellular polyamines (predominantly putrescine, as discussed later). The salient features of these

studies are summarized in Table 3, including the type of cell used, the relative increase in ODC activity, the change in intracellular polyamines where measured, the growth and tumor phenotype observed relative to the control plasmid-only infected cells, and the molecular phenotype observed by the investigators.

TABLE 3. Constitutive Ornithine Decarboxylase Overexpression, Elevated Putrescine and Cancer

Cell type/ transgenic animal	Fold increase in ODC	Intracellular polyamines			Growth/tumor phenotype alterations	Molecular phenotype	Reference
		P[a]	SD[b]	SP[c]			
Rat 6 (R6) fibroblast (embryo derived)	5–40×	—	—	—	No change in growth parameters; marked increase in susceptibility to morphological transformation by activated c-ras^{Ha} oncogene		Hibshoosh et al. (1991)
NIH/3T3, fibroblast	3–6×	—	—	—	Decreased population doubling time; loss of contact inhibition; efficient anchorage-independent cell growth; increased tumor production in mice	Elevation of both basal and ligand-induced EGF-R tyrosine kinase activity	Moshier et al. (1993, 1994)
NIH/3T3, fibroblast	50–100×	4×	2×	N.C.	Increased cell transformation and anchorage-independent cell growth (blocked by DFMO or ODC antisense); highly tumorigenic in nude mice (rapidly growing, highly vascularized, large fibrosarcomas)	Tumors had down-regulated growth factor receptors and appear to secrete a "novel" angiogenic factor Downregulated thrombospondin-1 and -2; tyrosine hyperphosphorylation of 130-kD protein	Auvinen et al. (1992, 1995, 1997) Paasinin-Sohns and Höltta (1997)

(*Table continues on next page*)

TABLE 3. Constitutive Ornithine Decarboxylase Overexpression, Elevated Putrescine and Cancer (*Continued*)

Cell type/ transgenic animal	Fold increase in ODC	Intracellular polyamines			Growth/tumor phenotype alterations	Molecular phenotype	Reference
		P[a]	SD[b]	SP[c]			
NIH/3T3-ras transfected with LTR inducible promoter (MMT Vras)					Ras expression induced increased ODC, polyamines, and transformation	NIH 3T3 or MMT Vras fibroblasts grew in soft agar if supplemented with polyamines	Tabib and Bachrach (1998)
10T1/2 mouse fibroblasts	4–6×	—	—	—	Increased colony formation and anchorage-independent growth	Enhanced MAP-kinase activity	Kubota et al. (1997)
MCF-10A human mammary epithelial cell	4–250×	5×	N.C.	N.C.	Reduced cell proliferation + or – serum in cell culture; marked (12×) ability to confer anchorage-independent growth (blocked by DFMO); specific effect upon transformation rather than proliferation	Increased activity of ERK-2 kinase in MAPK kinase cascade Interaction with HER-2 neu in promoting mammary-cell transformation	Manni et al. (1997, 1995, 1995, 1995, 1998)
Normal keratinocytes (BK-1) dermal fibroblasts murine papilloma lines 308 (mutated c-ras^{Ha}) Sp1 (mutated c-ras^{Ha}) K6/ODC transgenic bred to TG.AC v-Ha-ras transgenic	250× 150× —	5× 5× 10× 8×	N.C. 1.5× 2× 1.3×	N.C. N.C. N.C. N.C.	Increased thymidine incorporation (2×); no increased tumors in skin grafts or following s.c. injection All form tumors following s.c. injection (no tumors in control) Only animals with both transgenes (ODC and v-Ha-ras) had highly malignant tumors	Elevated proteinase expression: increase tumor urokinase plasminogen activator and increase stromelysin-1 mRNA in stromal cells Increased amount, activity and nuclear translocation of casein kinase 2 in ODC overexpressing BALB/MK cells	Clifford et al. (1995), Smith et al. (1997, 1998), Shore et al. (1997)

TABLE 3. Constitutive Ornithine Decarboxylase Overexpression, Elevated Putrescine and Cancer (*Continued*)

Cell type/ transgenic animal	Fold increase in ODC	Intracellular polyamines			Growth/tumor phenotype alterations	Molecular phenotype	Reference
		P[a]	SD[b]	SP[c]			
Transgenic mouse (K6/ODC) ODC-over-expression targeted to hair follicle keratinocytes with keratin promoter	Dermis 125× Epidermis 28×	45× 3.3×	4.7× 2.3×	N.C. N.C.	Mice highly sensitive to initiation by low-dose DMBA Following DMBA, marked/rapid ↑ in papillomas No requirement of chemical promotion (TPA) for tumor (papilloma) development; tumors inhibitable and actually reversible by DFMO, with no effect on proliferation of normal keratinocytes Clonal expansion of a population of initiated cells not promoted by chemicals	In ODC transgenic mouse tissue, putrescine controls development and maintenance of neoplastic phenotype	Megosh et al. (1995, 1998), Soler et al. (1996), O'Brien et al. (1997), Peralta-Soler et al. (1998)

Note. —, Polyamine levels not measured. Fold increase relative to vector-only control. N.C., no change from vector-only control values.

[a]Putrescine.

[b]Spermidine.

[c]Spermine.

A remarkably consistent observation among the various cell types employed was that cells overexpressing ODC exhibited an increased ability to achieve anchorage-independent growth. In general, the ODC-overexpressing cells were also more tumorigenic when placed back into appropriate animals. The tumors observed from these ODC-overexpressing cells were more highly invasive and highly vascularized.

The ability of ODC overexpression to result in efficient anchorage-independent cell growth and increased tumor production in animals does not appear to be related directly to a putative growth advantage provided by increased production of polyamines. This can be seen in the studies by Manni (Manni et al., 1995a, 1995b, 1995c, 1997) of the ODC-overex-

pressing MCF-10A human mammary epithelial cells, which have a reduced cellular proliferation capacity in the presence or absence of serum in cell culture, yet have a markedly increased ability to confer anchorage-independent growth and grow tumors in animals. In addition, Gilmour has shown that normal keratinocytes and dermal fibroblasts with ODC overexpression have an increased thymidine incorporation of up to twofold relative to the controls, yet will not form tumors in skin grafts or following subcutaneous injection into animals (Clifford et al., 1995).

The landmark studies by O'Brien (O'Brien et al., 1997; Megosh et al., 1995, 1998; Soler et al., 1996; Peralta-Soler et al., 1998) of the production of an ODC-transgenic mouse are noteworthy. This investigator targeted ODC overexpression to the basal keratinocytes of the interfollicular epidermis as well as outer root sheath (ORS) of the hair follicle using a bovine cytokeratin promoter. In these ODC-overexpressing transgenic mice no tumors were seen unless the animals were treated with a very low dose of initiating agent, in this case dimethylbenz[a]anthracene (DMBA) (cf Megosh et al., 1995). At low doses of DMBA, these animals all developed large numbers of rapidly growing papillomas within a very short time. Gilmour also observed similar effects in that only those ODC-overexpressing mouse cell lines with a mutated c-ras^{Ha} gene were capable of forming tumors following ODC overexpression (Clifford et al., 1995). By crossing the K6/ODC transgenic mouse with the T.G. AC v-Ha-ras transgenic mouse, she also recently confirmed that ODC overexpression and activated Ha-ras are sufficient to produce a high rate of malignant transformation in the absence of chemical tumor promoters (Smith et al., 1998).

O'Brien also concluded that ODC overexpression was sufficient to activate such initiated cells and to expand them clonally to form epidermal tumors (Peralta-Soler et al., 1998; Megosh et al., 1998). There was no requirement for a chemical promoter such as tetradecanoylphorbol-13-acetate (TPA) for tumor or papilloma development in these ODC-overexpressing mice. In normal skin, TPA is a pleiotropic agent causing numerous and profound biological changes including chronic hyperplasia, edema, a large inflammatory response, and an increased polyamine biosynthesis. Numerous changes in gene expression also occur following TPA treatment, but ascertaining which genes contribute directly to the driving forces for tumor promotion has been difficult in this and other models. Furthermore, in this ODC-transgenic model, tumors developed in the absence of epidermal hyperplasia and dermal inflammation, suggesting that those events are unnecessary for tumor promotion. Various other locally acting growth regulatory models such as epidermal transforming growth factor-α, the transforming growth factor-β family, and interleukin 1A have been implicated in the epidermal mechanism for tumor promotion (Vassar & Fuchs, 1991). These agents may well be essential mediators of promotion by TPA and other exogenous agents, although it is conceivable that these molecules function predominantly by inducing and maintaining high levels of ODC

expression. While the levels of putrescine observed in the dermis and epidermis in the ODC-transgenic mice were higher in terms of fold of increase compared to other ODC-overexpressing cell lines (Table 3), the increased activity of ODC and levels of the polyamine were very similar in magnitude and fold of increase to the previously reported data which compared normal epidermis to epidermal tumors (papillomas and carcinomas) in outbred nontransgenic mice (Koza et al., 1991) (cf Gilmour et al., 1991). O'Brien et al. recently showed that in the ODC-transgenic mouse it is the increased concentration of tissue putrescine that controls the development and maintenance of the neoplastic phenotype (1997). Difluormethyl ornithine (DFMO) caused a marked and rapid inhibition of tumor proliferation and actual tumor regression (with no effect upon tumor apoptosis), while proliferation of normal epidermal keratinocytes was unaffected.

The tumors resulting from injection of ODC-overexpressing cell lines have been shown to exhibit a more malignant phenotype. In particular, Gilmour has shown recently that the tumors have an increased urokinase plasminogen activator activity and an increased stromelysin-1 mRNA in the stromal cells next to the tumor cells in the deepithelialized rat trachea assay employed for tumor-cell invasiveness (Smith et al., 1997). In another cell line, overexpressing ODC was associated with an increased ability to penetrate Matrigel-coated filters as another indication of malignancy and metastasis ability (Kubota et al., 1997). Höltta (Auvinen et al., 1997) has recently shown that tumors from his ODC-overexpressing fibroblast cell line had downregulated growth factor receptors and secreted a novel angiogenic factor that may explain the highly vascularized large fibrosarcomas that he observed in his studies (cf Auvinen et al., 1997, for further comments). Promotion by constitutive ODC overexpression in the K6/ODC transgenic mice caused the clonal expansion of a population of DMBA-initiated cells not promoted by chemical agents (Megosh et al., 1998). Analysis of the ras gene mutational spectra revealed a remarkably different distribution of mutations of C-Ha-ras and C-Ki-ras genes in the tumors from the K6/ODC animals in comparison to chemically promoted (TPA) tumors.

The potential mechanism by which high levels of ODC may bring about malignant transformation/progression is likely to be mediated by increases in both intracellular and extracellular putrescine. The ODC protein itself has no known functions except for the production of putrescine, and to a reduced extent cadaverine, through the decarboxylation of lysine (McCann & Pegg, 1992; Hawel et al., 1994a). This conclusion is at least partially supported by the fact that difluormethyl ornithine, which inhibits production of putrescine by ODC, inhibited or reversed the ability of the ODC-overexpressing cells to grow in an anchorage-independent manner and produce tumors in animals. It should be noted that the stable transfection of ODC producing large constitutive increases in ODC activity (upward of 250-fold), only resulted in modest increases of intracellular putrescine and small or no changes in intracellular spermidine and spermine levels (Table

3). Since the actual amount of ODC protein in a cell is very low even when highly induced (<0.002% of total cell protein), the capacity for putrescine biosynthesis is not large. Furthermore, it is difficult to predict the intracellular concentration of putrescine produced by a known amount of intracellular ODC activity.

The ability of ODC to produce putrescine is a function of both the intracellular concentration of substrate ornithine and the relative ability of the cell to export intracellular putrescine from the inside of the cell to the outside of the cell (Hawel et al., 1994a, 1994b; Tjandrawinata et al., 1994a, 1994b; Tjandrawinata & Byus, 1995; Fukumoto & Byus, 1996; Pastorian & Byus, 1997; Wan & Erlander, 1997). Ornithine levels are low relative to the K_m of ODC for ornithine in most, if not all, normal tissues, leading to a submaximal production of putrescine at any given enzyme concentration. It has been shown, however, that a number of tumors have significantly higher levels of ornithine, which may partially explain at least one mechanism by which they are able to maintain higher levels of intracellular putrescine (Koza et al., 1991; Byus & Wu, 1991; Gonzalez & Byus, 1991). Of equivalent or greater importance in the regulation of intracellular putrescine is the putrescine export system (Hawel et al., 1994a, 1994b; Gonzalez & Byus, 1991; Tjandrawinata et al., 1994a, 1994b; Tjandrawinata & Byus, 1995; Fukumoto et al., 1996; Pastorian et al., 1997). An export system with reasonably high capacity, capable of exporting putrescine and cadaverine from inside the cell to outside the cell, has been characterized. The great majority of putrescine synthesized within the cell is exported to the exterior, and the putrescine export can be regulated independently of biosynthesis. In this regard, at least two investigators have shown in their ODC-overproducing cell lines that not only was intracellular putrescine increased but also that extracellular putrescine was increased markedly in amount (Auvinen et al., 1997; Clifford et al., 1995).

EMF-Mediated Alterations in ODC and Polyamines Numerous investigators have now observed relatively small but reproducible transient increases in ornithine decarboxylase (ODC) activity in both cultured mammalian cells and animals exposed to amplitude modulated radiofrequency or microwave fields and 50–60 Hz electric/magnetic fields (Table 4). Exposure of cells to 50–60 Hz sinusoidal magnetic fields at 100 μT and below, as well as pulsed electromagnetic fields of similar dosimetry, has been shown to result in moderate (up to fivefold) transient increases in ODC activity within 1–8 h of initiation of field exposure. Similar increases in ODC activity in animal tissues exposed to microtesla magnetic fields for somewhat longer periods of time have also been observed to increase in a linear dose-response fashion. However, several investigators have also observed a moderate decrease in ODC activity following exposure to 50- and 60-Hz magnetic fields (Table 4). Increases of two- to threefold in both putrescine and spermidine in cells and in animals exposed to 100-μT continuous 50-Hz magnetic fields have also been reported.

TABLE 4. Modulated Microwave and 50–60 Hz Magnetic Fields EMF-Induced Alterations in Ornithine Decarboxylase (ODC) Activity and Polyamines

Cell/tissue	EMF exposure	E/C[a]	Time[b]	Reference
Reuber H35 hepatoma	450 MHz, AM 16 Hz, 1.7 Watts PEP	1.5 2.6 (+ TPA)	1–4 h 4 h	Byus et al. (1987, 1988)
Chinese hamster ovary	1.0 mW/cm^2 field intensity, SAR 0.08 W/kg, 1 h exposure	2.0 2.0 (+ TP)	1–2 h 4 h	Byus and Hawel (1997)
294T melanoma	Effects seen at 12 Hz, 16 Hz, 20 Hz	2.0	0–1 h	
L929 mouse fibroblasts	Amplitude-modulated RF, 915 MHz; AM: 50 Hz, 60 Hz, 65 Hz SAR 2.5 W/kg (coherence effects similar to AC magnetic fields) No response	2 ↓ 2	8 h ↓ 8 h	Litovitz et al. (1993)
	835 MHz; AM: 16 Hz, 55 Hz, 60 Hz, 65 Hz 6 Hz and 600 Hz SAR 2.5 W/kg AMPS analog cell phone DAMPS digital cell phone FM, 60 Hz	1.5–2.1 No effect No effect 1.4 No effect	8 h 8 h 	Penafiel et al. (1997)
Primary rat bone cells	Pulsed electric field (25 μs, 3 Hz rep.), 5-min exposure 12 V/cm 22 V/cm 55 V/cm	 2 1.2 3	 4 h 4 h 4 h	Sömjen et al. (1983)
Primary mouse bone cells	Pulsed electromagnetic field (PEMF) (+ 100 μs, –2 ms, 15 Hz) 1-h exposure Induced magnetic field 8 G E-field 0.6 V/cm Current 20 μA/cm^2	 1.7 (6 days basal) 5.0 (8 days basal) 1.5 PTH	 3.5 h 3.5 h 3.5 h	Cain et al. (1985)
CEM (human lymphoma)	450-MHz RF field			Byus et al. (1987)
P3 (mouse myeloma)	60-Hz electric field	3.5	1–2 h	
Reuber H35 (rat hepatoma)	10 mV/cm–0.1 mV/cm (nonlinear dose response) 1–3 h	1.75 1.5	2 h 1 h	

(*Table continues on next page*)

TABLE 4. Modulated Microwave and 50–60 Hz Magnetic Fields EMF-Induced Alterations in Ornithine Decarboxylase (ODC) Activity and Polyamines (*Continued*)

Cell/tissue	EMF exposure	E/C[a]	Time[b]	Reference
L929 mouse fibroblasts	60 Hz, 10 μT rms magnetic field, 4-h exposure, sinusoidal signal, coherent for 5–10 s; 30–90 Hz incoherent (noise) field blocks ODC response	2.1	4 h	Litovitz et al. (1991, 1994)
Jurkat (human lympho-blastoid) HL 60 ELD F9 (embryonal)	50 Hz, 100 mT_{rms}, vertical polarization, 30 min–4 h	1.5 (P, SD also increase)	3 h	Valtersson et al. (1995)[c], Mattson et al. (1992)[c], Valtersson et al. (1997)
C3H/10T1/2 fibroblasts	60 Hz 50 mG 100 mG 200 mG	 0.84 0.53 0.75	 3 h 3 h 3 h	Cain et al. (1993)[c]
Chicken embryo (26 h)	60 Hz sinusoidal 4 μT	2.0 0.5	15 h 25 h	Farrel et al. (1998)
ODC transgenic (K2) mouse epidermis	50 Hz MF 100 μT continuous 24 h	0.75 (2–3× increase in P and SD at 24 h)	24 h	Juutilainen et al. (1996)[c]
Sprague-Dawley rat (various tissue)	50 Hz MF 50 μT 24 h/d, 7 d/wk	2.0 (mammary tissue) 1.42 (spleen) 1.0 (liver, small intestine, bone marrow, ear skin)	6 wk 6 wk 6 wk	Mevissen et al. (1995)
Rats (Fischer) (various tissues)	60 Hz 2 μT 20 μT 200 μT 24 h/d, 6 d/wk (in utero, d 13 pregnancy)	Linear dose-response increase ODC up to 5.0-fold time/flux density 5, 15, 32 wk Liver, brain, intestine, spleen, spinal cord, kidney		Mandeville et al. (1997)

[a]E/C: exposed level of ODC activity relative to the control or sham-exposed values.

[b]Time: The time indicated is the time following initial exposure epoch when ODC activity was assayed.

[c]Abstract.

At least two laboratories have studied the ability of amplitude-modulated radiofrequency fields to lead to an alteration in ODC activity at SAR values well below those thresholds recommended for exposure to workers by Safety Code 6 (0.08 W/kg and 2.5 W/kg) (Table 4). Three cultured cell lines exposed in a Crawford cell to a 450-MHz radiofrequency field at an SAR of 0.08 W/kg for a 1-h exposure period resulted in a 1.5–2.6 times increase in the level of ODC activity following a 1- to 4-h period. In this study, the amplitude-modulated microwave field was capable of further increasing ODC activity above that seen by a classic inducer of ODC activity in the cell line, the phorbol ester tetradecanoylphorbol acetate (TPA). Of particular significance was the observation that an unmodulated 450-MHz RF field was incapable of altering ODC activity. These authors established that, in a manner similar to the calcium efflux studies discussed earlier, only low-frequency amplitude modulation of between 10 and 20 Hz caused increases in ODC activity.

These early RF studies have been extended and related to the alterations in ODC activity seen following magnetic fields in an additional series of studies. The authors also have observed that an 835–915 MHz RF field was capable of altering ODC activity following several hours of exposure with SARs of 2.5 W/kg only if the field was amplitude modulated at between 16 and 60 Hz. Such exposure produced a transient increase in ODC activity that reached a peak at 8 h of exposure and returned to control levels after 24 h. An increase in ODC activity was also observed after 8 h of exposure with a typical signal from a TDMA digital cellular phone operating in the middle of its transmission frequency range, approximately 850 MHz. This signal was burst modulated at 50 Hz with approximately 30% duty cycle. However, similar exposure to an amplitude-modulated microwave field modulated with speech produced no significant changes in ODC activity. Furthermore, these investigators showed that 8 h of exposure to amplitude-modulated microwaves reveal that the response was frequency dependent, decreasing sharply at 6 Hz and 600 Hz. Classic FM or frequency-modulated 835-MHz microwave fields produced no changes in ODC activity. Similar exposure to a signal from an AMPS analog cellular telephone produced no significant enhancement of ODC activity. These authors concluded the data suggested that the same coherence requirements necessary for ELF-induced bioeffects apply to the modulation of ELF amplitude-modulated microwaves.

Potential Relationship: EMF Exposure, ODC, Polyamines, and Cancer

The data in regard to ODC activity clearly indicate that mammalian cells and tissues are capable of sensing exposure to low-frequency components of both magnetic and microwave or radiofrequency fields. It also would appear that cells or tissues have the ability to sense this low-frequency field at magnetic field intensities in the microtelsa range, and following SARs of between 0.1 and 2.5 W/kg. The activity of the enzyme is also capable of increasing within a short time (<1 h following initiation of field exposure). The detailed dose-response parameters of either increasing magnetic

field intensity or SARs have not been clearly delineated for this ODC marker of exposure.

A very important indicator of alterations in ODC activity following ELF exposure is whether or not such an increase in activity of the enzyme leads to adverse health effects. While changes in ODC activity and polyamines have been linked to a large variety of pathogenic responses in mammals, the potential link to cancer risk is perhaps the most relevant with respect to exposure to ELF. There have been historically two major criticisms of the potential linkages between ELF-mediated increases in ODC activity and cancer. ODC and the polyamines have been related most closely to the promotional phase of cancer, rather than to its initiation or progression. Most, although not all, of the recent literature summarized in Table 3 is consistent with that suggestion. Tumor promotion has been most closely correlated with a proliferative response in the tissue in which promotion was occurring. If a given agent or treatment did not cause proliferation, it was not believed to be able to serve as a tumor promoter or tumor progressing agent. The new data, generated with the ODC transgenic animals and in the various cell culture models, clearly now show that stable ODC overexpression is sufficient to cause tumor promotion in the absence of any proliferative response of the tissue. Thus, the lack of a major proliferative response in the tissue or cell line following ELF exposure does not necessarily mean that ELF is incapable of serving as a tumor promoter, particularly if alterations in ODC activity are involved.

The second major criticism of the linkage between ELF-mediated ODC and polyamine levels and cancer/tumor promotion has been that the level of increase in ODC activity, brought about by either magnetic or amplitude-modulated radiofrequency fields, has only been small relative to the large increases elicited by chemical tumor promoters. Chemical tumor promoters can cause up to 500-fold changes in the enzyme activity of ODC in relevant tissues. If the magnitudes of the changes in ODC activity brought about by ELF in Table 4 are compared to changes in ODC activity resulting from stable ODC overexpression eliciting the cancer phenotype shown in Table 3, the increases in ODC activity brought about by ELF appear to be significantly smaller than those brought about by stable ODC overexpression. However, at least some of the reports of ODC overexpression resulting in transformation phenotype cause only a fivefold change in enzyme activity. This is not far from the range of ELF-mediated ODC increases. It seems unlikely that ELF (magnetic or amplitude-modulated RF) would be sufficient to elicit a tumor promotional response in a cell or tissue by itself based upon the observed increases in ODC activity. It is much more likely that if ELF exposure has any procarcinogenic or promotional effects mediated by ODC, then these effects would require a greater increase in enzyme activity and the additive or synergistic response of the tissue or cell to other stimuli. The potential additive or synergistic responses be-

tween various environmental hazards need to be considered in assessing the risks of ELF exposure.

The other factor that must be considered is that it is not ODC activity itself that is causing the pro-promotional effects of ODC overexpression, but rather the presence of increased levels of intracellular putrescine. It is well known that large changes in ODC activity are not always accompanied by significant changes in polyamine and putrescine levels. Examination of Table 3 illustrates the dissociation between large ODC activity increases and equivalently large accumulations of putrescine and polyamines. Few studies to date have actually measured changes in polyamines following exposure to ELF. Those studies, summarized in Table 4, suggest that the changes in polyamines, particularly putrescine and spermidine, that have been observed following ELF, while small, are closer in magnitude to those changes brought by stable ODC overexpression in Table 4. It is possible that this small change in ODC activity brought about by ELF is unrelated to human cancer risk. However, both the apparent persuasiveness of the data and the potential for interaction suggest that further research in this area is needed.

Melatonin

Circulating levels of melatonin, a hormone produced and secreted by the pineal gland, have a strong circadian rhythm, with peak levels in the human occurring at night (in the dark period). Melatonin has profound effects on the mammalian reproductive system, as well as other physiological and biochemical functions (Reiter, 1991). The function of the pineal gland is strongly influenced by visible light, with seasonal as well as circadian rhythm in some mammals, particularly photoperiodically dependent rodents (Reiter, 1991, 1993). The possibility that electromagnetic energies outside the visible spectrum influence pineal function was first suggested by research with extremely low frequency (ELF) electric field exposure of laboratory rats. Wilson et al. (1981) reported that exposure to 60-Hz electric fields for many weeks suppressed nocturnal pineal function and circulating melatonin levels. This work and subsequent research with animals by various investigators led to the development of a "melatonin hypothesis" that ELF electric and magnetic fields could alter pineal-gland function in animals (Stevens, 1987). The question of alterations in melatonin secretion and metabolism from exposure to ELF fields has been discussed by various review panels (NRC et al., 1997; NIEHS, 1998) as one of the key topics in considering biological effects of electric power frequency (ELF) fields. Some studies have also observed changes in melatonin excretion in humans exposed to ELF fields (NIEHS, 1998). The data from both animals and humans, however, are inconsistent with respect to melatonin, and it is not clear what effects on pineal function may result from exposure to ELF fields.

In view of the significance of the effects of visible light on pineal function, and the possibility, though unclear, that ELF fields may also affect pineal function, it is reasonable to ask if radiofrequency fields might have an effect on the pineal. The RF photon energies are much higher than those at ELF, and radiofrequencies lie between ELF and visible frequencies in the electromagnetic spectrum. Thus, it is reasonable to hypothesize that RF fields may also influence pineal production and secretion of melatonin. However, this hypothesis has not been adequately evaluated because there has been very little research on the influence of RF fields on pineal function. Mann et al. (1998) studied several endocrine parameters in humans exposed at night in the laboratory to a low level (0.2 W/m^2) RF field at 900 MHz and found no changes in serum melatonin levels. Stark et al. (1997) studied dairy cattle herds located in the vicinity of a shortwave (3–30 MHz) radio antenna. Their data showed no chronic effect on salivary melatonin levels, although a short-term rise in melatonin was noted when the antenna was energized after being turned off for 3 days. In a laboratory study specifically designed to study pineal function of rats and hamsters exposed to low-level (SAR ranged from 0.06 to 0.6 W/kg) 900-MHz fields for up to 6 h, no effects on nocturnal melatonin were found (Vollrath et al., 1997). These few studies with differing exposure regimes, and different biological models, are not sufficient to evaluate the hypothesis that RF exposure would alter melatonin regulation. In addition, Liburdy and his colleagues (Liburdy et al., 1993; Harland & Liburdy, 1997) recently demonstrated an effect of ELF fields on the target cell activity of melatonin in cultured human breast cancer cells. These studies, while not directly applicable to the RF field evaluation, do raise the possibility that ELF (and presumably RF) exposure could have effects on target cell utilization of melatonin as well as on melatonin regulation. Thus, there is still a need for additional research on the possible effects of RF fields on pineal function and circulating melatonin levels, and the utilization of melatonin by target tissues and cells.

Cell Membrane Effects

Biological membranes are composed of proteins embedded in a lipid matrix. An evaluation of the effects of radiofrequency electromagnetic fields on membrane structure must consider both of these structural elements. Of the membrane proteins, the ion channel proteins are among the most studied. Ion channel proteins control the transmembrane flow of ions such as Na^+, K^+, and Ca^{2+}. This, in turn, affects the electrical excitability of the membrane as well as the biological function of the cell for such processes as neurotransmitter release. RF fields have been reported to affect a variety of ion channel properties, such as decreased rates of channel protein formation, decreased frequency of single channel openings, and increased rates of rapid, burstlike firing (these studies involved both CW and pulsed RF fields at a number of intensities; Repacholi, 1998).

Various studies have identified influences of microwave (MW) exposure on Ca^{2+} release from cell membranes (Dutta et al., 1984; Bawin et al., 1975). These studies have documented increased release of Ca^{2+}. However, other studies using different exposure modulation characteristics have shown no effect on Ca^{2+} release (Merritt et al., 1982). Effects of RF/MW fields on transport of cations such as Na^{+} and K^{+} across cell membranes have also been documented, and Cleary (1995) has suggested that these effects may occur without measured changes in temperature. These effects have been reported to occur over a wide range of SARs (0.2–200 W/kg) and frequencies (27 MHz–10 GHz). Although it appears that RF fields affect membrane channels, no specific interaction mechanism has been put forth. Any possible mechanism for the effects of RF/MW fields on the molecular structure of proteins remains unresolved. Equally unresolved at a mechanistic level are any putative effects of RF/MW fields on membrane lipids. Free radicals have been proposed to participate in RF-induced phase transitions in lipid vesicles exposed to CW fields at 0.2 W/kg (Phelan et al., 1992).

Thus, conflicting experimental data support the possibility of an effect of RF/MW field exposure on biological membranes. Nevertheless, they are not sufficiently well established nor are any implications they pose to human health sufficiently well understood to provide a basis for determining health effects (Repacholi, 1998).

Blood–Brain Barrier

Effects have been found in the blood–brain barrier in response to exposure to RF fields. In 1977, Albert reported increased permeability to horseradish peroxidase (HRP) in Chinese hamsters irradiated with 2450-MHz microwaves at a power density of 100 W/m^2. At the same time, Oscar and Hawkins (1977) found an increase in the blood–brain barrier permeability for mannitol and insulin (but not dextran) when irradiating rats to 1300 MHz at 30 W/m^2. Effects were reported at 1 W/m^2 and lower, and effects were different for different microwave parameters. In 1981, Oscar et al. further reported that irradiations at 2500 MHz with a power density of 150 W/m^2 increase blood flow. In 1990, Neubauer et al. reported that 2450 MHz (100 W/m^2, 2 W/kg) increased blood–brain barrier permeability in rats to a rhodamine–ferritin complex. However, they found that a lower power density (5 mW/m^2) at a shorter time (15 min compared to 30 min) had no effect. On the other hand, Moriyama et al. (1991) also exposed rats to 2450 MHz (100 W/kg) for 30 or 60 min, but reported no increase in blood–brain barrier permeability to HRP if temperature increases in the brain were reduced by water cooling of the transmit antenna. In an exhaustive series of experiments, Williams et al. (1984a, 1984b, 1984c) reported that rats exposed to 2450 MHz (13 W/kg) showed (a) no increase or decrease in permeability to sodium fluorescein (1984b); (b) reduction in HRP-labeled microvessel endothelium (1984a); and (c) increased permeability to

[^{14}C]sucrose (1984c). Recently, Fritze et al. (1997) found no significant increase in extravasation of serum proteins after rats were exposed to 900-MHz microwaves modulated at 21 MHz at SAR values of 0.3 and 1.5 W/kg. At an SAR of 7.5 W/kg, a significant increase in serum albumin extravasations was seen.

With the advent of magnetic resonance imaging (MRI), the possibility of increased blood–brain barrier permeability from RF exposure has recently been reexamined. The results have been inconclusive with respect to radiofrequency irradiation; however, SAR values were generally <0.01 W/m^2 (Prato et al., 1994). More recently, however, Salford et al. (1992, 1994) have shown that microwave irradiation of rats (915 MHz, 0.016-5 W/kg, continuous wave or pulse modulated at 8, 16, 50, 200 Hz) significantly increased blood–brain barrier permeability to albumin in all exposed groups. No significant difference between pulsed and continuous wave exposures was found; however, the frequency of occurrence of extravasates (26%) was found to be independent of SAR for SAR < 2.5 W/kg, but rose significantly for the higher SAR values. It is extremely important to note that for the group exposed to SAR values between 0.016 and 0.1 W/kg (whole-body exposure), there was a significant increase in permeability.

In summary, the work of Salford et al. (1992, 1994) provides evidence that at SAR values below Safety Code 6 limits, changes in blood–brain barrier permeability occur. Further, the work of Oscar and Hawkins (1977), using much lower power densities than recommended as safe limits in Safety Code 6 (1 W/m^2 vs. 10 W/m^2 at 2850 MHz), also showed increases in blood–brain barrier permeability. However, not all studies have shown significant increases, suggesting that the changes may be related to the RF frequency or the extremely low frequency modulation of the RF carrier frequency. The possibility exists that the nonthermal effect of RF on ornithine decarboxylase activity or calcium ion concentrations may initiate this small increase in blood–brain barrier permeability (Koenig et al., 1989).

Biobehavioral Effects

Behavioral effects of microwave irradiation have been reported by at least two groups. Thomas et al. (1979) reported a significant synergistic effect between a psychoactive drug, chlordiazepoxide, and low-level microwave fields (2450 MHz, 2-μs pulses, 550 pps, 10 W/m^2) in rats. Lai et al. (1992a, 1992b, 1994) have shown that a 45-min exposure to pulsed microwave fields (2450 MHz, 2-μs pulses, 550 pps, 10 W/m^2, 0.6 W/kg) affects radial-arm maze performance in rats. A significant amount of related data, using biochemical endpoint in rats, has been produced by Lai et al. and indicates that microwave exposure reduces high-affinity choline uptake in the frontal cortex and hippocampus. Opioid antagonists to μ, δ, and κ opioid receptors blocked this effect in the hippocampus but not in the frontal cortex. The microwave-induced decrease in central cholinergic activity was examined with respect to dose response. Groups of rats

were exposed to SAR values of 0, 0.3, 0.45, 0.6, 0.75, 0.9, and 1.2 W/kg (average power). The whole-body SAR that elicited 50% of the maximal response was 0.65 W/kg for the striatum, 0.38 W/kg for the frontal cortex, and 0.44 W/kg for the hippocampus. This suggests that effects might occur below the Safety Code 6 limit for workers (0.4 W/kg) but not below that for the general public (0.08 W/kg).

In other experiments carried out by Lai (1996), rats were exposed to a 60-Hz magnetic field (45 min, 0.75 mT, SAR of 0), and a similar decrease in spatial learning was observed. The 60-Hz magnetic field was also observed to reduce high-affinity choline uptake in both the hippocampus and frontal cortex of the rats. This uptake could be blocked in both regions of the brain by both μ and δ opioid antagonists. Although there are subtle differences between the 60-Hz and microwave results with respect to the effectiveness of opioid antagonists to block the effect in the frontal cortex, the studies conducted by Lai implicate the opioid system in the biobehavioral effects produced by both frequencies. That the ELF exposures have an effective SAR of zero suggests that if the observed effects are due to a similar mechanism in both the microwave and 60-Hz exposures, it is a nonthermal one.

Independent work by Rojavin et al. (1998) suggests that exposure to microwave fields (61.22 GHz, 15 min, incident power density of 150 W/m^2) triggers the release of opioid in mice. Although this level of exposure is known to cause thermal effects, it is not clear that the release of opioid is a thermal effect.

All of the work just described indicates that the opioid system is sensitive to microwave exposure. It is interesting to note that the opioid system has also been implicated in behavior experiments associated with nonthermal ELF exposures. Besides the work of Lai (1996), at least three other groups have shown effects on opioid-induced analgesia of nonthermal ELF exposures (Betancur et al., 1994; Del Seppia et al., 1995; Kavaliers et al., 1994). Further experiments by Prato et al. (1995, 1996) have implicated a nonthermal detection mechanism, suggesting that these reported microwave effects might be nonthermal ones.

Lai and Carino (1988) reported that the hippocampus of the rat responded to pulsed but not continuous-wave microwaves. As the SAR was constant for these exposures, biologically different effects seem to be related, at least in some cases, to the ELF modulation of the microwave irradiation.

In summary, there is strong evidence that microwave irradiation produces behavioral and associated biochemical changes at or below the occupational exposure limits in SC6. Further, the opioid system appears to be affected by these exposures in some way, and similar effects appear to occur with nonthermal ELF exposures. These results suggest the possibility that the effects reported are nonthermal and hence dependent on another field characteristic.

Mechanism

As reviewed in previous sections of this chapter, there is evidence in a number of systems that biological effects not dependent on increases in sample temperature do occur. At RF frequencies, both the electric field and the magnetic field penetrate tissue (Postow & Swicord, 1996) and deposit heat. However, these tissue magnetic and electric fields could elicit separate effects if tissue contains magnetic field detectors, electric field detectors, or potential difference detectors and these detectors are effectively coupled to a physiological or biochemical pathway in the organism. For example, it has been recently shown that magnetic stimulation can reduce depression in drug-resistant clinically depressed patients. However, the effect is dependent on the extremely low frequency (ELF) waveform as well as the amount of current induced (i.e., two waveforms, each of which induces the same tissue current, can have a different effect if the information content is different). For this reason, it is not surprising that continuous-wave and ELF-modulated RF can produce different nonthermal effects but do not necessarily do so.

If such tissue detectors exist, it is unlikely that they can respond quickly enough to detect the carrier frequencies. For example, an electric field detector at a membrane could not respond significantly to an external force which lasted less than a nanosecond. Rather, the carrier provides a method by which an ELF pulse sequence can be delivered to the tissue without significant electric field attenuation. Any effect of such ELF-modulated RF would, of course, require the existence of some amplitude-dependent demodulation mechanism to extract the ELF from the RF carrier.

What is striking in this literature are the similarities between the RF effects and the ELF effects for Ca^{2+} efflux, ornithine decarboxylase activity, and behavior associated with opioid effects. For ELF exposures, only the magnetic field penetrates the tissue, and this can induce an EMF and induced current through Faraday's Law of Induction. An ELF-modulated RF field can deliver that same EMF and induce current directly, since the electric field now penetrates the tissue. This suggests that many of the efforts now underway to understand the mechanism associated with ELF effects could be used to investigate the mechanisms by which ELF-modulated RF fields elicit nonthermal effects. Engstrom (1996) recently suggested how hypothesis testing should be undertaken to discriminate between different characteristics of the detection mechanism.

If nonthermal effects occur, it is important to determine the underlying mechanism(s). Otherwise, it will be very difficult to determine, on a trial-and-error basis, which manner of ELF modulation of an RF carrier viable for wireless communication reduces the risk of inducing unwanted biological and possible health effects. This is because there are an infinite number of ways the RF carrier can be modulated and it is likely that the subset that can be used to carry wireless communication and the subset

that can transmit information to tissue do not completely overlap. Without such an understanding, each time the communication industry modifies its waveform, it will have to be extensively tested in biological samples to determine whether it might elicit a biological effect that might be detrimental to health.

Summary

Most of the RF exposures used in the studies described in this section exceeded the limits in Safety Code 6 for whole-body exposures of nonradiation workers (SAR = 0.08 W/kg; power density = 2–10 W/m^2 depending on RF frequency). However, effects on cell proliferation, Ca^{2+} efflux, blood–brain barrier permeability, behavior, and ornithine decarboxylase activity have been reported to occur below these levels (see Table 5). Many of these latter studies have also been repeated in independent laboratories. Because these effects occur at exposures not thought to elicit thermal effects, it is likely that these effects, even if they also occur at higher exposure levels, are nonthermal biological effects.

An interesting aspect to these results is that they strongly suggest that nonthermal effects do not follow a simple dose response. That is, the effects do not necessarily increase as the dose increases. For example:

TABLE 5. Summary of Biological Effects Below SC6 Levels for Nonradiation Workers

Biological effect	Exposure parameters	Reference
Cell proliferation	C6 glioma; 5.9 mW/kg; 836 MHz, TDMA; 24 h	Stagg et al. (1997)
Cell proliferation	Human epithelial amnion cells; 0.021, 0.21, 2.1 mW/kg; 920 MHz, GSM; 30 min	Kwee and Raskmark (1998)
Ca^{2+} efflux	In vitro neonatal chick brain; 1 W/m^2; 450 MHz, 16 Hz	Bawin et al. (1978)
Ca^{2+} efflux	Cultured nerve cells; 915 MHz; 0.05, 1.0 W/kg	Dutta et al. (1984)
Blood–brain barrier permeability	Rats, mannitol; 1.3 GHz; 5 pps, 10 μs, 0.3 W/kg; 1000 pps, 0.5 μs, 1 W/kg	Oscar and Hawkins (1977)
Blood–brain barrier permeability	Rats, albumin; 915 MHz; 0.1 W/kg	Salford et al. (1992, 1994)
Biobehavioral	Rats, radial-arm maze; 2.45 GHz, 2 μs, 550 pps; 0.4 W/kg	Lai et al. (1992a, 1992b)
	0.08 W/kg; 450 MHz	
Ornithine decarboxylase activity	Chinese hamster ovary cells; 450 MHz; 0.08 W/kg	Byus & Hawel (1997)

- In terms of cell proliferation, Stagg et al. (1997) showed effects at 5.9 mW/kg but not at 0.59 mW/kg or 59 mW/kg.
- In terms of Ca^{2+} efflux, Bawin et al. (1975, 1978) showed that effects at 10 W/m^2 were bounded by no effects at 0.05 W/m^2 and 20 W/m^2.
- Also in terms of Ca^{2+} efflux, Blackman et al. (1979, 1980a, 1980b) replicated Bawin's power density window and further discovered that there was also a frequency modulation window (effects at 16 Hz but not at 30 Hz; Blackman et al., 1979).

Further, the work presented in this section suggests that ELF modulation of an RF carrier may produce different biological effects than those of continuous-wave irradiation, even if the exposures are normalized to the same power density (Ca^{2+} efflux, biobehavioral, blood–brain barrier permeability, ornithine decarboxylase). This trend has been reported before (cf Postow & Swicord, 1996, Chap. 12).

In summary, nonthermal biological effects probably occur. The relationship of these effects to exposure parameters is not currently understood. Once this relationship is understood, it may provide insight into the underlying mechanisms by which exposure to RF fields produces biological effects.

GENOTOXIC EFFECTS OF RADIO FREQUENCY FIELDS

Introduction

Popular concern over the potential negative health effects of RF field often centers on issues related to cancer and mutation. Genotoxicology has thus become the focal point of a large number of studies available in the literature. These studies include a variety of endpoints including tumorigenesis, promotion, progression, altered cell proliferation, and other studies more directly related to DNA damage including chromosomal aberrations, micronuclei, and mutation. A survey of such articles has been performed and many of these studies are listed in Table 6.

An analysis of the literature reveals that the vast majority of studies on the genotoxic effects of RF field have proven to be negative, suggesting that there is no reason for concern on the part of the public. Indeed, most experiments have revealed no untoward effect of RF field exposure, while those studies that have provided an indication of a genotoxic effect have generally suffered from poor methodologies, inadequate numbers for proper statistical evaluation, or, as is most frequently the case, reflect a hyperthermal incident. In the sections that follow we review some of the current approaches to assess genotoxicity and examine some of the more pertinent issues.

In this section we address some of the issues and assays related to genotoxic effects of RF field and assess some of the current views on the issues.

TABLE 6. RFR Effects on Cancer-Related Endpoints

Type of study	Exposure	Results	Reference
Longevity studies			
Mice	92.7 GHz	Increased life span	Prausnitz and Susskind (1962)
Mice	0.80 GHz for 2 h/d, 5 d/wk for 35 wk (43 W/m^2)	No effect on life span	Spalding et al. (1971)
CFW mice (in utero exposure to RF and implantation of tumor cells)	2.45 GHz (leading to an increase in body temperature of 2.24°C) for 20 min/d for 3 d (d 11–14 of gestation) (dose rate 35 W/kg)	Increased life span in tumor-bearing and tumor-free animals	Preskorn et al. (1978)
100 Sprague-Dawley rats	2.45-GHz + 8-MHz pulse for 25 mo	No effect on life span, although incidence of benign pheochromocytomas of the adrenal gland	Chou et al. (1986)
CD1 mice	2.45-GHz for 1 h/d, 5 d/wk throughout life (3–10 W/m^2)	Significantly shortened life span of mice exposed to 10 mW/cm^{2}and slightly but not significantly longer average life span of mice exposed to 3 mW/cm^2	Liddle et al. (1994)
New Zealand rabbits	2.45 GHz for 90 d (5.5 W/kg to the head and 7 W/kg to the back) for 2 h/d 6 d/wk (0.5 and 5 W/m^2)	No effect on life span	Chou et al. (1983)
Initiation studies			
Mice	92.7 GHz	Increased incidence of leukosis and leukemia	Prausnitz and Susskind (1962)
C3H/HeA mice (mammary tumor prone animals)	2.45 GHz for 28 d (whole-body SAR 6 to 8 W/kg) for 2 h/d, 6 d/wk (5 or 15 W/m^2)	Significant increase in incidence of spontaneous mammary tumors in animals exposed to 15 mW/cm^2 ($p < .01$)	Szmigielski et al. (1982)

(*Table continues on next page*)

TABLE 6. RFR Effects on Cancer-Related Endpoints (*Continued*)

Type of study	Exposure	Results	Reference
Initiation studies (*continued*)			
New Zealand rabbits	2.45 GHz for 90 d (5.5 W/kg to the head and 7 W/kg to the back) for 2 h/d, 6 d/wk (0.5 and 5 W/m^2)	No effect on 28 specimens of organs and tissues examined	Chou et al. (1983)
Sprague-Dawley rats	2.45 GHz square modulated at 8 Hz pulse days (whole-body SAR 0.4 to 0.15 W/kg), 21.5 h/d for 25 mo (0.5 and 5 W/m^2)	Increase incidence of pheochromocytoma (7 vs. 1 in controls) Fourfold increase in primary malignancies	Chou et al. (1992)
Pin1 mice (transgenic animals prone to leukemia)	0.90 GHz (with a repetition frequency of 217 Hz and a pulse of 0.6 ms) for 1 h/d, 18 mo (2.6 to 13 W/cm^2 and whole-body SAR 0.13 to 1.4 W/kg)	Twofold increase in the risk of developing lymphoma	Repacholi et al. 1997
C3H/HeA mice (mammary tumor prone animals)	0.435 GHz for 22 h/d, 7 d/wk for 21 wk (1.0 W/cm^2 and whole-body SAR 0.32 W/kg)	No statistically significant difference in the rate of tumor incidence, growth rate, or latency in 22 tissues	Toler et al. (1997)
C3H/HeJ mice (mammary tumor prone animals)	2.45 GHz for 20 h/d, 7 d/wk for 18 mo (1.0 W/cm^2 and whole-body SAR 0.3 W/kg)	No effect on mammary tumor incidence, latency, or tumor growth rate	Frei et al. (1998)
Promotion studies			
CFW mice (in utero exposure to RF and implantation of tumor cells)	2.45 GHz (leading to an increase in body temperature of 2.24°C) for 20 min/d for 3 d (d 11–14 of gestation) (dose rate 35 W/kg)	Lower incidence of transplantable lymphoreticular cell sarcoma after 2.5 mo	Preskorn et al. (1978)
CFW mice (in utero exposure)	2.45 GHz for 20 min/d for 3 d (d 11–14 of gestation) (dose rate 35 W/kg leading to an increase in body temperature of 2.24°C)	Lower incidence of transplantable lymphoreticular cell sarcoma after 2.5 mo Slight increase in tumor incidence after 36 mo (46% compared to 40% in sham-exposed)	Preskorn et al. (1978)

TABLE 6. RFR Effects on Cancer-Related Endpoints (*Continued*)

Type of study	Exposure	Results	Reference
Promotion studies (*continued*)			
BALB/*c* mice exposed to irradiation and/or a chemical carcinogen (benzopyrene)	2.45 GHz for 28 d (whole-body SAR 6 to 8 W/kg) for 2 h/d, 6 d/wk (5 or 15 W/m^2)	Increased incidence of skin cancer (significant accelerated growth) in animals exposed to RF fields before, during, or after benzopyrene treatment	Szmigielski et al. (1982)
Sprague-Dawley rats exposed to benzopyrene	0.90 GHz pulsed wave 2 h/d for 10 d	No effect on sarcoma development	Chagnaud et al. (1995)
CBA/S mice exposed to ionizing radiation	Two groups: (a) 0.90 GHz 1.5 h/d, 5 d/wk, for 10 d and (b) 0.90 GHz pulsed wave 1.5 h/d 5 d/wk, for 10 d	No effect on survival or growth	Juutilainen et al. (1998)
F344 rats exposed to ethylnitrosourea in utero	0.836 GHz circularly polarized (near-field and far-field exposures), 2 h/d for 23 mo	No effect on brain tumor promotion	Adey et al. (1997)
Partially hepatectomized F344 rats exposed to diethylnitrosamine	0.989 GHz near field with a modulated TDMA signal (90 min/d, 5 d/wk for 6 wk	No effect on liver foci promotion	Imaida et al. (1998a)
Sprague-Dawley rats	0.85 GHz d (whole-body SAR 0.9 W/kg), 6 h/d for 6 mo	No effect on CNS tumors	Zook et al. (1998)
Progression studies			
BALB/*c* mice injected iv with L1 sarcoma	2.45 GHz (whole-body SAR 6 to 8 W/kg) for 2 h/d, 6 d/wk for 28 d (5 or 15 W/m^2)	Increased incidence of lung metastasis in animals exposed to 5 and 15 mW/cm^2 ($p < .01$)	Szmigielski et al. (1982)
C57Bl/6J mice	2.45 GHz (whole-body SAR 6 to 8 W/kg) for 2.5 h/d, 6 d/wk, until death (1.0 W/m^2)	No effect on animal survival No effect on B16 melanoma development	Santini et al. (1988)
BALB/*c* mice exposed to a chemical carcinogen (dimethylhydrazine) and TPA as a tumor promoter	2.45 GHz for 3 h/d, 6 d/wk for 5 mo (10 W/cm^2)	No effect on incidence of colon cancers Increase in the number and size of tumors Increase in incidence of protuberant and infiltrative types	Wu et al. (1994)

(*Table continues on next page*)

TABLE 6. RFR Effects on Cancer-Related Endpoints (*Continued*)

Type of study	Exposure	Results	Reference
Progression studies (*continued*)			
F344 rats	0.915 GHz (continuous and modulated at 4, 8, 16, and 200 Hz in 0.5-ms pulses (2 W/pulse) and 50 Hz in 6-min pulses (2 W/pulse); exposure started 5 d after tumor inoculation (7 h/d, 5 d/wk for 2–3 wk)	No effect on RG-2 glioma development Increased albumin leakage from brain	Salford et al. (1993)
Other			
Wistar rats brain	GSM 3 exposure levels for 4 h: (a) 0.3 W/kg; (b) 1.5 W/kg; and (c) 7.5 W/kg	Minor stress response but no lasting adaptive or reactive changes in the brain	Fritze et al. (1997)
PC12 pheochromocytoma cells of rats incubated with nerve growth factor	836.55 MHz modulated	No changes in c-fos transcript levels Inhibition of c-jun after 20-min exposure at 9 mW/cm^2; multiple hits of RF fields did not alter the dynamic of c-fos and c-jun expression	Ivaschuck et al. (1997)
Molt-4 cells (T-lymphoblastoid cell lines)	813.56 MHz pulsed signals (IDEN) 836.55 MHz (TDMA signal)	IDEN signal (SRA 2.4 mW/kg) for 2 or 21 h significantly inhibited DNA damage IDEN signal (SRA 24 mW/kg) for 2 or 21 h significantly increased DNA damage TDMA signal (SRA 2 or 26 mW/kg) for 2 or 21 h significantly inhibited DNA damage	Phillips et al. (1998)

Longevity

Most studies on mammalian aging, including those on the influence of RF field on longevity, make use of mouse or rat models. In an investigation of the effects of RF field exposure, Spalding et al. (1971) carried out a study using virgin female mice that had been exposed to 800 MHz with an average incidence of 43 mW/cm^2 for 2 h/d, 5 d/wk, for 35 wk. While no effects were seen on peripheral blood characteristics (RBC, WBC,

hemoglobin and hematocrit), the mean life span of the RF-exposed group (664 d) was slightly, though not significantly, longer than that of the sham group (645 d). In work by Chou et al. (1986), 100 Sprague-Dawley rats were chronically exposed to 2450 MHz and an 8-MHz pulse for 25 mo along with 100 sham-exposed animals. No effect was observed on longevity although the incidence of benign pheochromocytomas of the adrenal medulla was enhanced sevenfold following exposure and the RF field significantly reduced the incidence of glomerulonephropathy ($p = .04$).

Liddle et al. (1994) examined the effects of 2450-MHz RF exposure on the life span of CD1 mice. Animals were exposed for 1 h/d, 5 d/wk throughout their life to CW microwave radiation at a power density of 3 to 10 mW/cm^2 at an SAR of either 2 or 6.8 W/kg. Life span was significantly shortened in mice exposed at 10 mW/cm^2 (median of 572 d vs. 706 d in the sham-exposed group, $p < .05$). The average life span of the animals exposed to 3 mW/cm^2 was slightly, but not significantly, longer (median of 738 d) than the sham-exposed group. The authors suggested that the heating from exposure at 10 mW/cm^2 was stressful enough to shorten the life span.

Though some indications of a shortening of life span have been observed in RF field studies, it seems likely that these effects are related to the thermal consequences of the exposure regime. The occasional report of an extension in life span upon RF field may be attributed to a reduction in caloric intake in exposed animals. In a study of New Zealand rabbits exposed to 5 mW/cm^2 of 2450-MHz continuous-wave microwave fields for 90 d (Chou et al., 1983), there was a significant ($p < .01$) decrease in food consumption. No other effects were observed.

Tumorigenesis

Tumor formation is thought to be a multistep process in which the steps of initiation (mutation), promotion, and progression have been identified (Prausnitz & Susskind, 1962; Spalding et al., 1971; Szmigielski et al., 1982; Wu et al., 1994; Santini et al., 1988). A number of tumorigenesis studies have been conducted to examine the carcinogenic potential of RF fields (see Table 6). The studies generally involve long-term experiments in which relatively large numbers of animals are exposed to a defined treatment regimen. At a defined age, the animals are then sacrificed and subjected to histopathological examination for tumor development. In some studies, the animals are inoculated with cells from a well-characterized tumor and then tumor development is monitored. In these studies, the establishment and growth of a tumor is examined, which is quite distinct from studies on promotion in which diverse molecular alterations occur following the initial mutation.

In 1962 Prausnitz and Susskind demonstrated that mice exposed to a 9270-MHz RF field had increased frequencies of leukosis and leukemia. Although this study has been severely criticized (e.g., Roberts & Michaelson, 1985) on the basis of experimental procedures, statistical methods,

the presence of recurrent pneumonitis, and the relatively high numbers of animals that were excluded from histopathological examinations, it did provide the first suggestion that tumorigenesis might be a consequence of RF field. The recognition of this possibility has stimulated much additional research.

Preskorn et al. (1978) obtained opposing results. They observed retarded tumor growth and enhanced longevity in mice after fetal irradiation by 2450-MHz microwaves. In their experiments, 48 CFW mice were exposed in utero during d 11–14 of gestation and lymphoreticular sarcoma cells were implanted in the offspring at d 16 postpartum. The RF field exposure produced a reduced incidence of tumors (13% vs. 46% in sham-exposed animals). In a second study, 84 CFW mice received RF field treatment in utero while 60 mice were sham treated. The offspring were then inoculated with the homogenate of cancer cells on day 16 postpartum and were monitored for nearly 36 mo for the development of palpable tumors. The original observation of a reduced incidence of tumors was confirmed at 2.5 mo. However, an examination of tumor incidence 4 mo after exposure indicated that the rate of tumor induction in the RF field-treated mice had increased. The percentage of RF field-treated mice with tumors (46%) slightly exceeded that of controls (40%). It was also noted that tumor-bearing and tumor-free animals that had been irradiated lived longer on average than respective controls. The authors concluded that in the short term, hyperthermal effects delay the onset of experimental neoplasms; however, there remains an open question as to whether this phenomenon is due to thermal augmentation of maturation of the immune system or another nonspecific stress reaction.

Szmigielski et al. (1982) and Szudzinski et al. (1982) exposed three groups of animals to microwave radiation. In the first group, C3H/HeA mice exposed to 2450-MHz microwaves at 5 or 15 mW/cm^2 for 2 h/d, 6 d/wk, enhanced levels of mammary tumors were found. The particular strain of mice used is characteristically sensitive to mammary tumors, and hot spots induced by the thermal treatments have been suggested as contributing factors. Survival time was also significantly shorter: 358 d in controls, 264 d for 5 mW/cm^2, and 231 d for 15-mW/cm^2 irradiated animals.

In the second group, BALB/*c* mice were treated with 3,4-benzopyrene (BP) as well as a 2450-MHz RF field. A significant acceleration in the development of BP-induced skin tumors in mice was observed in the animals simultaneously exposed to the RF field: 285 d in controls, 220 d for 5 mW/cm^2, and 121 d for 15 mW/cm^2. These results were obtained whether the animals were exposed to RF field before, simultaneously or following the BP treatment.

In a study by Szmigielski et al. (1982), BALB/*c* mice were injected with 2×10^6 L1 sarcoma cells, and then exposed to RF fields (2450 MHz at 5 or 15 W/m^2 for 2 h/d, 6 d/wk). Controls included both sham-exposed animals and animals subject to "chronic confinement stress." Fourteen days

after the inoculation, the animals were sacrificed and the tumor colonies in their lungs were enumerated. The mean number of tumor foci was 2.8 in controls, 6.1 in mice exposed at 5 W/m^2, and 10.8 in those irradiated at 15 W/m^2 ($p < .01$). As the animal exposures were at a whole-body SAR of 6 to 8 W/kg, thermal effects may have been a contributing factor. The authors also suggest that confinement stress may have played a role.

Repacholi et al. (1997) published a report indicating that exposure to 900 MHz with a repetition frequency of 217 Hz and a pulse width of 0.6 ms, which is similar to that used in mobile telecommunications, increased the incidence of lymphomas in Eμ-pim1 mice. Exposure was associated with a statistically significant 2.4-fold increase in the risk of developing a lymphoma ($p < .01$). No increases in the incidence of other types of tumors were found. Although the Eμ-pim1 mice are moderately predisposed to spontaneous lymphomas, these studies indicate the potential of RF field to induce lymphomas in mice. Other studies attempting to confirm these results have not produced similar results.

This potentially positive response to RF fields has been the subject of much discussion. The field intensities used by Repacholi et al. (1997) ranged from 0.008 to 4.2 W/kg. The guidelines for public exposure as recommended in the ANSI/IEEE standard are below 0.08 W/kg for the general public and below 0.4 W/kg for occupational exposure. While this study is very interesting, its impact on the regulation of RF exposure of the general public is unclear. The study will need to be repeated with both normal and lymphoma-prone mice. If the effect can be replicated, it will be critical to determine the dose-response relationship for lymphoma induction, and to determine whether the effect occurs for other tumors and/or in other species.

In a recent investigation of whether RF fields can induce breast cancer, Toler et al. (1997) exposed 200 mammary-tumor-prone mice to pulsed 435 MHz for 22 h/d, 7 d/wk for 21 mo. The study was designed to determine if chronic, low-level exposure of mice prone to mammary tumors promotes an earlier onset, a faster growth, or a greater incidence of mammary tumors than in sham-exposed controls. The complete histopathological examination (22 tissues) of all exposed and sham-exposed controls was determined. This carefully conducted study revealed no significant differences with respect to latency, tumor onset, tumor growth rate, and overall tumor incidence.

In a similar experiment, Frei et al. (1998) published a carefully conducted study on 100 mammary-tumor-prone C3H/HeJ mice exposed to continuous-wave 2450-MHz RF radiation for 20 h/d, 7 d/wk for 18 mo. Results showed no significant differences between groups with respect to incidence of mammary tumors and tumor growth rates. Moreover, survival analysis showed no significant difference in cumulative survival between groups. In particular, there was no difference in the lymphoma, leukemia, or brain tumor rate between the exposed and the control group.

Promotion Studies

Various studies have examined the effect of microwave radiation, RF field, digital cellular telephone fields, and electromagnetic fields on the acceleration of tumor development in experimental mice and rats. Experimental animals were treated with various immune suppressive agents. After a defined time period all the animal were sacrificed and subjected to histopathological examination for enumeration of cancer colonies.

In a study by Szmigielski et al. (1982), three groups of animals were exposed to microwave irradiation. The first group consisted of C3H/HeA mice with a high incidence of spontaneous breast cancers, the second of BALB/*c* mice treated with 3,4-benzopyrene, and the third of BALB/*c* mice injected intravenously with 2×10^6 L1 sarcoma cells. Animals were then exposed to 2450-MHz microwaves at 5 or 15 mW/cm^2 for 2 h/d, 6 d/wk. Controls included both sham-exposed animals and animals subject to "chronic confinement stress." Acceleration of cancer development in all tested systems and a lowering of natural antineoplastic resistance was similar in mice exposed to microwaves at 5 mW/cm^2 or to confinement stress but differed significantly from the data obtained from animals exposed at 15 mW/cm^2, where local thermal effects (hot spots) were possible.

There was a significant effect of microwave radiation on the acceleration of breast cancer growth and on the reduction of survival rate in C3H/He mice. Breast cancer appeared within 322 d in controls, 261 d for 5 mW/cm^2, and 219 d for 15-mW/cm^2 irradiated mice. Animals irradiated with 15 mW/cm^2 had the shortest survival rate, 231 d, compared with 358 d in controls and 264 d in animals irradiated with 15 mW/cm^2.

The same pattern of effect was observed on the development of BP-induced skin tumors (285 d in controls, 220 d for 5 mW/cm^2, and 121 d for 15 mW/cm^2). Shorter survival times were also observed for irradiated mice.

Irradiated mice were more likely to experience a significant lowering of natural antineoplastic resistance. Two weeks following the injection of tumors, all animals were sacrificed and lung colonies were enumerated. There was a high number of lung colonies in mice irradiated at 15 mW/cm^2, compared with 2.8 in controls and 6.1 in mice exposed at 5 mW/cm^2 ($p < .01$).

Wu et al. (1994) exposed BALB/*c* mice at 4 wk of age to the chemical carcinogen dimethylhydrazine (DMH) as a tumor initiator once a week and to 12-*O*-tetradecanoylphorbol 13-acetate (TPA) as a tumor promoter once a week for 10 wk. The mice were also irradiated with 2450-MHz RF radiation at 10 mW/cm^2. Radiation exposure was for 3 h/d, 6 d/wk for 5 mo.

Chagnaud et al. (1995) studied the effect of pulsed microwaves on chemically induced tumors in rats. They exposed male and female Sprague Dawley rats to 900-MHz pulsed wave for 2 h/d for 10 d. There was no observed effect on tumor latency and survival and no effect on lymphocyte subpopulations or transformation in a benzo[a]pyrene rat sarcoma bioassay.

Juutilainen et al. (1998) have studied the effect of radiofrequency (902 MHz) on the development of cancer in mice. In their study, which is still in progress, they exposed 300 female CBA/S mice to ionizing radiation at the beginning of the experiment. The animals were divided into two groups and were exposed to two different types of radiation. Group C was exposed to continuous RF radiation of 902.5 MHz and group D received pulsed RF radiation (902.5 MHz). Exposure time was 1.5 h/d, 5 d/wk. No significant differences in survival or in growth between exposed groups and controls were found. Final conclusions about possible cancer-promoting effects of RF exposure are yet to be completed.

At the Second World Congress in 1997, Adey et al. (1997) briefly reported on the effect of a frequency-modulated 836.55-MHz CW PW (TDMA) signal with 12.5 kHz maximum deviation. Pregnant F344 rats were randomly assigned into six groups. They received either a single tail-vein injection of the carcinogen ethylnitrosourea (ENU, 4 mg/kg) or inert buffer solution on gestational day 18. Far-field exposures (horn radiator, 836 MHz, circularly polarized) began on day 19 and continued after parturition until weaning at age 23 days. Offspring (n = 540) of the six maternal groups then became treatment cohorts. Exposures simulating near fields at a phone user's head began at 35 d, and continued for the next 23 mo. Exposures were for 2 h/d, antenna power 2.5 W, fields on 7.5 min, fields off 7.5 min). Survivors of the original 540 rats (n = 372; 69%) were sacrificed at 730–733 d.

The authors reported the absence of enhancing effects on type of brain cancer, or on location and incidence of spontaneous nervous-system tumors in rats. The RF field animals had actually reduced tumor incidence and tumor size compared with controls. As regards survival rates, lifetimes of ENU-exposed animals were significantly shorter than controls ($p < .0005$). These differences were not influenced by FM field exposures.

Imaida et al. (1998a) have studied the effect of 929-MHz near-field radiation with a modulated TDMA signal through a quarter-wavelength monopole antenna on rats. The animals were exposed for 90 min/d, 5 d/wk for 6 wk. A group of 24 rats, given only DEN and partial hepatectomy, served as controls. The cases were 6-wk (wk 0) male F344 rats. They were initially exposed to a single dose of 200 mg/kg of diethylnitrosamine (DEN). After 2 wk (wk 2), exposure (47 rats) or sham exposure (48 rats) was started. A week later (wk 3), all rats underwent a two-thirds partial hepatectomy. At wk 8, all rats were sacrificed and the numbers and areas of the carcinogenic potential of glutathione *S*-transferase placental form (GST-P) positive foci was compared in the livers of all animals. The authors did not find significant differences in the areas and numbers of GST-P positive foci between the exposed and the sham-exposed animals.

The same finding was observed in a study by Zook et al. (1998). In their study, male and female Sprague-Dawley rats were exposed to 850-MHz CW and PW (MIRS), carousel irradiator/SAR 0.9 W/kg. Exposure

was for 6 h/d, for 6 mo. No effect was reported on central nervous system (CNS) tumors.

Progression Studies

Few studies have looked at the effect of radiation on tumor progression. Of those published, neither has demonstrated an association between radiation and tumor progression.

Santini et al. (1988) have exposed C57B1/6J mice to 2450-MHz RF radiation for 2.5 h/d, 6 d/wk until death with a power density of 1.0 mW/cm^2. RF field exposure had no effect on survival time or tumor growth rate of sc implanted B16 melanoma cells.

Salford et al. (1993), in their study on Fischer 344 rats, studied the effect of RF field on tumor size between exposed and control animals and also investigated the permeability of the blood–brain barrier. Fischer 344 rats were implanted with brain tumors (RG-2 glioma models). Rats from both sexes were uniformly exposed to 915-MHz microwaves both as continuous wave (1 W) and modulated with 4, 8, 16, and 200 Hz in 0.5-ms pulses (2 W/pulse) and 50 Hz in 6-min pulses (2 W/pulse). Exposure started 5 d after tumor inoculation (7 h/d) for 5 d/wk during 2–3 wk. All rat brains were examined histopathologically and the tumor size was determined by measuring the axes in an ellipsoidal volume. This study did not show any significant difference in tumor size between exposed and control animals. Nevertheless, controls showed albumin leakage in 15% of the examined rat brains, while 915-MHz microwave pulse-modulated field exposure resulted in albumin leakage in 24% of the exposed rat brains.

RF Field-Induced DNA Damage

The studies reviewed include studies on purified DNA, plants, insects, bacteria, cultured mammalian cells, and in vivo mammalian assays, as well as three studies involving the assessment of DNA damage in humans with long-term exposures to RF fields. Much of the data has been assembled in studies prepared for government or industrial organizations in response to the need for legislation regarding public and occupational exposures to radiofrequency radiation. The main data sets have been assembled by Brusick et al. (1998) and Verschaeve and Maes (1998) and these data are heavily relied upon in the preparation of Table 7(f). Additional information, though largely concerning the effects of lower frequency electromagnetic radiation, is available in a report prepared by a working group at the National Institute of Environmental Health (NIEHS Working Group Report, 1998).*

Studies of the Genotoxic Effects of Radiofrequency Fields

In vitro mutation studies In vitro mutation studies are the least expensive and most rapid methods available to assess genotoxicity. Despite

*The associated web site is http://www.niehs.nih.gov/emfrapid/html/WGReport/Preface.html

TABLE 7. Effects of Exposure to RF Fields

Test system	Exposure	Results	Reference
	(a) In vitro mutation studies of RF fields		
E. coli	70,000–75,000 MHz, 10 W/m^2; 3 h	No effect on mutation frequency	Bertraud et al. (1975)
S. cerevisiae	9100, 17,000, 70,000–75,000 MHz, less than 60 W/m^2 and 28 mW/kg; 30 min	No effect on mutation frequency	Dardalhon et al. (1981)
E. coli	9100, 17,000, 70,000–75,000 MHz, less than 60 W/m^{2}and 28 W/kg; 30 min	No effect on mutation frequency	Dardalhon et al. (1981)
S. typhimurium (TA1535, TA100, TA98)	8500–9600 MHz pulsed, 1, 5, 45 W/m^2 up to 2 h	Increased mutation frequency	Dutta and Nelson (1978); Dutta et al. (1979a)
S. cerevisiae	8500–9600 MHz pulsed, 1, 5, 45 W/m^2; up to 2 h	Increase mutation frequency	Dutta and Nelson (1978); Dutta et al. (1979a)
E. coli	7000 or 7500 MHz; 30 min	Increased mutation frequency	Averbeck et al. (1976)
S. cerevisiae	7000 or 7500 MHz; 30 min	Increased mutation frequency	Averbeck et al. (1976)
S. typhimurium (TA100, TA98, TA1535, TA1537)	3100 MHz pulse wave electric and magnetic fields, 90 W/kg; 6 h	Increased mutation frequency	Hamnerius et al. (1985)
E. coli (strain WWU)	2450 MHz; 10 and 50 W/m^2; 15 and 79 W/kg; 3–4 h	Increased mutation frequency	Blackman et al. (1976)
S. typhimurium (TA1535, TA100, TA98)	2450 MHz; 20 W/m^2; 40 W/kg; up to 2 h	Increased mutation frequency	Dutta and Nelson (1978); Dutta et al. (1979a)
S. typhimurium (TA1535, TA1539, TA100)	2450 MHz, 3070 MHz	Increased mutation frequency	Anderstam et al. (1983)
E. coli (WP2)	2450 MHz	Increased mutation frequency	Anderstam et al. (1983)
S. cerevisiae	2450 MHz (CW); 20 W/m^2; 40 W/kg; up to 2 h	Increased mutation frequency	Dutta and Nelson (1978); Dutta et al. (1979a)
S. typhimurium (TA100, TA98, TA1535, TA1537)	3100 MHz (CW) e&m, 130 W/kg; 5.7 h	No effect on mutation frequency	Hamnerius et al. (1985)
S. typhimurium (TA100, TA98, TA1535, TA1537)	27.12 MHz (CW), magnetic, 22 W/kg; 6 h	No effect on mutation frequency	Hamnerius et al. (1985)

(*Table continues on next page*)

TABLE 7. Effects of Exposure to RF Fields (*continued*)

Test system	Exposure	Results	Reference
	(a) In vitro mutation studies of RF fields (*continued*)		
E. coli (strain WWU)	1700 MHz; 3 W/kg; 3–4 h	No effect on mutation frequency	Blackman et al. (1976)
Mouse lymphoma assay	2450 MHz; 48.8 W/m^2; 30 W/kg	No effect on mutation frequency	Meltz et al. (1989, 1990a)
S. typhimurium (strains TA1535, TA100, TA98, TA1537, TA1538)	2450 MHz, 5100 W/m^2; up to 23 s exposure in microwave oven	Bacteria were exposed in a commercial microwave oven. Increases in mutation were observed in all five strains at 5100 mW/cm^2 after 8–10 s. Temperature studies from 45–100°C showed that mutation frequency started to increase at 65°C but never to the magnitude of the RF field-treated samples. Though the T° of the microwaved samples were never controlled, the authors suggest a synergistic interaction between T° and RF field. Other experiments in which the T° was controlled failed to elicit positive results, suggesting that T° is the essential component to the induction of mutation.	Blevins et al. (1980)
Bacteria	2.45 GHz for 3.5 h (whole-body SAR 1.18 W/kg) (20 W/m^2)	No effect on bacterial mutation	Miller et al. (1987)
	(b) In vivo mutation studies of RF fields		
D. melanogaster	3100 MHz (PW) e&m, 60 W/kg; 6.0 h	No effect on somatic mutation	Hamnerius et al. (1985)
D. melanogaster	2450 MHz, 2.1, 2.75, 3.0 kW; 45 min	No effect on somatic mutation (SLRL)	Pay et al. (1972)
D. melanogaster	2450 MHz (CW), 110 W/kg; 6 h	No effect on somatic mutation	Hamnerius et al. (1979, 1985)
D. melanogaster	146 MHz, 12 h	No effect on somatic mutation (SLRL)	Mittler (1975, 1976)

TABLE 7. Effects of Exposure to RF Fields (*continued*)

Test system	Exposure	Results	Reference
	(b) In vivo mutation studies of RF fields (*continued*)		
Drosophila X-linked chromosome	Radio-transmitter building of the U station at 45 m from the base of a 300-ft antenna tower; the transmitter operated at 50,000 W at a frequency of 98.5 MHz (0.3 V/m)	No difference in the percentage of recessive lethals on the X-chromosomes	Mittler (1977)
D. melanogaster	146 MHz	No effect on chromosome loss	Mittler (1976)
D. melanogaster	2375 MHz (15 W/m^2 for 60 min or 20 W/m^2 for 10 min or 25 W/m^2 for 5 min for 5 d)	No effect on somatic mutation (SLRL)	Marec et al. (1985)
Male C3H mice Dominant lethal assay	2450 MHz, CW, 43 W/kg, 30 min	No effect on somatic mutation (low sperm count from thermal effects)	Saunders et al. (1983)
Male C3H mice	2450 MHz, CW, 100 W/m^2, 4 W/kg, 6 h/d for 8 wk	No effects on chromosome aberrations, dominant lethality, reciprocal translocations, or sperm count	Saunders et al. (1988)
Male rats	2450 MHz, CW, 5 mW/cm^2, 4 h/d, d 6 of gestation to 90 d of age; 10 mW/cm^2	No sperm mutagenesis	Berman et al. (1980)
Male Swiss mice	Males mated postexposure: 2450 MHz, 100 mW/cm^2 for 10 min; 50 mW/cm^2 for 10 min three times a day; 50 mW/cm^2 for 10 min 4 times over 2 wk	No decrease in the number of implants, small increase in mutagenicity	Varma et al. (1976)
Male Swiss albino	2450 MHz, CW, 1.7 kW/m^2 for 70 s	Dominant lethal mutations, abnormal sperm (temperature not controlled)	Goud et al. (1982)
Swiss mice	1700 MHz, 50 W/kg, 30 min	Induced dominant lethal mutations	Varma and Traboulay (1976)
Rat kangaroo bone marrow cells	2450 MHz 0.2, 1.0, or 5.0 W/cm^2 for up to 30 min	Increased chromosomal aberrations	Yao and Jiles (1970)

(*Table continues on next page*)

TABLE 7. Effects of Exposure to RF Fields (*continued*)

Test system	Exposure	Results	Reference
	(b) In vivo mutation studies of RF fields (*continued*)		
Human lymphocytes	954 MHz	Increased chromosomal aberrations	Maes et al. (1995)
Human lymphocytes	167 MHz	Increased chromosomal aberrations	Khalil et al. (1993)
In vivo mammalian chromosomal aberrations			
Chinese hamster blood lymphocytes	2450 MHz CW, up to 21 W/kg, 15 min/d, 5 consec. days	No chromosomal aberrations	Huang et al. (1977)
Chinese hamster cells	2450 MHz, 12 min	No chromosomal aberrations	Janes et al. (1969)
Mammalian, C3H mice	2450 MHz CW, 100 W/m^2, 4 W/kg, 6 h/d = 120 h over 8 wk	No chromosomal aberrations	Saunders et al. (1988)
Mouse sperm cell of male mice	2450 MHz CW, 1, 100, 400 W/m^2, 30 min/d, 6 d/wk, 2 wk	No increase in chromosomal aberrations in sperm cells of male mice (exposed as stem cells): temperature not controlled—significant increase in rectal temp. for 400 W/m^2 only: slight increases in chr. aberr. due to temp.	Beechey et al. (1986)
Mouse	2450 MHz	No chromosomal aberrations	Banerjee et al. (1983)
Rat regenerating hepatic tissue	13 MHz (CW or PW)	No chromosomal aberrations	McLees and Finch (1972)
Human lymphocytes (radiolinemen)	0.4 to 20,000 MHz: occupational	No chromosomal aberrations	Garson et al. (1991)
Human lymphocytes (antenna maintenance workers)	Various freq. (incl. 450 and 950 MHz) ≥ 1 h/d for at least 1 yr: occupational	No chromosomal aberrations	Maes et al. (1995)

TABLE 7. Effects of Exposure to RF Fields (*continued*)

Test system	Exposure	Results	Reference
	(b) In vivo mutation studies of RF fields (*continued*)		
Human subjects	30–300 GHz, 10–50 W/cm^2: occupational	Increased chromosomal aberrations	Garaj-Vrhovac et al. (1990b)
BALB/*c* mice	9400 MHz (PW), 0.1–10 mW/cm^2, 1 h/d, 5 d/wk	Increased chromosomal aberrations	Manikowska et al. (1979)
Sperm cells of male CBA/CEY mice	2450 MHz CW, 0.05–20 W/kg, 30 min/d, 6 d/wk, 2 wk	Increased chromosomal aberrations; increased chromosome translocations and other cytogenetic effects	Manikowska-Czerska et al. (1985)
	(c) Studies of chromosomal aberrations in vivo and in vitro following exposure to RF fields		
In vitro mammalian chromosomal aberrations			
Human lymphocytes	2450 MHz CW, up to 200 W/kg, 20 min	No chromosomal aberrations	Lloyd et al. (1984, 1986)
Chinese hamster ovary cells	2450 MHz, PW, 33.8 W/kg, 2 h	No chromosomal aberrations	Kerbacher et al. (1990)
Chinese hamster ovary cells	2450 MHz, 30 min	No chromosomal aberrations	Alam et al. (1978)
Chinese hamster ovary cells	2450 MHz, 49 mW/cm^2 33.8 W/kg	No chromosomal aberrations	Meltz et al. (1990b)
Chinese hamster ovary cells	1200 MHz, 24.33 W/kg	No chromosomal aberrations	Meltz et al. (1990b)
Chinese hamster ovary cells	850 MHz, 18 mW/cm^2, 14.4 w/kg	No chromosomal aberrations	Meltz et al. (1990b)
Chinese hamster ovary cells	100 MHz, 12.5 h	No chromosomal aberrations	Wolff et al. (1985)
Human lymphocytes	100 MHz, 12.5 h	No chromosomal aberrations	Wolff et al. (1985)
Chinese hamster ovary cells	15 MHz, 14 h	No chromosomal aberrations	Wolff et al. (1985)
Chinese hamster V79 cells	7700 MHz, 0.5 mW/cm^2, 15, 30, 60 min	Increased chromosomal aberrations	Garaj-Vrhovac et al. (1990a, 1991)
Human lymphocytes	7700 MHz, 0.5 (30 min), 30 mW/cm^2 (10, 30, or 60 min)	Increased chromosomal aberrations	Garaj-Vrhovac et al. (1992)

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TABLE 7. Effects of Exposure to RF Fields (*continued*)

Test system	Exposure	Results	Reference
(c) Studies of chromosomal aberrations in vivo and in vitro following exposure to RF fields (*continued*)			
Human lymphocytes	2450 MHz, 30 and 120 min	Increased chromosomal aberrations	Maes et al. (1993)
Rat kangaroo RH16 cells	2450 MHz CW, 15 W/kg, up to 320 d (50 passages)	Increased chromosomal aberrations	Yoa (1976, 1982)
Chinese hamster cells	2450 MHz, 20–500 mW/cm^2, 4–20 min	Increased chromosomal aberrations	Chen et al. (1974)
(d) In vivo and in vitro micronuclei formation following exposure to RF fields			
In vivo micronucleus formation			
Human subjects	Unknown (30–300 GHz); occupational	No effect on micronucleus formation	Garaj-Vrhovac et al. (1990b)
Chinese hamster corneal epithelium cells	2450 MHz, 100 mW/cm^2, 30 min	Increased micronucleus formation	Yao (1978)
Mouse hepatocytes	2375 (CW), 2750 (pulsed) MHz, 0.1, 0.5, 5.0 W/m^2; 7 h/d, 45 d	Increased micronucleus formation	Antipenko and Koveshnikova (1987)
Peripheral blood of Latvian Brown cows (2000 erythrocytes)	Farm close to and in front of the Skrunda Radar	Significant differences in the frequency distribution of micronuclei ($p < .0001$)	Balode (1996)
C3H/HeJ mice (mammary tumor-prone animals) peripheral blood	2.45 GHz for 28 d (whole-body SAR 1 W/kg)	No effect on micronuclei in polychromatic erythrocytes in peripheral blood and bone marrow	Vijayalaxmi-Frei et al. (1997)
In vitro micronucleus formation			
Tradescantia cuttings bearing young flower buds	10–21 MHz, 30 h	Increased micronucleus formation	Haider et al. (1994)
Chinese hamster V79 cells	7700 MHz, 0.5 mW/cm^2; 15, 30, 60 min	Increased micronucleus formation	Garaj-Vrhovac et al. (1991)
Human lymphocytes	2450 MHz, 30 and 120 min	Increased micronucleus formation	Maes et al. (1993)

TABLE 7. Effects of Exposure to RF Fields (*continued*)

Test system	Exposure	Results	Reference
(d) In vivo and in vitro micronuclei formation following exposure to RF fields (*continued*)			
Human lymphocytes	7700 MHz, 0.5 (30 min), 10 (30 min), 30 mW/cm^2 (10, 30, or 60 min)	Increased micronucleus formation	Garaj-Vrhovac et al. (1992)
(e) In vivo and in vitro sister chromatid exchange (SCE) following exposure to RF fields			
In vitro			
Human lymphocytes	2450 MHz, CW, up to 200 W/kg, 20 min	No effect on SCE	Lloyd et al. (1984, 1986)
Human lymphocytes	2450 MHz, 30 and 120 min	No effect on SCE	Maes et al. (1993)
Human lymphocytes	2450 MHz, 30 and 120 min	No effect on SCE	Maes et al. (1993)
Chinese hamster ovary cells	2450 MHz, PW, 33.8 W/kg, 2 h	No effect on SCE	Ciaravino et al. (1987)
Chinese hamster ovary cells	2450 MHz, PW, 33.8 W/kg, 2 h	No effect on SCE	Ciaravino et al. (1991)
Chinese hamster ovary cells	2450 MHz, 49 mW/cm^2, 33.8 W/kg	No effect on SCE	Meltz et al. (1990b)
Chinese hamster ovary cells	1200 MHz, 24.33 W/kg	No effect on SCE	Meltz et al. (1990b)
Chinese hamster ovary cells	850 MHz, 18 mW/cm^2, 14.4 W/kg	No effect on SCE	Meltz et al. (1990b)
Chinese hamster ovary cells	100 MHz, 12.5 h	No effect on SCE	Wolff et al. (1985)
Human lymphocytes	100 MHz, 12.5 h	No effect on SCE	Wolff et al. (1985)
Human lymphocytes	167 MHz	Increased SCE	Khalil et al. (1993)
Mouse bone marrow	2450 MHz, CW, 21 W/kg, 8 h/d, 28 d	No effect on SCE	McRee et al. (1981)
CD1 mice bone-marrow cells	2.5 GHz for 28 d, 8 h/d (SAR = 15 or 75 W/kg) (10 or 50 W/m^2)	No effect on SCE	McRee and MacNicols (1981)
Whole blood cells	Continuous 935.2 MHz alone (4.5 W) (SAR 0.3–0.4 W/Kg) 935.2 MHz + mitomycin C	No direct chromosomal damage Highly reproducible synergistic effect in the presence of mitomycin C (very weak increase in the frequency of sister chromatid exchange)	Maes et al. (1997)

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TABLE 7. Effects of Exposure to RF Fields (*continued*)

Test system	Exposure	Results	Reference
(e) In vivo and in vitro sister chromatid exchange (SCE) following exposure to RF fields (*continued*)			
In vivo			
C3H mice	2450 MHz, CW, 100 W/m^2, 4 W/kg, 6 h/d = 120 h over 8 wk	No effect on SCE	Saunders et al. (1988)
Mouse bone marrow	800 MHz, 4 W/kg, 8 h	No effect on SCE	Brown and Marshall (1982)
Mouse bone marrow	2450 MHz	No effect on SCE	Banerjee et al. (1983)
Mouse bone marrow	400 MHz, 4 W/kg, 8 h	No effect on SCE	Brown and Marshall (1982)
Sperm cells of male CBA/CEY mice	2450 MHz CW, 0.05–20 W/kg, 6 h over 2 wk	Increased SCE	Manikowska-Czerska et al. (1985)
(f) In vivo and in vitro DNA damage/repair			
In vitro			
E. coli Pol A$^+$/A$^-$ (normal/repair deficient)	8600, 8800, 9000 MHz; 1, 10, 20 mW/cm^2; 1, 5, 10, 25 h	No effect on DNA damage	Dutta et al. (1978a)
E. coli Pol A$^+$/A$^-$ (normal/repair deficient)	8600 MHz, 12 W/kg, up to 7 h	No effect on DNA damage	Dutta et al. (1979b)
E. coli B	2600–4000 MHz, 20 W/kg, 10–12 h	No effect on DNA damage	Corelli et al. (1977)
Aspergillus nidulans	2450 MHz (CW or PW), 10 mW/cm^2, 1 h	No effect on DNA damage	Mezykowski et al. (1980)
In vitro microbial, *A. nidulans*	2,450 MHz, 10 mW/cm^2; 10–240 min	No effect on DNA damage	Baranski et al. (1976)
Human MRC-5 fibroblasts	1200 MHz (CW or PW), 1 (or 5), 10 mW/cm^2, 2.7 ± 1.6 W/kg, 1–3 h	No effect on DNA damage	Meltz et al. (1987, 1990b)
Human MRC-5 fibroblasts	850 MHz (CW or PW), 1 (or 5), 10 mW/cm^2, 4.5 ± 3.0 W/kg, 1–3 h	No effect on DNA damage	Meltz et al. (1987, 1990b)
Human MRC-5 fibroblasts	350 MHz (CW or PW), 1 (or 5), 10 mW/cm^2, 0.39 ± 0.15 W/kg, 1–3 h	No effect on DNA damage	Meltz et al. (1987, 1990b)
Human glioblastoma cells (U87MG) and fibroblasts (C3H/10T1/2)	2.45 GHz (SRA 0.7 to 1.9 W/kg) for 2 h followed by a 4-h or 24-h incubation at 37°C	No effect on DNA breaks in alkaline Comet assay	Malayapa et al. (1997a)

TABLE 7. Effects of Exposure to RF Fields (*continued*)

Test system	Exposure	Results	Reference
	(f) In vivo and in vitro DNA damage/repair (*continued*)		
Human glioblastoma cells (U87MG) and fibroblasts (C3H/10T1/2)	835.62 MHz and 847.74 MHz for various periods of time up to 24 h (SAR 0.6 W/Kg)	No damage could be observed in alkaline Comet assay	Malayapa et al. (1997b)
In vivo			
Comet assay used for rat lymphocyte DNA	945 MHz, 1–5 wk	No effect on DNA damage, breaks in controls and exposed animals were equivalent	Verschaeve and Maes (1998)
Swiss albino mice	2450 MHz, 1 mW/cm^2; 2 h/d for 120, 150, 200 d	Increased DNA damage, DNA samples from testes and brain contained altered band patterns	Sarkar et al. (1994)
Mice	Police radar (34 GHz)	No effect on DNA synthesis	Rotkovskar et al. (1993)
Sprague-Dawley rats, cerebral cortex	2.5 GHz for 28 d (whole-body SAR 0.648 W) (2 W/m^2)	No effect on DNA breaks (alkaline Comet test)	Malayapa et al. (1998)
Swiss male mice	1700 MHA, CW, 50 W/kg, 30 min	Increased DNA damage; chemical changes in testicular DNA (parameters assessed: hyperchromicity and melting temp., results indicate strand separation possible), temperature not controlled	Varma and Traboulay (1977)
Swiss mice	1700 MHz, 50 mW/cm^2 for 30 min, 10 mW/cm^2 for 80 min	Positive effect on DNA damage; mutagenicity indicated by changes in properties of DNA (melting temperature, base composition, optical density) indicative of strand separation	Varma and Traboulay (1976)

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TABLE 7. Effects of Exposure to RF Fields (*continued*)

Test system	Exposure	Results	Reference
	(f) In vivo and in vitro DNA damage/repair (*continued*)		
Swiss mice	985 MHz, 10 mW/cm^2, 80 min	Positive effect on DNA damage; mutagenicity indicated by changes in properties of DNA (melting temperature, base composition, optical density) indicative of strand separation	Varma and Traboulay (1976)
DNA damage/repair, mammalian	2450 MHz, 0.6 and 1.2 W/kg for 2 h	Increased DNA damage, Comet assay measured single-strand and double-strand breaks induced by rat brain DNA; both continuous and pulsed exposures	Lai and Singh (1995)
Sperm abnormalities; mammalian, mice	2450 MHz CW, 36 mW/cm^2, 16 h, 30 d	No sperm abnormalities	Cairnie and Harding (1981)
Sperm abnormalities mammalian, sperm cells of male CBA/CEY mice	2450 MHz CW, 0.05–20 W/kg, 6 h over 2 wk	Sperm abnormalities	Manikowska-Czerska et al. (1985)
In vitro			
Cell transformation, mammalian, mouse embryo fibroblasts C3H/10T1/2	2450 MHz, 4.4 kg, 24 h	No effect on cell survival or induction of neoplastic transformation + TPA = increase transformation + x-rays = additive effects	Balcer-Kubiczek and Harrison (1989, 1991)
Cell transformation, mammalian, mouse embryo fibroblasts C3H/10T1/2	2450 MHz, with x-ray or benzo[a]pyrene, 4.4 W/kg, 24 h	Increased cell transformation	Balcer-Kubiczek and Harrison (1985)

TABLE 7. Effects of Exposure to RF Fields (*continued*)

Test system	Exposure	Results	Reference
	(f) In vivo and in vitro DNA damage/repair (*continued*)		
Cell transformation, mammalian, mouse embryo fibroblasts C3H/10T1/2	2450 MHz, with TPA; 4.4 kg, 24 h	Increased cell transformation	Balcer-Kubiczek and Harrison (1989, 1991)
C3H/10T1/2 mouse cell transformation assay	836.55 MHz TDMA-modulated fields (SAR 0.15, 1.5, and 15 mW/kg), repeated cycles of 20 min on/20 min off, 24 h/day for 28 d	No effect on tumor promotion in vitro, no enhancement of TPA-induced focus formation	Cain et al. (1997)

Note. Based largely on: Brusick et al. (1998) and Verschaeve and Maes (1998).

this, the majority of carcinogens and mutagens detected in mammalian systems yield positive results in many of these so-called "rapid assays." Although the mechanism of any potential RF field-induced events remains obscure, there is no a priori reason to suggest that these assays would not be predictive. Results however, have been on the whole negative through a wide range of test systems including *Escherichia coli, Salmonella typhimurium* (the Ames mutagenicity test), *Saccharomyces cerevisiae,* and the mouse lymphoma assay. A single positive report for 2450 MHz (Blevins et al., 1980) using the Ames testing strains involved thermal effects and could not be repeated when these were controlled for. The overall conclusion is that RF fields are not mutagenic in these in vitro assays.

In vivo mutation studies Significant and uniformly negative studies have been performed using *Drosophila melanogaster* over a range of RF field frequencies and energy levels. Similarly, negative mutational studies have been undertaken in mice and rats, though these studies using traditional methods may not be extremely sensitive to mutation. Some of the earlier mouse work, particularly with male Swiss albino animals, did show some mutational effects for extended exposures. Unfortunately, these experiments did not control for thermal influences, which was a common deficiency in the earlier experiments. When taken collectively, no evidence has been obtained that convincingly indicates a mutational outcome for RF field exposures; furthermore, several well-conducted experiments have produced negative results.

Chromosome aberrations in in vitro and in vivo studies Chromosomal aberrations represent a variety of microscopically visible chromosomal rearrangements often of unknown origin. Their presence is usually

interpreted as indicative of genotoxic effects that represent DNA or DNA–protein interactions. Agents causing chromosomal rearrangements are typically classed as clastogens and are often associated with developmental abnormalities. Cellular sensitivity to chromosomal rearrangements can be quite high, as they generally do not cause cellular toxicity and they therefore accumulate in nondividing cells. The biological effects in people resulting from these aberrations remain somewhat unclear, although they include miscarriages. Cells with chromosomal aberrations are often lost upon cell division, though chromosomal rearrangements can alter the control of important oncogenes and consequently contribute to the development of cancer.

Radiofrequency radiation effects on chromosomal aberrations have been thoroughly studied both in vivo and in vitro. The results are mixed, as several studies do report a significant increase in chromosomal aberrations after diverse exposures in a range of systems, while often very similar studies show negative results. It is not clear to what extent thermal effects can be considered responsible, especially in the more recent experiments. Perhaps some of the most important observations are those obtained from in vivo studies with occupationally exposed individuals who were followed for over a year without any indication of an induction of chromosomal aberrations (Maes et al., 1995).

Micronuclei formation in vitro and in vivo Micronuclei (MN) are considered to be the visible consequence of DNA breakage. MN assays are generally quite sensitive measures of genotoxic effects, as MN can accumulate, especially in nondividing cells. Despite being sensitive indicators of DNA damage, their importance to human health is not well understood. The in vivo studies of MN tend to be positive whether plant or mammalian cells were studied. Doses, however, tend to be high and thermal effects have been poorly managed. The one available in vivo study involves occupationally exposed human subjects; however, exposure management was not well documented (Garaj-Vrhovac et al., 1990b).

Chromatid exchanges in vitro and in vivo Sister chromatid exchanges (SCEs) rank among the earliest and most widely used tests for genotoxicity. It is believed that SCEs reflect the replication of damaged DNA, though precise mechanisms remain poorly defined. Because of the case of use and the general acceptance of SCE results, RF fields have been extensively studied using this approach. Negative results have been repeatedly reported for a wide range of exposure frequencies (15–2450 MHz) in both Chinese hamster ovary (CHO) cells and human lymphocytes. There is one positive report of the in vitro induction of SCEs by 167-MHz RF field in human primary lymphocytes (Khalil et al., 1993), although thermal effects cannot be excluded.

Similar to these results, in vivo studies of the induction of SCEs by RF field are also dominated by negative results in two mouse test systems. The only positive report is of a study of mouse sperm cells following

2450-MHz exposures at relatively high fluxes, making the possible influence of thermal events likely.

DNA Damage Assessment DNA damage can be assessed directly by either biological or physical methods. Biological methods usually depend upon the differential survival of repair proficient and repair deficient cells. In contrast, physical methods may involve the general measurement of DNA size by such methods as alkaline sucrose gradients. In this case, fragmented single-stranded DNA is found toward the top of a sucrose gradient in a centrifuge tube. More recently, a biological method for the detection of DNA fragmentation has been developed. This assay, known as the single-cell microelectrophoretic or Comet Assay, permits the detection of DNA damage by examining the extent of migration of DNA from gently lysed individual cells.

The in vitro studies of DNA damage, regardless of the approach, have been uniformly negative. In vivo studies have produced mixed results, but until recently all of the positive reports likely involved thermal effects because of faulty experimental design which lacked appropriate controls for these effects. However, recent experiments of Lai and Singh (1995), who used the comet assay to assess 2450-MHz-induced DNA damage in the brain of rats, have reopened the question. In carefully conducted experiments they report a dose response for DNA breakage. The question remains unresolved, however, as several other laboratories have failed to reproduce these results despite repeated international efforts. Collaborative efforts involving several of these researchers are currently in progress to resolve the issue. But the Lai and Singh data present one of the few cases that must be (and is being) taken seriously as an indication of the potential genotoxicity of RF fields.

Cell transformation assays Cell transformation is one step on the way to malignancy and involves the release of cells from contact inhibition so that cell growth continues despite the close proximity of other cells. The result is the appearance of small piles of cells or "plaques" that can be visualized by staining. The typical test system involves a cell line known as NIH C3H/10T1/2. The results obtained for 2450-MHz RF fields indicate that transformation is not induced by RF fields alone. However, there is some suggestion that RF field may work synergistically in combination with other known mutagens or promoting agents (Balcer-Kubczek & Harrison, 1985, 1989, 1991).

While these effects may be real, they are difficult to assess due to the technical challenges of the available test systems. This is an area where human epidemiological data eventually may provide some resolution.

Summary

A large number of laboratory studies of the potential health effects of radiofrequency fields have focused on genotoxicity, including studies of tumorigenesis, promotion, progression, altered cell proliferation, and DNA

damage. The great majority of these studies have failed to demonstrate genotoxic effects due to exposure to radiofrequency fields.

Prausnitz and Susskind (1962) reported an increased frequency of leukosis and leukemia in mice following exposure to RF fields. Although an increased incidence of lymphomas in mice exposed to RF fields was noted by Repacholi et al. (1997), the implications of this investigation are unclear because of methodological limitations. Other animal studies have shown a reduction in the risk of breast cancer, lymphoma, leukemia, and brain cancer. Tumor promotion studies have suggested an acceleration in breast and skin cancer formation and decreased survival in mice. However, there is no evidence of an effect of radiofrequency fields on tumor progression. Further investigation is required to clarify these mixed results, including replication of reported positive findings, before definitive conclusions can be drawn.

RF fields have not resulted in increased mutation frequencies during in vitro mutation studies; some in vivo mutation experiments have suggested a reduction in mutation frequency. In vivo and in vitro studies of chromosomal aberrations have produced inconsistent results. Although most studies examining sister chromatid exchange have not demonstrated any effects of RF fields, one in vitro study did report an increase in SCE following exposure to a 167 MHz RF field. Similarly, there is limited evidence of micronuclei formation following in vitro RF field exposure. In vitro studies of DNA damage have failed to demonstrate an effect of RF field exposure; in vivo studies have produced diverse results. Cell transformation assays of radiofrequency field exposure are difficult to interpret because of technical difficulties. Overall, a number of different assays for studying genotoxicity have failed to produce consistent positive findings regarding RF fields.

HEALTH EFFECTS (NONTHERMAL)

Epidemiological Evidence

In this chapter, a review of the published, peer-reviewed literature is presented (Table 8), with a discussion of the criteria for the evaluation of epidemiological research and an assessment of the evidence for an increased risk of major health effects from RF fields: specifically, cancers among adults and children, reproductive outcomes, and congenital anomalies.

Epidemiologic Criteria for Causation Epidemiological studies of the distribution and determinants of health conditions in human populations provide the most direct evidence of risks to human health. However, generally they cannot provide definitive evidence of causality on their own. Since virtually all epidemiological investigations of factors that affect health risk are observational rather than experimental in nature, the interpretation of these results is difficult. Potential bias or nonrepresentativeness in the selection or participation of study populations, the existence of confounding variables (factors, both genetic and environmental, that relate both

TABLE 8. Epidemiologic Studies of Radiofrequency Fields and Health Effects

Type of study	Exposure	Results	Reference
Population cohort in West Midlands, adult and childhood cancer incidence	Residential; 2 km and 10 bands of increasing distance to 10 km around Sutton Coldfield TV and FM radio transmitter (West Midlands)	Adult: O/E leukemia, within 2 km = 1.83 (23 cases observed) (CI = 1.22–2.74); skin melanoma and bladder significant trend but not significantly different O/E; all other cancers not statistically significant Child: O/E cancer within 10 km = 0.91 (97 cases observed); O/E leukemia within 10 km 1.14; not significantly different	Dolk et al. (1997a)
Population cohort Great Britain, adult and childhood cancer incidence	Residential; 2 km and 10 bands of increasing distance to 10 km around Sutton Coldfield TV and FM radio transmitter (Great Britain)	Adult cancers within 2 km had O/E near 1 (not statistically significant); O/E (leukemia within 2 km) = 0.97 (CI = 0.78–1.21); O/E skin melanoma within 2 km) = 1.11 (CI = 0.84–1.46); O/E bladder cancer within 2 km) = 1.08 (CI = 0.94–1.24) Childhood cancers within 2 km or 10 km all near 1 and not statistically significant O/E (leukemia within 2 km) = 1.12 (CI = 0.6–2.06); O/E (brain tumor) = 0.62 (0.17–1.59)	Dolk et al. (1997b)
Occupational cohort, U.S. Navy, adult cancer incidence	Job title; ELF workers and radio operators/workers	No excess risks for jobs associated with radiofrequency exposure	Garland et al. (1990)
Nested case-control; occupational cohort, U.S. Air Force, adult cancer incidence	Job-exposure matrix, ELF and radiofrequency/microwave exposures separately	Ever vs. never exposed OR = 1.39 (CI = 1.01–1.90) borderline significance; no trend with increasing exposure	Grayson (1996)

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TABLE 8. Epidemiologic Studies of Radiofrequency Fields and Health Effects (*Continued*)

Type of study	Exposure	Results	Reference
Hospital case-control, largely military personnel, adult testicular cancer incidence	Job title and self-reported occupational exposure to microwaves and other radiowaves	ORs based on self-report were elevated: OR for radar exposure = 1.1 (CI = 0.7–1.9); OR for microwave = 3.1 (CI = 1.4–6.9); not confirmed with job title analysis	Hayes et al. (1990)
Population cohort, NSW, Australia, adult and childhood cancer, incidence and mortality	Residential; calculated power density of RF fields from TV towers in 9 municipalities	Adult cancer incidence, inner vs. outer regions: OR (leukemia) = 1.24 (CI = 1.09–1.4) (1206 cases); OR (brain tumors) = 0.89 (CI = 0.71–1.11) (740 cases) Childhood cancer incidence, inner vs. outer regions: OR (leukemia) = 1.58 (CI = 1.07–2.34) (134 cases) OR (brain tumor) = 1.1 (CI = 0.59–2.06) (64 cases)	Hocking et al. (1996)
	Reanalysis of local government areas	Findings not supported in local government area analysis	McKenzie et al. (1998)
Case-control study; electrical/ electronics workers in United States, adult brain tumor mortality	Proxy reports of occupational history; job title and classification by occupational hygienists	Risk by job title: exposure to MW/RF radiation in an electrical/electronics job, RR = 23 (CI = 1.3–4.2); exposure to MW/RF radiation but not an electrical/electronics job, RR = 1.0 (CI = 0.5–1.9); risk by job exposure classification: exposure to MW/RF radiation but not organic solvents or lead RR = 0.4 (CI = 0.7–3.1) (2 cases)	Thomas et al. (1987)
Occupational cohort, female plastics workers, Italy, adult mortality	Job title and period of job assignment; 30 yr and 2933 person-years follow-up in RF scalers and two comparison groups	RF sealers: SMR (cancer) = 2.0 (CI = 0.7–4.3) (6 deaths observed, including 1 brain, 1 leukemia); SMR (all causes) = 1.4 (CI = 0.7–2.7) (9 deaths)	Lagorio et al. (1997)

TABLE 8. Epidemiologic Studies of Radiofrequency Fields and Health Effects (*Continued*)

Type of study	Exposure	Results	Reference
Proportional mortality analysis of adult male deaths in Washington State by occupation	Occupation reported on death certificates; exposed group includes both ELF and RF-exposed jobs	PMRs for radio and telegraph operators: PMR (acute leukemia) = 212 (3 deaths observed); PMR (lymphosarcoma) = 73 (1 death observed); PMR (multiple myeloma and non-Hodgkin's lymphoma) = 342 (4 deaths observed) PMRs for radio and television repairmen: PMR (acute leukemia) = 344 (6 deaths observed); PMR (lymphosarcoma) = 90 (1 death observed); PMR (multiple myeloma and non-Hodgkin's lymphoma) = 86 (1 death observed)	Milham (1985)
Occupational cohort, Washington and California amateur radio operators, adult cancer mortality	Two federal licensing files; 232,499 person-years at risk	SMR (all causes) = 71; SMR (cancer) = 89; SMR (brain cancer) = 139 (CI = 93–200); SMR (acute myelogenous leukemia) = 176 (CI = 103–285); SMR (other lymphatic cancer) (multiple myeloma, non-Hodgkin's lymphoma) = 162 (CI = 117–218) SMR (circulatory) = 70 (CI = 66–74)	Milham (1988)
Occupational cohort, U.S. electromagnetic pulse test program, adult cancer mortality	Employees who had undergone health exams because of their work in the testing program; 3362 person-years	SMR (all causes) = 56 (CI = 31–95) (14 deaths); SMR (cancer) = 32 (CI = 4–115); (1 lymphoma death, 1 leukemia death); SMR (cardiovascular) = 103 (CI = 51–184) based on 11 observed deaths	Muhm (1992)

(*Table continues on next page*)

TABLE 8. Epidemiologic Studies of Radiofrequency Fields and Health Effects (*Continued*)

Type of study	Exposure	Results	Reference
Occupational case-control study, U.S. naval personnel, adult morbidity and mortality	Occupation with microwave (radar); high exposure and low exposure groups defined by job title, duties, period in job, equipment use	All results n/s; total group taken as reference: SMR (all diseases) = 0.96 (310 deaths); SMR (all cancer) = 1.04 (96 deaths); SMR (lymphatic and hematopoetic) = 1.18 (26 deaths); SMR (circulatory) = 0.93 (151 deaths)	Robinette et al. (1980)
Occupational cohort, Polish military, adult cancer incidence	Service records; documented exposures at service posts (128,000 persons/year with approximately 3% exposed/year)	O/E annual cancer incidence (exposed vs. nonexposed): 2.07 (CI = 1.12–3.58) (estimated 119 cancers observed per year); O/E (hematopoietic and lymphatic cancer) = 6.31 (CI = 3.12–14.32); O/E (nervous system tumors) = 1.91 (CI = 1.08–3.47)	Szmigielski (1996)
Cluster investigation: case control, Hawaii, childhood leukemia incidence	Radio towers within 2.6 miles of residence	OR (leukemia) = 2.1 (CI = 0.6–7.2); OR (cancer in family) = 3.4 (CI = 0.7–16.4); OR (leukemia) = 2.0 (CI = 0.06–8.3)	Maskarinec and Cooper (1993) (abstract) Maskarinec et al. (1994)
Case-control study of Rumanian microwave workers, gonadic function	Job title plus information on duration and intensity (EMF measurements)	Significantly lower number of spermatozoa/ejaculate; significantly lower motility and significantly higher number of abnormal spermatozoa in exposed group	Lancranjan et al. (1974)
Nested case-control study in Danish cohort of female physiotherapists, reproductive outcomes	Job title; self-reported work tasks and work environment	ORs for high vs. not exposed groups: OR (gender ratio in offspring) = 4.9 (CI = 1.6–17.9); 4 boys and 13 girls in offspring of high exposed group; OR (spontaneous abortions) = 1.4 (CI = 0.7–2.8); OR (subfecundity) = 1.7 (CI = 0.7–4.1); OR (stillbirth or death within 1 yr) = 2.9 (CI = 0.6–10.7)	Larsen et al. (1991)

TABLE 8. Epidemiologic Studies of Radiofrequency Fields and Health Effects (*Continued*)

Type of study	Exposure	Results	Reference
Case-control study of children in Latvia; motor and psychological functions	Residential proximity to the Skrunda Radio Location Station in Latvia; 3 groups compared: schoolchildren living in front of the radar, behind it, and in another region	Male/female ratio in exposed Skrunda region 68% of that in Preiji control region, based on 86 males and 138 females in exposed region; significantly poorer performance in several performance tests in exposed vs. control groups	Kolodynski and Kolodynska (1996)
Nested case-control study in U.S. cohort of female physiotherapists, reproductive outcomes	Job title; self-reported microwave/shortwave diathermy use 6 mo prior to first trimester or during first trimester	Unconditional OR (spontaneous abortion for those exposed to microwave diathermy) 1.28 (CI = 1.02–1.59); unconditional OR (spontaneous abortion for those exposed to shortwave diathermy) = 1.07 (CI = 0.91–1.24)	Ouellet-Hellstrom and Stewart (1993)
Nested case-control study in cohort of female Swedish physiotherapists, reproductive outcomes	Job title; self-reported exposure by type of equipment, and frequency of use over pregnancy	Sex ratio of infants, perinatal death rate, malformation rate not different from expected; rate of low-birth-weight infants, and premature infants, lower in exposed group	Kallen et al. (1982)
Nested case-control study in cohort of female Finnish physiotherapists, reproductive outcomes	Job title; self-reported exposure and use of equipment by type, frequency	OR (spontaneous abortion): for shortwave exposure = 1.6 (CI = 0.9–2.7); for microwave exposure = 1.8 (CI = 0.8–4.1); for deep heat therapy = 1.6 (CI = 1.0–2.7); OR (congenital malformation): for shortwave exposure = 1.0 (CI = 0.3–3.1); for microwave exposure = 0.5 (CI = 0.1–3.9); for deep heat therapy = 0.9 (CI = 0.3–2.7)	Taskinen et al. (1990)

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TABLE 8. Epidemiologic Studies of Radiofrequency Fields and Health Effects (*Continued*)

Type of study	Exposure	Results	Reference
Case-control study, Boston area, Down's syndrome	Interview about radar and other microwave exposures, with record-based verification of military exposures of fathers	No significant difference in paternal radar exposure before conception of cases vs. controls either from interview or record-based analyses	Cohen et al. (1997)
Nested case-control study of a cohort of female Swiss physiotherapists, gender ratio	Job title; self-reported exposure by type of equipment, duration, and period of exposure	No significant difference in gender ratio of offspring by type or duration of exposure, either for shortwave or microwave radiation; no significant difference in birthweight by exposure to shortwaves	Guberan et al. (1994)
Cohort study of Ontario police officers, cancer incidence	Police officer job title	SIR (all cancer) = 0.90 (CI = 0.83–0.98); SIR (testicular cancer) = 1.3 (90% CI, one-tailed test = 0.9–1.8); SIR (skin melanoma) = 1.45 (90% CI, one-tailed test = 1.1–1.9)	Finkelstein (1998)
Clinical assessment of patients with Wolff–Parkinson–White syndrome treated with DC or RF current in Oklahoma, thrombus formation	Treatment with DC or RF current	Intracardiac thrombus not identified as outcome in this group of 95 patients at 18 h after therapy	Goli et al. (1991)
Nested case-control study of cohort of police officers in north-central United States, testicular cancer incidence	Police officer job title; self-reports on work environment	O/E 69 (6 observed vs. 0.87 expected)	Davis and Mostofi (1993)
Cohort cluster study (U.S.) adult testicular cancer incidence	Occupational; hand-held radar; self-reported	O/E 6.9; $p < .001$ (6 cases)	Davis and Mostofi (1993)

TABLE 8. Epidemiologic Studies of Radiofrequency Fields and Health Effects (*Continued*)

Type of study	Exposure	Results	Reference
Case-control study, western United States, uveal melanoma incidence	Occupational; questionnaire-based, job title	OR = 2.1 (CI = 1.1–4.0) (9 cases)	Holly et al. (1996)
Case-control study, adult breast cancer mortality	Occupational; job exposure matrix	OR (most likely exposed) = 0.99 (CI = 0.8–1.2); OR (highest level exposed) = 1.14 (CI = 1.1–1.2)	Cantor et al. (1995)
Case-control study; adult breast cancer incidence	Occupational; questionnaire-based; job title	OR = 2.9 (CI = 0.8–10) (7 cases)	Demers et al. (1991)
Population-based cohort study; adult breast cancer incidence	Job title	SIR = 1.5	Tynes et al. (1996)
Nested case-control study; Canada, France; adult cancer incidence	Occupational (utility workers); job-exposure matrix and PEMF measurements	OR (lung cancer) = 3.11 (CI = 1.6–6.04); no excess in other cancers	Armstrong et al. (1994)
Population cohort, San Francisco; childhood cancer incidence	Residential; distance to microwave tower	No excesses seen in leukemia, brain cancer, lymphoma incidence	Selvin et al. (1992)

Note. O/E, observed numbers divided by expected numbers; SIR, standardized incidence ratio, can be based on 1.0 or 100 for reference group; SMR, standardized mortality ratio, can be based on 1.0 or 100 for reference group; PMR, proportionate mortality ratio, can be based on 1.0 or 100 for reference group; CI, confidence interval (at the 95% level unless otherwise stated); n/s, not statistically significant.

to exposure and health risk), and difficulties in assessing exposures represent important limitations of epidemiological studies. As a consequence, small relative risks (less than 1.5- to 2-fold) are difficult to estimate and interpret (Taubes, 1995). The results of each study, therefore, need to be evaluated in terms of the overall quality of the study design and execution, and interpreted in relation to criteria for disease causation.

Hill (1965) outlined a set of criteria that addressed both the statistical and biologic aspects of epidemiologic assessment of causality. The statistical criteria Hill proposed to evaluate a potentially causal relationship between an agent and a disease outcome include statistical significance (the probability that the observed association was not due to chance); the magnitude or strength of the relationship (the size of the effect of the agent on the risk of occurrence of disease); and the existence of an exposure-response relationship (an increasing effect with increasing exposure).

Statistical association alone is insufficient to establish causality. Several biological criteria need also to be met: internal consistency of results (meaning that different measures of exposure within a study show the same direction of effect); external consistency (the same effect is seen in different studies, populations, and time periods); the existence of a hypothesized biological mechanism; compatibility with biological mechanisms (evidence from laboratory or animal studies supporting the hypothesis); temporal relevance, including latency (a biologically rational delay between exposure and health outcome); specificity of outcome (evidence for the postulated effects from the proposed mechanism, rather than a multiplicity of effects not predicted from the hypothesis); and congruence or similarity with like factors (assuming agents with similar biological mechanisms cause the same types of effects).

Methodological Criteria for Assessment

Overall design issues Important components in the assessment of any epidemiologic study are evaluations of the study population and data collection methods including exposure assessment and collection of data on confounders and analysis.

Two main study designs are employed in observational epidemiologic investigations. In cohort studies, a group of exposed individuals is identified. The mortality or morbidity experience of this group is determined and compared to a group of individuals not exposed. In a case-control study, a group of subjects with the outcome of interest is identified, and the exposure experience of this group is compared to that of a comparison or control population. In a nested case-control study, cases and controls are recruited from a known cohort.

In a well-designed study, the population at risk of disease and the selected study sample from this population should be defined, and should be large enough to provide adequate statistical power, given the prevalence of the exposure and the disease in the population, in order to provide reasonably precise risk estimates. Comparison groups should be selected in a manner that minimizes the possibility of non-representative samples. Participation rates of subjects should be high enough to ensure representativeness.

Information on case status, exposure status, and other relevant variables should be as comprehensive and complete as possible. The variables should be relevant to the underlying metrics. Sources of data and procedures for data collection should be chosen to maximize accuracy of the information, and should be collected in as timely a manner as possible, in order to reduce error due to recall. Analytic methods and comparisons should be appropriate to the study design, and provide information on the level of precision and variability in the results. Adjustment should be made for other possible risk factors and confounding variables.

Exposure assessment The first issue in assessment of exposure is identification of the metric of interest, that is, the specific agent that induces

the effect being studied. In the case of radiofrequency fields, a biologically meaningful metric, based on a hypothesis or evidence from laboratory studies, has not been identified. This means also that a biologically relevant time period of exposure is not known. Therefore, in the absence of verifiable hypotheses, and based on experience with other agents, measures of total average exposure, and components of exposure that describe the exposure conditions in terms of frequency (counts), the power frequency range, the type of exposure (continuous or pulsed), the duration and intensity of exposure, and the period of exposure have been chosen as surrogates for an actual biologic agent at this time.

Measurement and analysis of these parameters, particularly for epidemiologic investigations, is limited by what is available for such a study. The usual sources of information on exposure include self-reports, records-based information, calculated exposure estimates, or direct measurements. Often multiple sources or surrogate variables are used, if information on the primary variable is not obtainable. Self-reports can only apply to surrogate measures of radiofrequency fields, as these fields are not ordinarily perceptible. Direct measurement instruments can only collect current data, without being able to account for changes in exposure conditions and prevalence over time, and often cannot exactly mimic human exposure conditions. No data source provides data on all the parameters of radiofrequency fields, and sometimes they provide only a limited level of detail or quantification. Problems with reliability and validity of surrogate measures can lead to exposure misclassification, which can modify or bias risk estimates.

There are only a few significant sources of radiofrequency field exposure, and these are easily identified. Individuals exposed to radiofrequency fields can be grouped into three main categories: those who are occupationally exposed, those who live in proximity to transmitters or base stations, and cellular or mobile telephone users. However, exposure profiles and exposure assessment issues vary considerably among these groups.

Identification of, and access to, occupationally exposed groups is reasonably straightforward. Exposures are higher than in the general population, and exposure settings are easily identified and measured. Follow-up can generally be achieved through workplace records. There is, however, considerable variability in personal exposure due to work duties and conditions, and variability of the fields with type of machine use, distance from the machine, time periods of exposure, and surroundings. In contrast, access to and follow-up of population groups living near base stations or transmitters can be extremely difficult. Overall exposure levels are much lower than for occupational groups, and personal exposure is difficult to measure but varies with distance and other characteristics. Users of cellular or mobile telephones can be identified through company records. However, personal use characteristics, telephone characteristics, and calling conditions again generate considerable variability in actual exposure. Finally,

choice of study design (case-control or cohort) has advantages and disadvantages with respect to quality of exposure assessment. Differences in exposure conditions and prevalence affect the choice of approach.

Major Studies There are relatively few published studies on risk of adult cancers, childhood cancers, reproductive outcomes, and congenital anomalies from RF exposure. A major review of epidemiologic studies of radiofrequency exposures and cancer has recently been published (Elwood, 1999). The results of these investigations and an evaluation of the quality of study design and execution, with a particular focus on the relevance and quality of exposure assessment, are presented here.

Adult cancers Many of the studies of risk of cancer in adults with exposure to radiofrequency fields have been conducted in occupational groups, specifically military personnel, electronics workers, medical workers, and industry groups with high exposures. Only two related studies from Great Britain and an ecologic study from New South Wales, Australia, have examined residential adult exposures. Limited data exists on cellular telephone users. The types (frequency range from ELF to RF, MW, and ionizing radiation) and levels of exposures vary considerably in these studies, making them difficult to compare and complicating the interpretation of the results. Moreover, in several of the studies exposure conditions are not clearly stated or measured.

1. *Military personnel.* In 1980, Robinette et al. reported on a study of two cohorts of U.S. enlisted naval personnel who had graduated from U.S. Navy technical schools from 1950 to 1954, and had served on ships in either an occupation with presumed high exposure (electronic equipment repair) or in one with presumed low exposure (equipment operation), as classified through a shipboard measurement and assessment process. Approximately 20,000 individuals were identified as belonging to each of these groups, and were followed using Navy and Veterans Administration records of hospital admissions (for 1952–1954, 1956–1959, and 1963–1976), disability compensation (to 1976), and mortality (to 1974). Exposure of the radio and radar operators in the low-exposure group was estimated to be well below 1 mW/cm^2, whereas the fire control technicians and electronics technicians in the high exposure group were presumed to have similar mean levels of exposure but infrequent exposures over 100 mW/cm^2. No elevated risks of mortality or hospital-based morbidity were observed. In particular, no elevated mortality for all diseases, all cancers, or lymphatic and hematopoietic cancers were reported.

This study has several methodological strengths. There was an attempt to provide a valid historical measure of individual exposure by developing an index based on measurement and on characteristics of microwave exposure. This study is based on a well-defined cohort with good-quality records-based follow-up over a long period of time, and of large enough size to provide reasonable statistical power, given the exposure prevalence, although the sample sizes are small for some outcomes. A weak-

ness in this study is that other potential confounders and risk factors were not assessed.

Garland et al. (1990) reviewed the incidence of leukemia among a group of occupations with presumed electromagnetic field exposure in a cohort of U.S. Navy personnel. Records of the Naval Health Research Center in San Diego were used to identify and follow the cohort, and inpatient medical records were searched to provide outcome data. Over 4 million person-years of exposure were observed among the cohort from 1974 to 1984, and 102 leukemia cases were identified and verified using other reports. No significant difference in leukemia risk was observed for any of the occupations reported as compared with U.S. population rates. Although this study was based on a large well-defined cohort and endpoints, there was no attempt to define or characterize an "exposed" category of occupations. Information on other potential risk factors was not available. Therefore, it is not possible to identify risks from radiofrequency exposure from this investigation.

In another study by Hayes et al. (1990), 271 testicular cancer cases diagnosed between 1976 and 1981 were identified from three Washington, DC, area hospitals, two of which were military hospitals. A total of 259 controls with other diagnoses were selected from these hospitals. Approximately two-thirds of the study subjects were active military personnel. Self-reported exposure to microwaves and other radio waves was associated with an excess risk of testicular cancer; however, an analysis of risk based on job titles produced an odds ratio of 1.1 (95% confidence interval 0.6–2.1) for risk of testicular cancer.

In an improvement over earlier exposure assessment methods, Grayson (1996) studied brain tumor risk among U.S. Air Force personnel using estimated cumulative ELF and RF/MW exposures from a job-exposure matrix developed by an expert panel. Over 11 million person-years of follow-up were documented among the 230 cases and 920 controls selected from a cohort of all male members of the U.S. Air Force who had completed at least 1 yr of service between 1970 and 1989. Higher socioeconomic status (as measured by military rank) was a strongly significant risk factor for brain cancer. An odds ratio of 1.39 (95% confidence interval 1.01–1.90) was reported between personnel ever exposed to radiofrequency/microwave radiation and those not exposed, but no trend with increasing exposure was observed. An odds ratio of 1.28 (95% confidence interval 0.95–1.74) was reported between personnel ever exposed to extremely low frequency fields and those not exposed. There was no interaction between exposures at these two different frequency ranges. However, exposure determination was still indirect and allowed for only a dichotomous categorization of exposure. Exposures to other substances possibly encountered in the case and control groups were not recorded. The strengths of the study are the well-defined case and control groups, improved exposure assessment, reduced misclassification, and the large numbers of partic-

ipants and person-years of exposure all of which provided increased precision in risk estimates.

Muhm (1992) reviewed the mortality of 304 male employees of an electromagnetic pulse (EMP) test program using death certificate information. This study has several limitations including its small size, indirect exposure assessment, lack of additional exposure information, and the fact that the exposures of this group were different from other studies.

A 1994 study by Armstrong et al. also examined exposure to pulsed electromagnetic fields (PEMF) in a nested case-control study of 2679 utility workers in Quebec, Canada, and France; recorded exposures covered a range that included RF fields. No excess risks were seen among most cancers; however, cumulative PEMF was related to excess risk of lung cancer, with an odds ratio of 3.11 (95% confidence interval = 1.60–6.04) in the highest exposed group of 84 cases. Adjustment for confounding by smoking and other occupational exposures did not explain the result; however, there is a lack of precision in the measurements and this association has not been seen elsewhere.

In a recent study conducted in Poland by Szmigielski (1996), cancer morbidity from 1971 to 1985 was assessed in subjects identified through military service records. Subjects were divided into those occupationally exposed to radiofrequency fields and microwaves, and a nonexposed group. RF monitoring was carried out routinely in areas where RF-emitting equipment was used. Only annual group data, relating to the number of individuals by age group, type of service, and other exposures, were available on the cohort. These were used to calculate cancer rates. Health records of "exposed" personnel were collected from records of central and regional military hospitals and the central military medical board. The methodology used to calculate rates and relative risks is not clear, but appears to be somewhat like a cross-sectional survey since person-years of exposure were not available. The authors reported significant excess cancers, particularly for cancers of the hematopoietic system and lymphatic organs, and for nervous system tumors. However, based on the annual numbers provided, the expected incidence rates appear to be low, about half of the rates expected in the male Polish population in these age groups, as reported in the International Agency for Research on Cancer publication on cancer incidence rates around the world (IARC, 1997). Unfortunately, the investigators were not provided with individual age information on these records, and variation in the age distribution within the 10-yr age groups may explain both the low expected rate and the differences seen between the exposed and unexposed groups.

2. *Studies of electronics workers.* Engineers and other employees of the telecommunications industry were included in categories of probable or possible EM field exposure in a study by Lin et al. (1985) on risk of brain tumor mortality. However, as the occupationally exposed categories were determined by exposure to electricity (mainly generating ELF fields)

the results do not provide any information specifically for those exposed to the RF/MW frequency range.

Milham (1985) analyzed the mortality experience of 486,000 male deaths occurring in Washington State from 1950 to 1982, and reported increased mortality from leukemia and non-Hodgkin's lymphomas in workers employed (according to their death certificates) in a group of occupations with presumed exposure to electric or magnetic fields, including radio and telegraph operators and repairmen. He reported a proportional mortality ratio (PMR) of 164 for non-Hodgkin's lymphoma, based on 51 deaths in the exposed group, and a PMR of 162 for acute leukemia, based on 67 deaths among the exposed group. A weakness of the PMR measure is that it can lead to misleading conclusions if the comparison groups have different distributions of causes of death.

In a follow-up study in 1988, Milham identified a group of amateur radio operators in Washington State and California through licensing records, and located 2485 deaths among this cohort of almost 68,000 in the period from 1979 to 1984. He reported significantly high standardized mortality ratios (SMR) for acute myelogenous leukemia (SMR = 176, 95% confidence interval 103–285), based on 15 deaths, and multiple myeloma and non-Hodgkin's lymphoma combined (SMR = 162, 95% confidence interval 117–218), based on 43 deaths. The SMR for brain tumors was 139, an elevated but not statistically significant ratio, based on 29 deaths. Unfortunately, although the studies are large and population based, interpretation of the results is difficult due to limitations of exposure assessment and study design. Death-certificate data on occupation are a poor surrogate for exposure, and the exposure profiles of this group of occupations include exposure over a wide range of the frequency spectrum, including ELF exposure. Death certificates can also misclassify cause of death, and provide no information on exposure to other factors that would also affect risk. Death certificates only provide information on mortality, however; for some less fatal cancers, incidence data are preferable.

Thomas et al. (1987) conducted a case-control study of 435 white men aged 30 yr and older who died of brain or other central nervous system tumors in the period 1979 to 1981 in selected areas of northeastern United States, and in the period 1978 to 1980 in the Gulf Coast area of Louisiana. A total of 386 controls were chosen who died of other causes, and matched for race, age, year of death, region, and educational class. Cause of death was verified for brain tumor deaths, and study subjects' next of kin were interviewed to provide job history information and data on other possible risk factors. Two methods for exposure classification were adopted. For comparability, men who had ever worked in the occupational groups defined by Lin et al. (1985) and Milham (1985) were designated as "exposed." An industrial hygienist also classified job titles according to presumed exposure to microwave/radiofrequency radiation exposure, and exposure to lead and soldering fumes. The authors reported an excess risk of brain tumor death in

men ever employed in an electronics occupation, particularly for astrocytic tumors however; this was independent of microwave/radiofrequency radiation exposure. Men with microwave/radiofrequency radiation exposure in jobs other than electronics jobs did not have an excess brain tumor risk. No other specific agent among the electronics workers could be identified in this study that was related to the excess risk in this group.

This was a well-designed and well-conducted study in several ways: The study was population based, and death records are a good source of case ascertainment for brain tumors where the fatality rate is high. The sample size was not large, but was sufficient for reasonable precision in risk estimates. Verification of the diagnosis, and information on exposure and other possible risk factors was obtained, with expert classification.

Data from a case-control study of breast cancer in men (Demers et al., 1991) were analyzed to determine risk from various occupational EMF exposures. Cancer registries were used to identify 227 cases diagnosed from 1983 to 1987, and 300 random-digit-dialed controls. An elevated but statistically nonsignificant odds ratio of 2.9 (95% confidence interval = 0.8–10) was seen for radio and communications workers, with 7 cases and 5 controls reporting these jobs on a standardized questionnaire. Low participation, particularly among controls, was identified by the authors as a problem with this study. Numbers are too small to provide reasonable confidence in the results and therefore the study is suggestive only of further research.

Tynes et al. (1996) examined cancer risk among female Norwegian radio and telegraph operators, by linking a cohort of 2619 Norwegian Telecom female operators working at sea from 1920 to 1980 to the country's cancer registry. In a nested case-control study, after adjusting for several known breast cancer risk factors, including maternal age at first birth, the relative risk for breast cancer associated with being a radio and telegraph operator was 1.5. Risk for other types of cancer was not elevated in this group. This was a large, well-designed study, with the advantage of collecting a considerable amount of information on other risk factors, although numbers for some categories were small.

3. *Other industries with high exposures.* A cluster of testicular cancer cases (6 cases reported in 12 yr vs. 0.87 expected) was reported from police officers in two police departments in the north-central United States who regularly used hand-held radar at least 4½ yr prior to diagnosis (Davis & Mostofi, 1993); no other risk factors were identified, and the officers tended to hold the radar gun close to their testicles. As the authors suggest, larger studies need to be undertaken to confirm this result. A subsequent NIOSH report (Lotz et al., 1995) underlined the difficulties in conducting such research, including the problem of exposure assessment, but did point out the low overall exposures from radar guns (in most cases less than 20 $\mu W/cm^2$). A retrospective study of cancer incidence among a cohort of over 22,000 Ontario police officers (Finkelstein, 1998) followed

from 1964 to 1995 reported an overall standardized cancer incidence (SIR) of 0.90 (with 95% confidence interval 0.83–0.98) compared to the general Ontario population, consistent with the assumption that police officers are healthier overall than the general population, but an increased incidence of both testicular cancer (SIR = 1.3, 90% confidence interval for one-tailed test = 0.90–1.8) and melanoma (SIR = 1.45, 90% confidence interval for one-tailed test = 1.1–1.9). No information on actual exposure and other risk factors was available.

In a study of female breast cancer mortality in the United States (Cantor et al., 1995), mortality records from 24 states, covering deaths from 1984 to 1989 and coded for occupation and industry, were analyzed using a job-exposure matrix. Probability of exposure was assessed using a scale from 0 to 4, and level of exposure was assigned a score from 0 to 3. No excess breast cancer mortality was found (odds ratio, OR, adjusted for age and socioeconomic status = 0.99, 95% confidence interval = 0.8–1.2), based on 199 case deaths and 699 controls in the "most likely exposed" category, and no trend in risk was seen with increasing likelihood of exposure. The adjusted odds ratio for highest level of exposure was 1.14 (95% confidence interval = 1.1–1.2), barely statistically significant. Using deaths rather than incident cases, and death certificate information for exposure information, limits the value of this study.

A case-control study in the western United States (Holly et al., 1996) was conducted to determine the relation between occupational or chemical exposures and uveal melanoma, using 221 hospital-based male cases and 447 random-digit-dialed controls. Exposure information was based on job title and specific questions on chemicals, determined using questionnaire-based interviews. The adjusted (for socioeconomic status) odds ratio for any exposure to microwaves or radar was 2.1 (with 95% confidence limits of 1.1–4.0), with 9 patients and 5 controls exposed. Given the small numbers of exposed subjects, and the authors' concern that referral bias may have influenced the results, this study can be considered only suggestive of further investigation.

The only published study of risks specifically among women was reported by Lagorio et al. (1997), who documented the mortality experience of a cohort of Italian plasticware workers exposed to radiofrequency fields generated by dielectric heat sealers. A total of 481 women were followed from 1962 to 1992, of whom 302 were sealers. In 6772 person-years of follow-up among the sealers, only 6 cancers were identified (compared to 3 expected in the regional population and 1.9 in the other worker population). This number of cases is too small to provide meaningful estimates of risk. In addition, although survey findings indicate that exposures were probably higher than 10 W/m^2, exposure assessment was based only on job title and duration, and the authors acknowledge that exposure to solvents and vinyl chloride monomer (both known carcinogens) among this group could be responsible for the observed cases of cancer.

4. *Residential exposures.* Hocking et al. (1996) published the results of an ecological study of cancer incidence and mortality from 1972 to 1990, in relation to residential proximity at time of diagnosis or death to TV towers in nine municipalities of northern Sydney, New South Wales, Australia. Information on operational characteristics of the towers was obtained and a power density estimate was calculated for the area. The municipalities were grouped into three inner areas (with estimated population size of 135,000) and six outer areas (population approximately 450,000). For all ages, the leukemia incidence rate in the inner areas was 1.24 times the rate in the outer areas (95% confidence interval 1.09–1.40), based on 1206 cases, and the incidence rate for brain cancer in the inner areas was 0.89 times the rate in the outer areas (95% confidence interval 0.71–1.11), based on 740 cases. Mortality for these cancers was also not different between areas.

Apart from the fact that proximity to TV towers is a poor proxy for RF field exposure, there are several major limitations of the ecological design of this study that make interpretation of these results problematic. The most serious flaw is that individual exposure data are not available. Information on potential confounders, even at the group level, is also not provided in this study. Furthermore, population movement cannot be accounted for in the exposure assessment or in calculation of rates. Although the authors attempted a measure of RF fields through to proximity to the TV towers, the calculated exposure levels for this study differed from measured power densities in the area, which were up to five times less, and geographic area boundaries did not actually correspond to defined distances from the towers. The calculated fields were also low (8.0 to 0.2 $\mu W/cm^2$ in the inner areas), which suggests that the "exposed" group were actually receiving only very little exposure from the towers.

Following a report of an excess of adult leukemias and lymphomas near the Sutton Coldfield TV and FM radio transmitter in the West Midlands, two case-control studies were conducted: first in the West Midlands, and then in all of Great Britain, by Dolk et al. (1997a, 1997b). Both studies examined the ratio of observed versus expected numbers of cancers among the population that resided within 2 km and within 10 km of a transmitter. The first study identified 17,409 incident adult cancer cases diagnosed between 1974 and 1986 in a population of approximately 408,000 living within 10 km of the Sutton Coldfield transmitter, compared to 16,861 expected. This 3% excess, which was not significant after adjusting for socioeconomic status, showed no trend with increasing distance from the transmitter. The ratio of observed to expected cancer cases living within 2 km of the transmitter was 1.09. The only specific cancer types to show an excess risk with proximity to the tower were the leukemias (O/E ratio 1.83, 95% confidence interval 1.22–2.74, based on 23 observed vs. 12.59 expected within 2 km of the tower). A decline in risk with distance from the tower was also reported, with the observed numbers in the more distant areas falling

below the numbers expected. None of the other cancer types reported (skin melanoma, non-Hodgkin's lymphomas, multiple myeloma, and cancers of the brain, breast, lung, colorectum, stomach, prostate, and bladder) showed any relationship of risk to distance from the tower, although increasing trends in incidence with proximity to the tower were noted for skin melanoma and bladder cancer.

In a larger study conducted in the whole of Great Britain, risk of leukemia, skin melanoma, and bladder cancer was assessed using the same methodology, and numbers of observed cases were all approximately equal to expected numbers, with no trends in rates with distance from towers. Two major limitations of these investigations are the use of proximity to a transmitting tower as a proxy for RF exposure, and the lack of individual exposure and confounder information due to the ecological design. Since the study period was so long, the effect of population movement also weakens the validity of the results.

5. *Cellular telephone users.* Rothman et al. (1996) reported on the overall mortality of two types of cellular telephone customers, users of portable telephones and users of mobile telephones, and found no difference in the mortality experience of portable and mobile phone customers from a cohort of 255,868 subscribers. This study does not address the relative risk of users of mobile telecommunications devices as compared to nonusers. Moreover, although Rothman et al. used a large cohort, follow-up is short and some specific outcome information is missing. Also, this study suffers from the limitations of exposure assessment imposed by using telephone company records.

Childhood cancer. The risk of childhood cancer among children living close to TV and FM radio transmitter towers has been examined in a number of studies published through to the middle of 1998, two of which were conducted by the same group of researchers in the United Kingdom. All have defined exposure as proximity of residence to TV and FM radio, or radio transmitters/towers.

Three statistical approaches were used by Selvin et al. (1992) to assess the relationship between distance to a large microwave tower in San Francisco and cancers diagnosed in children under age 21 yr for the years 1973 to 1988; the incidence patterns of leukemia (51 cases), brain cancer (35 cases), and lymphoma (37 cases) were found to be essentially random with respect to distance to the tower.

Maskarinec et al. (1994) reported the results of an investigation of a childhood leukemia cluster in Hawaii, where an excess of cases was noted between 1982 and 1984. Since 1985, the incidence of childhood leukemia in the area has been within the expected range. An unusual gender, age, and subtype distribution was reported for the 12 cases diagnosed in the area between 1979 and 1990. The characteristics of the seven cases diagnosed during the period with excess incidence were not specifically reported. A case-control study (matched for gender and age) examined sev-

eral environmental and familial risk factors, and found that only proximity to a radio tower of the last residence before diagnosis, and family history of cancer, had odds ratios higher than 1, although neither result was significant statistically. For children living within 2.6 miles of radio towers, an odds ratio of 2.1 (with 95% confidence limits between 0.6 and 8.3) was observed. The lack of a prior hypothesis and the small numbers of cases in this study (both failings of cluster-based investigations), the inadequacy of the exposure assessment measure, and the lack of adjustment for other potential confounders such as socioeconomic status and chemical exposures, limits the interpretation of these results.

Hocking et al. (1996) published the results of an ecological study of cancer incidence and mortality from 1972 to 1990, in relation to residential proximity at time of diagnosis or death to TV towers in nine municipalities of northern Sydney, New South Wales, Australia. Information on operational characteristics of the towers was obtained and a power density estimate was calculated for the area. The municipalities were grouped into three inner (with estimated population size of 135,000) and six outer (population approximately 450,000) areas. A significant excess of leukemia cases among children aged 0–14 yr (rate ratio of 1.58, with 95% confidence limits between 1.07 and 2.34) was observed when comparing the inner with the outer municipalities, based on 134 cases. The excess was present in all subtypes (lymphatic myeloid, and other leukemias). Childhood leukemia mortality was also higher (RR = 2.32, 95% confidence interval 1.35–4.01). Brain tumor risk, however, was not elevated [RR(incidence) = 1.10, with 95% confidence interval 0.59–2.05; RR(mortality) = 0.73, with 95% confidence interval 0.26–2.10].

There are several major limitations of the ecological design that weaken the strength of these results. The most serious flaw is that individual exposure data are not available. Information on potential confounders, even at the group level, is also not provided in this study. Furthermore, population movement cannot be accounted for in the exposure assessment or in calculation of rates. Calculated exposure levels for this study were low (8.0 to 0.2 $\mu W/cm^2$ in the inner areas), and differed from measured power densities in the area, which were up to five times less. Geographic area boundaries did not correspond to defined distances from the towers; again, proximity to TV towers is a poor proxy for exposure.

A follow-up study reanalyzed these cases using local government area (LGA) boundaries (McKenzie et al., 1998). It was found that all of the excess was observed in one highly exposed area, where no excess was seen in a similarly exposed district. Therefore the observed association in the Hocking study was not supported in this analysis.

Following a report of an excess of adult leukemias and lymphomas in the Birmingham area, two case-control studies were conducted, first in the West Midlands, and then in all of Great Britain, by Dolk et al. (1997a, 1997b). Both studies examined the ratio of observed versus expected num-

bers of cancers among the population with residence within 2 km and within 10 km of a transmitter. The first study identified 97 cancer cases diagnosed in the 0 to 14 yr age group between 1974 and 1986 while living within 10 km of the Sutton Coldfield transmitter (106.7 cases were expected). Thirty-four leukemia cases were observed, compared to 29.7 expected. Two cases lived within 2 km of the transmitter (1.1 expected). In the larger study, 10 leukemia cases were identified (8.9 expected) and 4 brain tumors were identified (6.5 expected), of which 3 were malignant (5.99 expected). Socioeconomic status was the only adjustment variable, and no information was provided on leukemia subtype. These results were not consistent with the New South Wales study. These investigations also are difficult to interpret because of the limitations of the exposure assessment variable, lack of information on other confounders, population movement, and small numbers.

In summary, none of the few investigations of risk of childhood cancer conducted so far can be regarded as providing useful information concerning the effect of radiofrequency fields on risk of childhood cancers.

Reproductive outcomes A small study by Lancranjan et al. in 1974 examined gonadic function in 31 young men with a reported mean duration of exposure to microwaves (frequently in the range of tens to 100 μW/cm^2) of 8 yr. They found alterations of spermatogenesis in 23 subjects. Cases were volunteers, and the control group was not defined. There was no description of the source of the subjects, nor was the method for determination of exposure described. The small numbers involved and methodological limitations make interpretation of this study impossible.

In Sweden, a nested case-control study was undertaken of Swedish female physiotherapists (Kallen et al., 1982). Thirty-three births with malformations or perinatal deaths were identified and matched to 63 control births in a nested case-control design. Exposure information was obtained through mailed questionnaire. Frequent (often or daily) use of shortwave equipment was significantly associated with risk of malformation or perinatal death, based on 11 case births and 9 control births. No information was provided on the gender distribution of the exposed cases. The same trend was observed among ultrasound users, but these two exposure categories were correlated. Although the study was of good design and a high participation rate, the numbers exposed to microwave equipment were too small to provide reliable risk estimates.

Taskinen (1990) reported on spontaneous abortions among a cohort of all registered physiotherapists in Finland who had miscarried between 1973 and 1983, in a nested case-control study. Population-based records were used to identify the cohort and their medical histories. Exposure information on occupation and use of therapeutic equipment was obtained via mailed questionnaires from 240 women who had bad a spontaneous abortion, and 483 control women. The response rate was very high (92%), although a proportion of the original group could not be traced. Exposure

was classified according to the mode of action of the equipment used. Other potential risk factors were adjusted for in the analysis. Compared to those not employed during pregnancy, more spontaneous abortions were seen among physiotherapists working with shortwave diathermy 5 or more hours per week (OR = 1.6, 95% confidence interval 0.9–2.7, based on 30 cases and 55 controls). The odds ratio for women working with microwave diathermy was also elevated (OR = 1.8, 95% confidence interval 0.8–4.1, based on 13 cases and 18 controls), but again not significantly so. Ultrasound exposure for 20 hours per week or more resulted in a statistically significant odds ratio of 3.4 (95% confidence interval 1.2–9.0).

In a Danish study of similar design (Larsen et al., 1991), 270 cases (166 miscarriages, 18 stillbirths/deaths within 1 yr, 86 preterm births, and 44 children with low birth weight) and 316 controls were ascertained over the period 1978–1985. Exposure was assessed for the first month of pregnancy using information on usual tasks, source and duration of exposure, and intensity of exposure (direct vs. indirect). From these data, a time-weighted exposure index was constructed with three categories of exposure. Information on some confounders was collected, and the contact rate and response rate were high (over 90%). There was no significant association of spontaneous abortion with exposure to shortwave radiation (OR = 1.4, 95% confidence interval 0.7–2.8, based on 15 cases and 20 controls); nor was there any association with the other outcomes studied, except for gender ratio, which was 4:13 (males:females) in the high-exposed group. A follow-up study in Switzerland (Guberan et al., 1994) of 1781 pregnancies occurring to Swiss female physiotherapists and including a self-administered questionnaire of use of short-wave and microwave equipment during the first month of pregnancy and pregnancy outcome did not observe a difference in gender ratio between exposed and nonexposed pregnancies, nor was the result affected by intensity or duration of exposure.

Ouellet-Hellstrom and Stewart (1993) collected reproductive histories, pregnancy outcome data, and occupational histories from 42,403 physical therapists in the United States through mailed questionnaires in 1989, and identified 1753 miscarriages, which were matched to the same number of other pregnancies (excluding ectopic pregnancies) in a nested case-control study. Exposure to shortwave and microwave diathermy was defined as numbers of reported exposures anytime during the 6 mo prior to or during the first trimester of pregnancy. The number of miscarriages was 26% higher among mothers exposed to microwave equipment (95% confidence interval 1.00–1.59), after adjustment for prior fetal loss, and risk increased with increasing level of exposure. However, risk of miscarriage was not associated with reported use of shortwave diathermy equipment (OR = 1.07, 95% confidence interval 0.91–1.24), and no trend with increasing exposure was seen. A low overall response rate and the lack of validity in interview-based exposure assessment limit the interpretation of these results.

A 1996 study (Kolodynski & Kolodynska, 1996) of motor and psychological functions of 966 children aged 9 to 18 yr in Skrunda, a region of Latvia, also reported a deficit of boys (16%), and a 25% deficit in the area defined as "exposed" (the region within a 20-km radius of the local radar station). This station would emit a pulsed RF field at a frequency of 24.4 Hz, whereas the stations operated at frequencies of 154 to 162 MHz. It is difficult to determine the significance of the male deficit around the radar location station, given the overall lower proportion of boys in the general area and the rather large area defined as the "exposed" area. Comparisons of neuromuscular reaction times, reaction times in response to aural and visual stimuli, attention switching, and short-term memory were based on standardized tests, and were reported between three groups: those in Skrunda living closer to the station, those living farther away, and children in another region of Latvia (Preili). Differences were found in all tested motor and psychological functions in exposed children as compared to children living in Skrunda farther from the radar station, and neighboring Preili children. Estimated rates of exposure to several chemical agents were provided for the two districts. No information on population mobility or duration of residence of "exposed" and "nonexposed" groups was available.

Congenital anomalies There are two studies identified from the literature that examine the risk of congenital anomalies with exposure to radiofrequency/microwave fields. Cohen et al. (1997) reported on the results of a case-control study of Down's syndrome in the Baltimore, MD, area, involving a combined case group of 372 cases and 371 controls with interview and record-based information on paternal exposure to radar before conception of the index child. This was a well-designed study, with information on many other potential risk factors. An original case group was born between 1946 and 1962, with results reported by Sigler et al. (1965); a subsequent group extended the case finding through births to the end of 1968. Exposure categories were based on expert panel review of both interview and record data on job title. The original, smaller study group showed a slight (not statistically significant) increase in the proportion of case fathers with radar exposure as compared to control fathers; the opposite finding was observed in the later series. In the combined, pooled series, there was no significant difference in radar exposure based on interview data between the case and control fathers, with 34 case fathers (10.8%) and 37 control fathers (12.5%) reporting a radar-associated job. Exposure status was unknown for 16% of the case fathers and 20% of the control fathers. An analysis based on records produced the same finding: 34 case fathers (10.0%) and 31 control fathers (9.3%) were classified as exposed, a nonsignificant difference. Unknown exposure status was noted for 9% of case fathers and 11% of control fathers.

Taskinen et al. (1990) reported on congenital anomalies among a cohort of all registered physiotherapists in Finland who had miscarried be-

tween 1973 and 1983, in a nested case-control study. Population-based records were used to identify the cohort and medical histories. Exposure information on occupation and use of therapeutic equipment was obtained via mailed questionnaires from 46 women who had had a child with a congenital anomaly, and 187 control women. The response rate was very high (89%), although a proportion of the original group could not be traced. Exposure was classified according to the mode of action of the equipment used, and other potential risk factors were adjusted for in the analysis. A higher risk estimate was seen for the group spending 1–4 h/wk administering deep heat therapy (OR = 2.4, 95% confidence interval 1.0–5.3, based on 15 cases and 35 controls) or shortwave therapy (OR 2.7, 95% confidence interval 1.2–6.1, based on 15 cases and 33 controls), but not for those exposed for longer duration.

Other Health Outcomes Disturbances of the circulatory system, such as heart-rate disturbances, impaired conduction, abnormal ECG recordings, and blood pressure changes, have been reported in the Soviet literature during the 1960s. Direct current shocks or radiofrequency current are being used for catheter ablation of arrythmogenic myocardium in treatment of several types of tachyarrhythimas. A review of 111 patients in an Oklahoma study (Goli et al., 1991) did not find evidence of subsequent abnormality in particular mural thrombus, in these patients. However, in a study of 71 AM broadcast station workers compared to 22 radio link stations without occupational electromagnetic field exposure (Bortkiewicz et al., 1997), electrocardiographic abnormalities, particularly rhythm disturbances, were detected significantly more frequently among the exposed workers.

Proposed and Ongoing Studies In addition to the studies published in the literature to the middle of 1998, there are several research projects either underway or proposed. In Denmark, a cohort study investigating the risk of developing brain (CNS) cancer, salivary gland cancer, and leukemia among adult cellular phone users is ongoing. Results are expected in the early 2000s. Operating company records are being used to identify the exposed group and for information on exposure itself. Information on duration of use of either analogue or digital systems (as recorded from time or billing data) among 800,000 individuals from 1981 to 1995 is being linked to cancer registry records. There are several sources of exposure misclassification using cellular telephone company records, including classification of the registered telephone owner rather than the user, and the lack of data on other parameters of exposure, for example, distance from transmitter during a call. No information on confounding will be available. Expected follow-up time is only 4 yr, which is insufficient if the latent period for development of cancer is longer.

A U.S. study sponsored by Wireless Technology Research involves over 1 million cellular telephone account holders, classified as analogue or digital telephone holders, and hand-held or mobile users, identified in 1994 and 1995. There is 1 yr of follow-up so far; however, follow-up of study subjects is suspended at present.

The American Health Foundation has conducted two hospital-based studies of cellular telephone use in relation to the risk of brain cancer and acoustic neuroma. The study of malignant tumors includes 459 cases of glioma and 422 controls. The risk of these tumors was examined in relation to the duration and frequency of cell phone use, and billing information (J. Muscat, unpublished).

The National Cancer Institute of the United States has conducted a case-control study of selected adult tumors and cellular telephone use, in collaboration with three major medical centers in the United States. Approximately 800 cases and 800 controls are anticipated to be enrolled (500 glioma patients, 200 meningioma patients, and 100 patients with acoustic neuromas); self-reported exposure information will be collected (with proxy interviews necessary for a portion of subjects). A preliminary report is planned in the next year.

Two multicountry collaborative studies of cellular telephone users and cancer are also in the planning stages. A population-based, case-control study of the risk of brain cancer, salivary-gland cancer, and leukemia in cellular telephone users, using cellular company records and linking these to the cancer registries, has been suggested by the Scandinavian countries of Sweden, Norway, and Finland. In addition, following recommendations of expert groups of both the International Association of Research on Cancer (IARC) and the European Union (EU), IARC is in the final stages of a feasibility study of a proposed case-control investigation of adult brain, head, and neck tumors and exposure to RF emitted by cellular telephones, also using cellular phone records. Nine countries are participating in the feasibility study, including Australia, Canada, France, Germany, Israel, Italy, New Zealand, Sweden, and the United Kingdom. The proposed study will provide more precision in risk estimates, due to the large numbers of subjects that would be recruited; the main issue in evaluating the feasibility of the study is the source, detail, and quality of exposure information.

Sweden and Norway have also collaborated on a cross-sectional survey of subjective symptoms of cellular telephone users, including headaches, discomfort, and sensation of warmth; analogue and digital systems were assessed separately.

Methodologic Assessment of Literature Overall, there are sufficient methodological problems in the studies published to date to preclude meaningful interpretation of results. Theses problems include difficulties with exposure assessment, complicated by the fact that the specific exposure metric is not known; lack of information on confounders; difficulties in identification of exposed groups or outcome; and lack of statistical power.

No occupational study utilized personal measurement of RF exposure. Most investigations used job title information only, which does not account for personal variation in exposure, exposure parameters such as frequency range, duration, and intensity of exposure, and time-dependent variation. Since RF exposure characteristics vary between different occupational groups, it is not possible to combine occupational groups, as some

studies have done, and have a homogeneous exposed category. Some occupational studies have combined occupational groups with both ELF and RF exposures, precluding meaningful interpretation of the exposure categorization. The best assessment of occupational exposure in the published literature so far was an expert job-exposure matrix; however, given the extensive variation in personal exposure and time-dependent exposure conditions, more attention and research are needed to characterize the variation in exposure.

Exposure assessment of populations living near base stations or RF transmitters, using contemporaneous measures of distance to station, is not adequate to determine exposure. Exposure levels are very low from this source, and are subject to variation depending on both distance from the transmitters and attenuation of the signal from buildings and other solid objects. Moreover, the populations studied in this way cannot be adequately identified or followed for the periods of time necessary to determine outcomes. For this group, it may be impossible to determine risk using epidemiological methods. However, assuming risk is related to dose, this may be a group that is not greatly exposed and therefore is not at significant risk.

Cellular telephone users are perhaps the most rapidly expanding exposed group. Because of the nature of use of cellular telephones, specific body sites (around the head and neck) can be assumed to be exposed and at potential risk of health effects. Cohort studies of users have the advantage of identification of (presumed) users, and can investigate multiple outcomes. However, complete cohort follow-up, particularly over several years, can be difficult to accomplish. Records of subscribers to cellular telephone services provide some information on presumed users and duration of use of cellular telephones but cannot account for personal, instrument, and usage variability. If companies change to prebilling systems, even duration of use information may not be available. Case-control studies have the limitation, however, of recall problems in assessment of exposure.

Conclusions

Overall results The epidemiological studies published to date are of fair overall quality, with exposure assessment being the greatest limitation to interpretation. No high excess risks were observed in any studies of adequate design, and risk estimates were generally less than 2, at the limit of what is detectable in most epidemiological investigations. In general, no statistical patterns of trend with any exposure parameter were observed, and results among different studies were inconsistent. Assessment of the temporal relation between exposure and outcome was impossible to evaluate in the studies because of their retrospective nature and lack of data on timing of exposure. Therefore at this point, the epidemiological evidence to date is inadequate for a comprehensive evaluation of risk and does not support a hypothesis of an association between exposure to radiofrequency fields and risk of cancer, reproductive problems,

or congenital anomalies. However, there is a need for additional, larger, well-designed studies, to provide further information on these relationships.

Neurology and Behavior Clinical Effects

Interest in the capacity of MW and electromagnetic fields to influence neurological events in a clinically relevant manner dates back more than 40 yr. The notion that the brain may somehow be especially susceptible to MW/RF fields is an old belief probably arising out of the Soviet Union in the 1950–1960s. The possibility that microwaves interact with neural tissue in a manner that did not require significant heating was suggested repeatedly by many Soviet investigators (Pressman, 1965; Gordon, 1970). A considerable body of literature was put forth by the Soviets on transient functional changes following low-dose (<10 mW/cm^2) MW radiation studied by conditional response experimentation. Soviet physiologists diligently sought the brain mechanisms that might be responsible for each MW-induced phenomenon. However, the studies of the Soviet investigators have been severely criticized because of inadequate controls, poor statistical analysis and lack of quantification of the results. Moreover, conditional response studies are not adequate for objective interpretation. Finally, the effects of low-level MW on neural tissue, as described in these early Soviet studies, have not been reproduced by other investigators using similar experimental set-ups.

Regardless of any inadequacies of experimental design, this early work did point out the need to remain vigilant to potential brain effects of MW. Accordingly, concerns about how MW may be deleterious to human brain function is long-standing and has received a diverse variety of in vitro and in vivo investigations over the past three decades.

Biological Justification for Neurological Clinical Effects of MW

Does neural tissue or brain tissue have unique susceptibility to MW? Is looking for clinical neurologic effects associated with exposure to MW justified in terms of a biological basis? These important questions may be answered in either structural terms (starting with gross anatomy, proceeding to cellular anatomy and ending at the molecular level of refinement) or in purely functional terms (including both electrophysiological and neuropharmacological considerations).

From a gross anatomical structural perspective, it is arguable that the brain may have unique anatomic vulnerability to MW exposure. Of all anatomical structures, the head has the closest proximity to mobile phones, radios and similar hand-held devices. This leads to a relatively high specific absorption rate (SAR) for the brain compared to the rest of the body. For example, Cleveland and Athey (1989) measured SARs in models of the human head exposed to hand-held portable radios transmitting at frequencies in the 800-MHz band using an isotropic implantable electric-

field probe to measure internal fields. This study showed that antenna type and orientation were important factors in determining energy absorption. Furthermore, atypical operation of the transceiver (e.g., holding it in front of the eye rather than down the side of the face) may lead to even higher specific absorption rates. Within the head, the temporal lobe is the part of the brain in closest proximity to the hand held phone. Temporal-lobe damage is well documented to produce a variety of clinical neurologic complaints including memory problems and seizures.

From a histological (cellular) structural perspective, data pertaining to the neuronal and glial effects of MW are highly variable. The human brain consists of approximately 100 billion brain cells (neurons); in addition, there are nonneuronal support cells called glial cells. Following exposure to RF fields (2450 MHz, 15 W/kg, 30 min), swollen neurons were documented in the hypothalamus and subthalamus of the Chinese hamster (Albert & De Santis, 1975). Neuronal swelling has also been reported by other workers (Hansson Mild et al., 1982; Hertz & Schousbee, 1975). Finally, decreased Purkinje cells in the cerebellum have been reported by Albert and Kerns (1981) (rat, 2450 MHz, 3.4 W/kg, 21 h/d for 5 d). However, the applicability of these results to the clinical situation is tempered by the fact that these effects are generally thermal rather than athermal, requiring high and atypical exposure. In addition to the neuronal effects, the effects of MW on glial brain cells have also been studied. For example, Cleary et al. (1990c) demonstrated statistically significant time-dependent alterations in glioma cell (LN71) proliferation when the cells were exposed to 2450-MHz continuous-wave radiofrequency radiation in vitro for 2 h under isothermal conditions. However, the most significant glial cellular effects may be on the blood–brain barrier (BBB). The blood–brain barrier, which is structurally composed of astrocytes and endothelial tight junctions, is the barrier that precludes the entry of a wide variety of chemicals, toxins, and drugs into the central nervous system (CNS). Some studies have suggested MW-induced increases in BBB permeability to compounds such as fluorescein (1200 MHz, continuous and pulsed, 2.4 mW/cm^2, rat), aluminum (900 MHz, continuous and pulsed, 7.5 W/kg, rat), mannitol (1200 MHz, continuous and pulsed, 75 mW/cm^2, rat), Evans blue (2450 MHz, pulsed, 240 W/kg, rat), inulin (1300 MHz, continuous and pulsed, 2 mW/cm^2, rat) and horseradish peroxidase (2450 MHz, continuous, 24 W/kg, mouse) (Frey et al., 1975; Fritze et al., 1997; Merritt et al., 1978; Lin & Lin, 1982; Oscar & Hawkins, 1977; Quock et al., 1986). Other studies have failed to show any effect of MW on BBB permeability (Preston et al., 1979; Ward et al., 1982). Still other studies have shown the BBB is only affected if it is a thermal effect (Sutton & Carrol, 1979; Moriyama et al., 1991; Goldman et al., 1984). If MW were to affect the structural integrity of the BBB, it would have clinical implications by permitting molecules such as certain drugs that normally are excluded from the brain to enter into the CNS.

From a structural perspective at the molecular level, many studies have addressed the effects of MW on brain neurochemistry. First, various studies have evaluated the effect of MW on brain energy molecules. Under diverse conditions of MW exposure, these studies have shown no change in calcium-activated ATPase levels (2450 MHz, amplitude modulated, 1.64 W/kg, mouse medial habenular nucleus), decrease in ADP with increase in NADH (591 MHz, 5.8 W/kg, continuous, pulsed and amplitude modulated, rat brain), and decrease in ADP but increase in NAD^+ (2450 MHz, continuous, 1 mW/cm^2, 60-d exposure, rat diencephalon and cortex) (Kittel et al., 1996; Sanders et al., 1980, 1985; Singh et al., 1994). Second, Ghandi and Ross (1989) showed increase incorporation of ^{32}P isotope into phosphoinositides in rat cerebral cortex synaptosomes following MW exposure (2800 MHz, pulsed, 1–30 W/kg). Third, several studies have addressed the effects of MW on neuronal Ca^{2+} metabolism. Increased Ca^{2+} release from cell membranes has been described (Blackman et al., 1979, 1980a) (147 MHz, amplitude-modulated, less than 0.5 mW/cm^2, chick brain tissue). Other studies, however, using different exposures, have demonstrated no change in Ca^{2+} release (2450 MHz, square-wave modulated, 2.9 W/kg, rat brain tissue) (Merritt et al., 1982).

Fourth, many studies have investigated the influence of MW on neurotransmitter release and activity in the CNS. These studies have yielded varying data: decreased acetylcholinesterase activity (Baranski et al., 1972; 3000 MHz, pulsed, 25 W/cm^2, guinea pig); increased acetylcholinesterase activity (Dutta et al., 1992; 147 MHz, amplitude modulated, 0.1 W/kg, human neuroblastoma); no effect on acetylcholinesterase activity (Millar et al., 1984; 2450 MHz, pulsed, 4.29 W/kg, ray fish); decrease in acetylcholine concentrations (Modak et al., 1981; 2450 MHz, single pulse, mouse); increase in hypothalamic norepinephrine activity (Grin, 1974; 2375 MHz, continuous, 0.5 mW/cm^2, rat); and decrease in hypothalamic norepinephrine activity (Inaba et al., 1992; 2450 MHz, continuous, 10 mW/cm^2, rat).

The possibility of nonstructural functional electrophysiological effects following MW exposure must also be considered in addition to purely structural effects at the anatomical, histological, or molecular levels. Arguably, the brain is the most electrically active part of the body, demonstrating a high degree of electrical activity. Conceivably, it is possible to hypothesize the possibility of MW-induced field effects on this high density of electrical activity within the human CNS. Some studies have suggested the MW can increase membrane conductance and alter spontaneous electrical activity in the CNS (Arber & Lin, 1984, 1985; 2450 MHz, continuous and amplitude modulated, 1414 W/kg, *Helix aspersa* neurons). However, other investigations, using sensitive patch clamp techniques have shown no electrophysiological effects (Wang et al., 1991; 2450 MHz, continuous, temperature-controlled, rat dorsal root ganglion cells). Still other studies have suggested suppression and alteration of evoked auditory responses in the eighth cranial nerves of guinea pig (918 MHz, pulsed), rat (2450 MHz,

pulsed), and cat (915 MHz, pulsed) (Chou & Guy, 1979; Chou et al., 1985; Seaman & Lebowitz, 1989) and altered electroencephalographic (EEG) patterns with increased beta waveforms in rabbit and rat (Shandala et al., 1979; Thuroczy et al., 1994).

Finally, the possibility of nonstructural functional neuropharmacological effects must be considered in the setting of MW and RF field exposure. Several studies have speculated on the role of MW exposure in influencing and altering normal responses to convulsive, stimulant, and/or paralyzing drugs (Thomas & Maitland, 1979; Thomas et al., 1979).

Thus, although the data are conflicting, there is a suggestion of MW-induced biological effects on the CNS. More importantly however, do these effects translate into any clinically relevant neurobiological effects? Do they have the capacity to worsen existing neurological diseases or to initiate new neuropathologies de novo?

Neurological diseases are categorized into diseases of the peripheral nervous system (PNS) and diseases of the central nervous system (CNS), with the latter being further subdivided into diseases of the brain and spinal cord. Although there are various ways to categorize diseases of the CNS, a mechanistic approach facilitates an understanding of the effects of MW on the brain. Accordingly, brain diseases may be considered as (a) developmental (e.g., cerebral palsy); (b) infectious (e.g., viral, bacterial, fungal or parasitic meningitis or encephalitis or abscess); (c) immune/inflammatory (e.g., multiple sclerosis); (c) neoplastic (e.g., meningioma, astrocytoma, oligodendroglioma); (d) degenerative (e.g., Alzheimer's, Parkinson's disease); (e) nutritional (e.g., Wernicke's encephalopathy); (f) vascular (e.g., stroke, hemorrhage), (g) traumatic (e.g., subdural hematoma); or (h) toxic (e.g., MPTP exposure, carbon monoxide). In seeking to identify possible clinically relevant effects of MW/RF fields on human neuropathology, it is necessary to correlate these eight putative mechanisms with the structural (gross anatomic, histological, molecular) and functional (electrophysiological, neuropharmacologic) influences of MW/RF field exposure. There are a number of conditions in which a correlation does exist. For instance, the degenerative diseases, such as Alzheimer's dementia (AD), involve a loss of acetylcholine leading to memory and cognitive impairments; MW has been implicated in influencing the activity of the cholinesterase enzyme. Accordingly, there is justification for evaluating whether the biological effects of MW/RF fields on the CNS are isolated laboratory findings or whether they translate into clinically relevant human effects.

Criteria for evaluating clinical evidence In evaluating the possible influence of MW/RF fields on brain function in a clinically relevant manner, it is necessary to assess the strength of the clinical data available. Consequently, available clinical data were divided into the following three classes:

- *Class I:* evidence from multiple well-designed controlled clinical trials, including overviews (e.g., meta analyses) of such trials.

- *Class II:* evidence provided by well designed observational studies with concurrent controls (e.g., case control and cohort studies).
- *Class III:* evidence provided by expert opinion, published case reports, published anecdotes and/or studies with historical controls.

Clearly, Class I evidence is the strongest and Class III evidence is the weakest. A definitive conclusion concerning an effect of MW on human clinical neurology could only be made with Class I evidence that directly addressed the specific clinical question. Moderate certainty of a MW induced clinical effect would require multiple Class II studies. If only Class III evidence were available, no definitive conclusions could be made. Inconclusive or conflicting evidence further weakens the certainty of the conclusions. Consequently, only data published in peer-reviewed journals was considered here.

Specific neurologic diseases

Seizures and epilepsy Epilepsy is a chronic disorder of the central nervous system characterized by recurrent seizures. A seizure, in turn, is defined as the clinical event which accompanies a sudden unexpected discharge of electrical activity from a group of neurons within the brain. Epilepsy is not a disease, but rather a symptom—any injury to the brain can produce seizures and thus ultimately culminate in epilepsy. When brain cells are injured they can respond in one of two ways: "hypofunction" or "hyperfunction" (the latter gives rise to seizures). Seizures arc the fundamental hallmark of electrical malfunctioning within the human central nervous system. At the molecular level, any process which influences the membrane structure of neurons or which alters neurotransmitter function in the CNS has the theoretical capacity to induce seizures. Since seizures are a disorder of CNS electrical function, the electroencephalogram (EEG) is relevant. EEGs measure electrical activity in the brain.

The acute effects of MW exposure on EEG have been evaluated in two studies using human volunteers. One of these studies used a commercially available digital mobile telephone at a distance of 40 cm (Reiser, 1995). This study employed pulsed 900 MHz exposure and demonstrated an increase in beta and delta powers after 15 min. The other study used a pulsed 150 MHz coil in the neck region with a 15 min exposure. This study demonstrated changes in alpha activity pattern immediately after the exposure. No paroxysmal or epileptiform changes in EEGs have been demonstrated following MW exposure (Hermann & Hossmann, 1997; Von Klitzing, 1995).

A potential cause of seizures is the existence of a brain tumor. The relationship between MW exposure and brain tumors has been discussed earlier in Chapter 8. To date, no convincing, reproducible data exist to demonstrate the ability of MW/RF field exposure to induce seizures or to worsen an existing seizure disorder in human patients.

Neurodegenerative diseases: Alzheimer's and amyotrophic lateral sclerosis Neurodegenerative diseases are also chronic disorders of the

central nervous system. However, unlike epilepsy, these disorders are characterized by a progressive loss of central nervous system function or "hypofunctioning." Of the central nervous system structures, Alzheimer's disease (AD) is a prototypic neurodegenerative disorder of the brain while amyotrophic lateral sclerosis is a prototypic neurodegenerative disorder of the spinal cord. Alzheimer's disease is the most common form of dementia, where dementia is defined as a decline in intellectual function of sufficient magnitude to interfere with the activities of daily life. AD is characterized by diffuse and ultimately severe atrophy of the cerebral cortex—at the microscopic level the most characteristic findings are the senile plaques and the neurofibrillary tangles. Speculations concerning the cause and mechanisms of this disorder have been controversial. Currently, a leading hypothesis invokes the protein beta-amyloid as the neurotoxic substance which kills neurons subsequently leading to a deficiency of acetylcholine which in turn results in the decreased memory and cognitive decline. In accord with this hypothesis, a currently available symptomatic therapy for AD block the acetylcholinesterase enzyme to increase levels of acetylcholine thereby producing functional improvement. Amyotrophic lateral schlerosis (ALS) is a form of adult motor neuron disease which is confined to the voluntary motor system, with progressive degeneration of corticospinal tracts and alpha motor neurons at the level of the spinal cord. Clinically the disease is characterized by weight loss, muscle cramps, muscle fasciculations, limb weakness, gait disorder, dysarthria and dysphagia. Pathologically, ALS is typified by atrophy and death of the large motor neurons of the anterior horn cells of the spinal cord.

Given the proposed neurobiological effects of MW/RF fields on acetylcholine metabolism in the CNS, there is justification for seeking a clinically relevant effect of MW/RF fields on brain neurodegenerative disorders such as AD. Various hypotheses have been put forth pertaining to the relationships between various EMFs such as MW/RF fields and dementias such as AD. Unfortunately, the only studies of Alzheimer's disease and EMF exposure conducted thus far dealt with exposure to ELF (power line) fields, not RF. Given the results of these ELF studies, similar studies of RF are desirable. Sobel and Davanipour (1996) proposed that EMFs contributed to the neurodegenerative processes which underlie AD while Feychting et al. (1998) postulated that the brain damage caused by EMFs can predispose to AD. A small number of studies have evaluated these hypotheses. However, these studies are difficult to complete and interpretation of their results is limited and problematic. The utility of these studies is limited by inability to judge the quantity of the exposure, lack of validation of the exposure of the study population, small study populations, inadequate control groups, overlap between vascular dementia and AD type dementia, no autopsy verification of AD, dependence on caregivers for medical history, use of questionnaires to assess exposure and job history, failure to consider confounding role of heredity, and the use of death certificates in trying to assess de-

mentia. At the present time, there are no convincing, reproducible data to suggest a relationship between AD and MW exposure.

Similar to AD, amyotrophic lateral sclerosis (ALS) and motor neuron disease and their relationship to occupational exposure to electromagnetic fields have been studied epidemiologically (Davanipour et al., 1997). Studies such as these have significant limitations: small number of ALS cases, insufficient information on patient families, use of death certificates in establishing diagnosis, and variable criteria for control selection. As with AD, there are no convincing, reproducible data to establish any relationship between MW and ALS. Again, since studies of ALS have been restricted to ELF, similar studies with RF are needed.

Sleep disorders The potential relationship between MW exposure and sleep is an interesting one and has received significant study. These studies have evaluated the influence of MW/RF fields on both the characteristics of sleep and the EEG patterns of sleep. During 8 h of nocturnal exposure to a digital mobile telephone (0.05 mW/cm^2), humans showed no change in total amount of sleep and no change in total amount of slow-wave sleep. However, there was a shortening of sleep onset latency and a relative reduction of rapid eye movement (REM) sleep (Mann & Roschke, 1996). No effect was seen at 0.02 mW/cm^2 (Wagner et al., 1998). Although the frequency (24.12 MHz) was not in the MW range, Reite et al. (1994) showed that acute exposure of human subjects for only 15 min to amplitude-modulated radiation (0.1–100 mW/kg) resulted in a shortening of the sleep onset latency and an increase in stage 2 sleep. Similarly, Pasche et al. (1996) using amplitude-modulated 27.12-MHz radiation for 20 min, 3 times per week, produced a decrease in sleep latency and an increase in the total amount of sleep. These results on the influence of MW/RF fields on sleep architecture are provocative and interesting, but are in conflict with animal studies showing a significant increase in slow wave activity sleep. Because of the lack of consistency in the results of these various studies, no conclusions could be drawn; accordingly, this topic needs further examination in the future.

Depression, suicide, and behavioral effects Interest in the behavioral effects of MW/RF fields has a relatively long history. Clinical and laboratory studies of workers in the Soviet Union and other Eastern European countries employed in the manufacture, maintenance, and operation of RFR equipment have resulted in the description of a so-called "RFR syndrome" or a "neurasthenic syndrome" related to RF field exposure (Roberts & Michaelson, 1985). The symptoms of this syndrome are subjective and include irritability, fatigability, loss of appetite, sleepiness, poor memory, difficulties in concentration, emotional instability, depression, and headache. These symptoms were variable and had no pathological correlations. The symptoms were said to be reversible in most cases in which the MW/RF field exposure was ended. [Over the years, multiple reviewers of these data have repeatedly emphasized the marked difficulties in rigorously

establishing the existence and quantification of these relatively subjective complaints (Roberts & Michaelson, 1985)].

As a result of these early observations by Soviet scientists, psychologists and industrial physicians have conducted epidemiological and clinical studies of EMF-exposed patient populations to ascertain any changes in psychological function. An excess risk of suicide was noted in one case-control study of magnetic field exposed workers (Perry et al., 1981). However, subsequent studies found no such excess. Other European psychology studies using volunteers in controlled laboratory settings found no deficit in behavioral responses under exposure conditions (Sagan, 1992).

Recently, another subjective symptom has been receiving increased attention: headache. Frey (1998) has speculated that "headaches can be the canary in the coal mine, warning of biologically significant MW-induced effects." Frey points out that headaches as a consequence of exposure to low-intensity MW were reported more than 30 yr ago and that recent work on the role of the blood–brain barrier and dopamine–opiate systems in headache pathophysiology support a potential aetiopathogenic involvement of MW in headache. However, headache is a very subjective symptom which can be difficult to quantify and to study. A recent epidemiological study by Hansson Mild et al. (1998) supports headaches as a subjective symptomatic complaint.

To further evaluate these subjective and potentially confusing results in humans, recent behavioral studies have concentrated on the effects of MW in animals. Significant studies have been carried out by Lai and co-workers (Lai et al., 1987a, 1987b, 1987c, 1988, 1989a, 1989b, 1990, 1991, 1992a, 1992b, 1994). For example, Lai et al. (1992b) exposed benzodiazepine receptors in rat brains to 45 min of MW exposure per day for 10 d) with a SAR of 0.6 W/kg. The single exposure produced an increase in cerebral cortex benzodiazepine receptor density. Given the role of benzodiazepines as anxiolytic agents, the authors speculated on the role of MW in inducing a stress response. Next, to investigate subtypes of opioid receptors in the brain involved in the effect of this 45-min exposure to pulsed MW, rats were pretreated with microinjections of opioid antagonists. These experiments confirmed that endogenous opioids mediate MW-induced decreases in cholinergic activity in the hippocampus of the limbic system but not in the frontal neocortex. Expanding upon these investigations, Lai et al. (1994) examined the roles of endogenous opioid systems and cholinergic systems in MW-induced spatial memory deficits using a radial-arm maze paradigm. Male Sprague-Dawley rats demonstrated a deficit in working spatial memory function and thus showed retarded learning. This retarded learning could be blocked by pretreatment with either a cholinergic agonist or an opiate antagonist indicating that both cholinergic and opioid neurotransmitters are involved in MW-induced observed learning deficits in the CNS. D'Andrea and co-workers have also examined

behavioral effects in experimental animals (D'Andrea, 1989, 1994). For example, when adult male Long-Evans rats were exposed 7 h/d for 90 d to continuous-wave 2450-MHz MW at a power density of 0.5 mW/cm^2, a definite but unpredictable effect on a time-related operand task was documented (DeWitt et al., 1987).

Therefore, a body of data supports the notion of a potential biological effect of MW on behavior in experimental animals. The translation of this to a human effect is not immediately apparent. Clearly, this is an area in which more data and research is required.

Cognitive function A study by Preece et al. examines whether simulated mobile telephone transmission (at 915 MHz) has an effect on cognitive function in humans. Thirty-six subjects in two groups were each given a series of cognitive function tests under three different exposure conditions, blinded for the participants, in a randomized three-way crossover design. A physical copy of an analogue phone was mounted on the left ear and the apparatus was oriented in a normal position for use. Approximately 1 W mean power at 915 MHz from a quarter-wave antenna as a sine wave, or modulated at 217 Hz with 12.5% duty cycle, or no power, was applied to the left squamous temple regions of the subjects. Results were expected in April 1999.

Conclusions Headache and fatigue are nonspecific complaints. For example, many factors can cause headache. Headache is not an indicator of "brain activity," and in general headaches occur in the absence of structural abnormalities of either the brain or the blood–brain barrier. Given the high variability of headache as a symptom, correlating headache with some MW-induced neurochemical alteration is very difficult. Although there is need to consider the possibility of MW-induced symptoms such as headache and fatigue, existing data to do not support the conclusion that MW can induce headaches. Once again, this is an area that deserves further study before definitive conclusions can be drawn. However, the anecdotal relationship between MW exposure and headache underlies the need to carry out such studies.

Anecdotally and in some controlled studies, RF fields and MW have been implicated in contributing to deleterious brain effects. However, due to the inability to replicate, contradictory results, and procedural problems, these results are disputed. Other biological problems, such as BBB permeability changes, may be ascribed to localized brain temperature elevations and probably do not have any clinical relevance. Although the reported data cannot definitely exclude the possibility of RF fields/MW mediated neural damage, at present there is no evidence that RF fields or MW in either continuous or pulsed exposure in the nonthermal range presents any clinically relevant risk or hazard to brain function or neurologic health. Nevertheless, given the variety of data on the neurobiological effects of MW/RF fields, more data and study are indicated.

Ocular

During the past 40 yr, many studies in animals, as well as surveys in human populations, have assessed the relationship between exposure to RF fields and the subsequent development of ocular pathologies. In particular there has been great interest in the alleged cataractogenic effects of exposure to microwaves.

When evaluating the effects of MW on the human eye, the structural uniqueness of the eye must be considered. First, when anatomical structures attempt to dissipate the effects of electromagnetic fields, such as thermal effects, they depend upon their inherent vascularity (i.e., richness of blood supply). The brain, for example, is richly vascularized and thus can dissipate heat, whereas, the eye has reduced vascularity in order to preserve optical clarity. Second, the eye is situated in a particularly vulnerable location. The brain enjoys a degree of protection from electromagnetic fields through the shielding effects of the skull; the eye does not enjoy this degree of bone protection. Finally, the eye may have artificial objects placed in front of it (e.g., glasses), which have the potential to alter the physical effects of electromagnetic fields. For example, it is theoretically possible for the metal arms of glasses to act as a "heat sink" for thermal effects. Therefore, although the eyes are an extension of the brain, their anatomical uniqueness must be appreciated when examining the potential effects of RF fields.

In evaluating the ocular effects of microwaves, extensive work has been carried out by Kues and co-workers. For example, to study the ocular effects of MW, Kues et al. (1985) exposed *Macaca fascicularis* to 2450-MHz CW (SAR = 5.3–7.8 W/kg) or pulsed microwaves for 16–48 h repeated at different intervals. Corneal endothelial abnormalities appeared after a 16-h latency period. Next, Kues and D'Arma (1987) studied a microwave-potentiated increase in vascular permeability in monkeys. Anesthetized monkeys were exposed to 2450-MHz pulsed microwaves on 3 consecutive days for 4 h each day. A clear correlation between the MW-induced iris vascular permeability change and the subsequent development of corneal endothelial lesions was demonstrated. Kues has also studied the influence of MW on commonly used ophthalmic drugs (Kues et al., 1992).

However, there are problems with currently available studies pertaining to the ocular effects of MW. Most studies have come from two research groups and the results are conflicting. Adverse effects are reported by Kues et al., but Kamimura et al. (1994) reported no such effects. Kues's experimental designs used small sample sizes, and different numbers of exposures for different animals. There are also differences in the use of continuous-wave versus pulsed doses. While it is true that Kues's results have not been reproduced, it is also true that no one has tried to do so in a rigorous fashion.

Issues of experimental design are also important in considering ocular effects. It is significant that of the many experiments on rabbits, none have demonstrated a time–power threshold for cataractogenesis (this

threshold is considerably higher for dogs and nonhuman primates). Moreover, in this particular area of research there appear to be numerous problems with reproducing studies due to the difficulties of experimental design.

In conclusion, high-level exposure to microwave-emitting sources may produce adverse effects in the eye, particularly in the retina, lens, iris, and cornea. The mechanisms responsible for ocular damage involve changes in either corneal or iris endothelial functions that may or may not be temperature related. At the present time, no definitive conclusions can be reached regarding RF field exposure and effects in the eye. Further research is indicated. The unique properties of the eye make this an area that should be treated with caution and concern.

Cellular Phones and Motor Vehicle Accidents

One area where an association has been demonstrated between cellular phone use and health risk is in the area of motor vehicle accidents. Ecological studies of the relationship between cellular phone use and traffic accidents have been shown to be inappropriate because the biases involved in even the most rigorous of these analyses are still large enough to hide any association (Min & Redelmeier, 1998). A recent Canadian study used a different method to examine this potential relationship (Redelmeier & Tibshirani, 1997; Tibshirani & Redelmeier, 1997). In this study of 699 drivers involved in motor vehicle accidents, where there was no personal injury but there was property damage, elevated risks from the use of cellular phones were found. This study employed a case-crossover design: comparing the drivers' cellular phone usage immediately before the time of the accident to that during various control periods. Adjusting for intermittent driving, drivers had a 4.3 times higher risk (95% confidence interval 3.0–6.5) of having a motor vehicle accident within 15 min of talking on a cellular phone than they had in periods when they did not use the phone. These results were stable across subgroups. Furthermore, the authors did not find any reduction in risk resulting from the use of hands-free phones instead of hand-held units.

Although this study clearly shows an association, it does not necessarily indicate a causation. For example, the increased phone calls and the collision could both be the result of some underlying distraction, or state of stress. Nevertheless, as Redelmeier and Tibshirani point out, the risks that they uncovered are comparable to those associated with a level of alcohol in the bloodstream just at the legal limit.

Radiofrequency Radiation Sickness Syndrome

Radiofrequency radiation (RF) sickness syndrome has been defined as a systemic human response to chronic low-intensity RF exposure. RF sickness symptoms include headache, ocular dysfunction, fatigue, dizziness, and sleep disorders (Hill, 1984). While RF sickness remains a controversial topic in the United States, it has enjoyed some level of recognition in

the former Soviet Union (Silverman, 1973). In North America, the tendency has largely been to dismiss this syndrome. Overall studies have tended to be subjective and to suffer from an awareness bias. Nevertheless, RF sickness syndrome has been legally recognized as "microwave radiation sickness" (New York Appellate Court, 1982).

In *Soviet Medicine* (Mitchell, 1985) the following clinical manifestations were accepted: dermographism, tumors, hematological alterations, reproductive and cardiovascular abnormalities, depression, irritability, and memory impairment (among others). In 1978, Justesen et al. (1979) recognized that Soviet research had "ecological validity," but they did not endorse the safety standard for the public (i.e., 10 mW).

North American literature contains some data in support of the RF sickness syndrome as a medical entity. Occupational studies (Hill, 1984; Silverman, 1973; McRee, 1972; Steneck et al., 1980; Goldsmith, 1992; McLees & Finch, 1973; Isa & Noor, 1991; Lilienfeld et al., 1978a, 1978b; McLaughlin, 1957; Williams & Webb, 1980; Castillo et al., 1988; *Microwave News,* 1993; U.S. EPA, 1995; NIEHS Working Group Report, 1998) conducted between 1953 and 1991 and clinical cases (McLaughlin, 1957; Williams & Webb, 1980; Castillo & Quencer, 1988; *Microwave News,* 1993) of acute exposure between 1957 and 1993 are quoted as evidence for the syndrome. Consequently, in 1995, the U.S. Environmental Protection Agency (EPA) and the National Council on Radiation Protection stated the need to formally address the health hazards of modulated RF radiation (U.S. EPA, 1995). However, the agency stressed the need for properly conducted, double-blind experiments and expressed the view that the data to date left considerable room for skepticism.

A recent survey of the literature concerning similar adverse health effects due to electromagnetic radiation (EMF) concluded that there was inadequate evidence for EMF-associated sickness including depression, suicide, and mood disturbances (NIEHS Working Group Report, 1998). The need for double-blind experimental design is considered essential and, despite several reports of negative health effects, none of eight double-blind experiments revealed any effect at all (NIEHS Working Group Report, 1998), though it was acknowledged that some individuals may "know" when they are exposed to such fields (NIEHS Working Group Report, 1998).

Summary

Epidemiological studies conducted to date have focused on cancers among adults and children, reproductive outcomes, and congenital anomalies. Studies of radio frequency fields and adult cancers have been conducted in occupational groups, such as military personnel, electronics workers, medical workers, and industrial groups. Only two studies (in Great Britain and Australia) have examined residential exposures. The types and levels of exposures ranged from ELF to RF, microwave, and ionizing radiation, complicating the interpretation of the results. Rothman et al. (1996)

examined the mortality experience of users of portable telephones and mobile telephones in the United States. They found no difference in mortality in comparison with other telephone subscribers; however, the period of follow-up was limited. Planned and ongoing studies of cellular telephone risk will provide important information on potential cancer risks in the future, including a multicountry case-control study of cancers of the head and neck currently being organized by the International Agency for Research on Cancer.

Although studies of childhood cancer have been conducted among children living close to TV and FM radio transmitter towers, such ecologic investigations are difficult to interpret, particularly in the absence of information on individual exposures. Case-control and cohort studies of radiofrequency field exposures and reproductive outcomes have failed to produce consistent results.

Radiofrequency radiation has been implicated in neural damage through case reports and limited clinical investigations, although the significance of these findings remains unclear in the absence of replication. Ocular effects have been the subject of several investigations in primates; however, the results available to date are contradictory. Because of the unique physiological characteristics of the eye, further studies in this area are needed.

The use of cellular telephones while driving has been associated with an increased risk of motor vehicle accidents, although this represents a safety rather than health concern. The panel did not find persuasive evidence of the existence of radiofrequency radiation sickness syndrome; however, some individuals may be able to sense when they are exposed to radiofrequency fields.

CONCLUSIONS

At the request of Health Canada, the Royal Society Expert Panel on Radiofrequency Fields conducted a comprehensive review of the potential health risks associated with exposure to radiofrequency fields. The objective of this review was to examine the potential biological and health effects from exposure to RF fields resulting from the use of wireless telecommunications technology. The panel was asked to address a number of questions, including whether the guidelines for worker and general public exposures to RF field laid out in the most recent revision of Health Canada's Safety Code 6 are adequate.

Based on its review of the currently available scientific data, the panel concluded that Safety Code 6 protects both workers and the general public from adverse health effects associated with whole-body thermal exposures to radiofrequency fields. Although the whole-body exposure limits given in Safety Code 6 appear to be protective against thermal effects of RF fields, the panel noted that protracted exposures of workers at the local

SAR limits of 8 W/kg for the head, neck, and trunk and 20 W/kg for the extremities could lead to thermal effects. Because Safety Code 6 does not specify a limit on exposure duration, this would permit occupational exposures at these levels 8 h/d, 5 d/wk. The panel further noted that while the U.S. Food and Drug Administration uses similar SAR limits (8 W/kg for the head, neck, and trunk, and 12 W/kg for the limbs) for patients undergoing MRI examination, the duration of such exposures is limited to 5 min. Consequently, the panel recommended that these local exposure limits for worker exposures be reviewed with respect to both intensity and duration of exposure. If necessary, the panel recommends that additional research be conducted to provide an adequate scientific basis for this review.

The panel noted that although exposure limits for the head, neck, and trunk given in Safety Code 6 also apply to the eye, Safety Code 6 suggests that even lower exposures for the eye are desirable. Because of the unique physiological characteristics of the eye, the panel recommends that the exposure limits given in Safety Code 6 for the eye be reviewed as new scientific information becomes available. Due to the lack of exposure duration limits, the expert panel recommends the lowering of the dose to the eye of RF workers to that recommended for the general public (1.6 W/kg) as an interim measure.

It is clear to the panel that there are a number of observed biological effects of exposure of cells or animals to nonthermal levels of exposure to RF fields. These observed biological effects meet the common standards for scientific observation in that the experiments were well designed, had appropriate positive and/or negative controls, contained valid RF exposure parameters, included appropriate statistical evaluation of the significance of the data, and have been observed to occur by more than one investigator (see body of report for details).

The importance of these observed biological effects mediated by nonthermal levels of RF exposure in relation to regulation of RF exposure to the human population as outlined in Safety Code 6 lies in the degree of association of these biological effects with documented health effects. Not all of the biological effects observed in cells and animals following exposure to a variety of stimuli result in adverse health effects to the organism. For example, when a phone rings, a person can hear the sound, is capable of responding to the sound by picking up the phone, or, in some cases, may be startled in response. Clearly, this is a biological effect that does not have any overt adverse health effects on the organism. For this reason, the panel was particularly sensitive as to whether the biological effects that have been observed in cells and animals following RF exposure have been documented by additional studies to show adverse health effects in the exposed organism. The panel found no evidence of documented health effects in animals or humans exposed to nonthermal levels of radiofrequency fields. The panel therefore does not recommend that

Safety Code 6 be altered to include regulation at the nonthermal levels of RF that have been shown to produce these biological effects.

If the specific biological effects observed following nonthermal levels of RF exposure had been of a nature that was more closely related to an effect known to be more causally linked to adverse health effects, the panel might have recommended inclusion of these nonthermal exposure levels in reformulating Safety Code 6. For example, if RF exposure had caused a specific mutation in a gene with a known relationship to causing cancer (e.g., mutations at known sites on protooncogenes that would turn them into mutated functional oncogenes), and if the dose and time dependence of exposure in relation to this observed effect were clearly understood, the panel might have recommended regulation of nonthermal RF fields, even in the absence of observable adverse health effects in RF-exposed animals or humans. However, the specific biological effects that have been observed in relation to nonthermal RF exposure, while correlative in their association with adverse health effects, were not appropriately causative in nature. The time and dose parameters that relate exposure to nonthermal RF fields to the intensity and duration of the specific biological effect in question have also not been clearly delineated. The panel also believes that many of the studies in humans and animals addressing the potential for adverse health effects do not have sufficient power to rule out completely any possibility of such effects existing. The panel supports additional research in this area.

Studies of exposed human populations provide the primary means of directly assessing the potential effects of RF fields on human health. Epidemiological studies reported to date have been largely uninformative because of methodological limitations. Although the potential health effects from exposure to radiofrequency fields from cellular telephones are being examined in ongoing epidemiological investigations, no results have yet been reported. The panel recommends that the results of these investigations be carefully reviewed when completed, and any implications for Safety Code 6 be carefully considered.

The panel is unaware of any ongoing epidemiological investigations focusing on population groups living near base-station transmitters. However, since public exposures in the vicinity of base-station transmitters are very low, the panel considers such epidemiological investigations to be of lower priority because they have low potential to provide useful information.

Since cellular telephones and similar devices have been in use for a relatively short period of time, further observation may be required to fully examine potential health effects due to long-term exposure to RF fields. With the exception of hand-held mobile phone devices using low-earth satellite systems, most of the new generations of communication devices operate with significantly lower output power, but at microwave frequencies inadequately investigated for human health effects. The

potential effects of ELF modulation of the RF signal also warrant attention. Recent scientific advances provide important opportunities for investigations with the level of sophistication required to address these issues.

RESEARCH RECOMMENDATIONS

Based on its review of the currently available scientific literature, the panel recommends that further research into the potential health effects of radiofrequency fields be conducted, particularly in the area of nonthermal effects. This research will require the collaborative efforts of researchers with expertise in a number of diverse areas, including engineering, radiation dosimetry, and the biological and health sciences.

The committee identified four distinct scientific approaches to further our knowledge of RF fields. In vivo and in vitro laboratory experiments conducted at both the cellular and animal level can be used to obtain information on the potential adverse health effects of radiofrequency fields using nonhuman test systems. Molecular studies provide an opportunity to elucidate the mechanisms by which biological effects occur at nonthermal exposure levels, thereby providing a basis for evaluating the significance of such biological effects. Clinical studies may be particularly useful in identifying susceptible population subgroups. Epidemiological studies are needed to monitor the potential health effects of long-term exposure to radiofrequency fields.

Laboratory Studies

Because the potential impact of RF fields on human health is not yet well characterized, there is a need for well-designed laboratory studies of relevant endpoints based on cellular and animal test systems. While these experiments may not be mechanistically based nor produce positive results, they are required to identify potential health consequences of RF exposures.

Laboratory-based studies should include many of the traditional assays for genotoxicity, with particular emphasis on in vivo mammalian experiments. Specific endpoints of interest include mutations in transgenic animals, chromosomal aberrations, and tumorigenesis in sensitive transgenic rodents. Assays, such as the Comet assay, that measure DNA damage are also important. In vitro studies of importance include mammalian cell studies of transmembrane signal transduction, mutation, cell transformation, and initiation/promotion.

Specific questions to be addressed include those listed here. The first question should be assigned a high priority in light of the limited information on the potential effects of RF fields on the eye noted previously.

- What are the potential ocular effects, including cornea and retinal pathology? To investigate this question, both in vitro and in vivo models should be utilized.

- Does RF radiation affect melatonin production and/or secretion?
- What are the effects of RF radiation on the opioid and cholinergic systems? This should be evaluated using both in vivo (behavioral) assays and in vitro (mammalian cells with opioid and cholinergic receptors) assays.
- Are there any RF effects on cellular proliferation for which the situation of local SAR deposition from devices like cellular phones may be important?
- How does RT exposure affect transmembrane ion transport—which is fundamental to brain function and electrical activity? Neuronal cell cultures could be used to investigate this question.
- What are the potential effects of RF field on the blood brain–barrier? A blood–brain barrier in a bottle—cultured capillary endothelial cells—could be used for evaluating potential effects.
- Are there neurodegenerative changes associated with RE fields (such as accumulation of amyloid related to Alzheimer's disease)? This investigation should involve the histopathology staining of neural tissue of appropriate research animals (amyloid does not occur in rodents) subjected to prolonged exposure to RF fields.
- Does ELF modulated RF exposure affect transmembrane signal transduction in mammalian cells, specifically cytosolic free calcium concentrations?

One important area of research that has been neglected involves the complexity of the communication protocols used in wireless telecommunications. These protocols often involve the use of a carrier radiofrequency (such as 900 MHz) as well as a pulse sequence (such as 217 Hz). Since exposures to RF fields may thus occur in combination with ELF, the possibility of effect modification by ELF warrants investigation.

- Are there any biological effects that result from specific ELF modulations of the carrier wave (TDMA, CDMA, GSM, IRIDIUM)? This should be evaluated using in vitro and in vivo (behavioral) biological models.

Studies of the Biochemical Mechanisms of Biological Effects

Studies need to be done to identify the biophysical detection mechanism that detects RF radiation and is sensitive to RF characteristics. Greater knowledge of this detection mechanism may enable the design of RF pulses that will be less likely to induce undesirable biological effects. To do this, the following questions need to be examined.

- What is the effector molecule involved in the biophysical detection mechanism for RF fields?
- What molecular interaction is involved between RF fields and the biophysical detection mechanism?

- How does the biophysical detection mechanism respond to the physical characteristics of RF fields, including carrier frequency, extremely low frequency (ELF) modulation, variation in power density, and electric and magnetic field polarity?

Clinical Studies

The possibility that certain population subgroups may be more sensitive to RF fields needs to be addressed. This issue can be examined in a clinical setting as outlined here.

- Are there people who are potentially more sensitive to radiofrequency fields? A double-blind challenge could be used to address this question.
- What are potential subgroup effects? For example, do epileptics have more seizures due to RF exposure from cell phones?
- Are there any identifiable markers for electrical hypersensitivity? This could be evaluated using accepted neurologic tests and endpoints such as Uthoff's phenomenon.
- What are the response patterns to RF exposure of human brain activity?

Epidemiological Studies

Continued epidemiological studies are essential, as they provide the only means of directly identifying and characterizing the potential effects of RF field exposure on human health. Microwave communications, including cellular telephones, have not been in general use for a duration sufficient for all potential health effects to have emerged. Not only is the use of this mode of communication expanding, but future systems will use radiofrequencies and protocols with divergent characteristics. Therefore, even though the trend in the industry is to reduce power emissions from devices, the range of radiofrequencies and transmission characteristics of the future will be different than those currently in use.

Although there is no epidemiologic evidence to date to suggest specific health effects from RF exposure, several health outcomes have been hypothesized, including cancer and cardiovascular malfunction. Additional epidemiological studies that may be informative include the following:

- Additional studies on exposure characterization of exposed population groups, including source, exposure, and extent of individual variation in exposure.
- Epidemiological studies of highly exposed groups, such as occupationally exposed populations, where there would be greater opportunity to identify adverse health effects.
- A cohort study of cell-phone users would allow assessment of multiple health endpoints in an exposed population. This design is of interest since the potential adverse health effects warranting further investigation are not clear.

The panel considered epidemiologic studies of populations living near base-station transmitters to be less valuable, given the low radiofrequency fields in the vicinity of these transmitters.

Research Funding

Since answers to these complex questions will not reveal themselves immediately, the panel would prefer that targeted research funds be made available for an extended period of 5–10 yr. Further, the panel strongly recommends that research initiatives designed to address these questions be investigator initiated and peer reviewed.

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MEMBERS OF THE PANEL

Craig V. Byus, *Division of Biomedical Sciences, University of California at Riverside, Riverside, California USA*

Dr. Byus holds a PhD in biochemistry from the University of New Hampshire, was a postdoctoral in the Department of Pharmacology at the University of Arizona Medical Center, and has been a faculty member in the Division of Biomedical Sciences and the Department of Biochemistry at the University of California, Riverside, for the past 21 years. Dr. Byus is currently a professor of biomedical sciences and biochemistry whose teaching duties include acting as course coordinator for the Medical Pharmacology course given to second-year medical students. Dr. Byus's research, since he was a graduate student, has centered around the role of polyamines and ornithine decarboxylase in the normal and neoplastic growth of cells and tissues. He has studied extensively the ability of both ELF and low-frequency-modulated RF exposure to cells and animals to lead to alterations in polyamine biosynthesis. For the past 5 years he has also been involved with long-term animal cancer bioassays designed to determine the risk of radiofrequency exposure to lead to brain tumors in exposed animals. His current efforts have expanded to the determination of thermal thresholds and markers of RF-exposed animals. (This work was supported by the Motorola Corporation.) Dr. Byus has served on numerous expert panels and review committees in relation to chemical carcinogenesis and in relation to ELF and RF. He was a member of the Metabolic Pathology Study Section at the National Institutes of Health, was a member of the Scientific Advisory Panel for the review of the RF risk assessment document for the U.S. Environmental Protection Agency, and is a past member of the Board of Directors of the Bioelectromagnetics Society. Dr. Byus is also currently a member of the Scientific Advisory Panel for the Air Resources Board for the State of California. During his tenure on the Scientific Advisory Panel, he has been closely involved in extensive risk assessment for a variety of airborne chemicals including lead, diesel exhaust, and environmental tobacco smoke.

Barry W. Glickman, *Department of Biology, Centre for Environmental Health, University of Victoria, Victoria, British Columbia, Canada*

Dr. Glickman is a molecular geneticist with experience in mutagenesis and carcinogenesis, evolution, and molecular biology. He received his BSc and MSc in genetics from McGill University and his PhD in molecular genetics from the University of Leiden. He served as an expert in microbial genetics at the National Institute of Environmental Health Sciences in North Carolina and as an adjunct professor in pathology at the University of North Carolina, Chapel Hill, before accepting an appointment as professor of

biology at York University in 1984. Dr. Glickman moved to the University of Victoria to become Director of the Centre for Environmental Health in 1991. Dr. Glickman's main research has involved analyzing the genetic material of organisms exposed to particular environmental hazards. In studying *E. coli,* mice and rats that had been exposed to specific mutagens including chemicals, ionizing radiation, UV light, and EMF, he demonstrated that each such agent produces a unique spectrum of changes in the DNA. Such mutational spectra are, in effect, a kind of DNA fingerprint enabling investigators to pinpoint the specific environmental agent causing the mutations. He has verified his findings in both mammalian cell cultures and animal model systems. Studies of mutation by the sequencing of mutations led to important discoveries of the role of DNA sequence in directing the nature of mutation. More recently, Dr. Glickman has been the study of mutation in people *in vivo.* Several studies have been carried out including the study of radiation accident victims in Brazil, Soviet cosmonauts, chemo- and radiotherapy patients, and young and the elderly. Work has also been initiated with cancer patients to investigate the question of individual susceptibility. Why some people develop cancer while others do not is a major issue in the cancer world.

Daniel Krewski, Panel Chair, *Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada*

Dr. Krewski is currently professor of medicine and professor of epidemiology and community medicine at the University of Ottawa, where he is involved in a number of activities in population health risk assessment within the new Institute of Population Health. He has also served as adjunct research professor of statistics in the Department of Mathematics and Statistics at Carleton University since 1984. Prior to joining the Faculty of Medicine at the University of Ottawa in 1998, Dr. Krewski was Director, Risk Management in the Health Protection Branch of Health Canada. He is a Fellow of the Society for Risk Analysis and a Fellow of the American Statistical Association. Dr. Krewski has contributed to over 300 publications in the scientific and technical literature, and is author or editor of five books. He is currently an associate editor of *Risk Analysis, Risk Abstracts,* and the *Journal of Epidemiology and Biostatistics*.

W. Gregory Lotz, *Physical Agents Effects Branch, Division of Biomedical and Behavioral Science, National Institute for Occupational Safety and Health (NIOSH), Cincinnati, Ohio, USA*

Dr. Lotz is currently chief of the Physical Agents Effects Branch, Division of Biomedical and Behavioral Science, at the National Institute for Occupational Safety and Health (NIOSH) in Cincinnati, OH. He holds the rank of Commander as a commissioned officer in the U.S. Public Health Service. Dr. Lotz received a BS in physics from Heidelberg College, and MS

and PhD degrees in biophysics from the University of Rochester School of Medicine and Dentistry, Rochester, NY. His duties at NIOSH include planning and supervising the NIOSH research programs in the health effects of physical agents (noise and nonionizing radiation), and managing the operation of the branch. He is also actively involved in NIOSH research on the bioeffects of electromagnetic fields with particular emphasis on occupational exposures to both extremely low frequency (ELF) fields and radiofrequency radiation. He is cochair of the NIOSH EMF Working Group. Dr. Lotz has been an active researcher in the bioelectromagnetics area for over two decades, with numerous publications on the physiological responses of animals exposed either to ELF fields or RF radiation. Prior to joining NIOSH, he worked for many years at the Naval Aerospace Medical Research Laboratory in Pensacola, FL. He is a member of the Bioelectromagnetics Society, the American Physiological Society, the American Association for the Advancement of Science, and the Commissioned Officers Association of the U.S. Public Health Service. He serves as a NIOSH representative to U.S. federal interagency working groups for both ELF and radiofrequency radiation health research, and as the NIOSH liaison for the World Health Organization's International EMF Project. He is a member of the Board of Directors of the Bioelectromagnetics Society. He is also a member of Scientific Committee 89-5, "Biological Effects and Exposure Criteria for Radiofrequency Electromagnetic Fields," of the National Council on Radiation Protection and Measurements (NCRP), and is on two subcommittees of the IEEE Standards Coordinating Committee 28, namely, Subcommittee 4 on Safety Levels with Respect to Human Exposure, 3 kHz–300 GHz; and Subcommittee 3, Safety Levels with Respect to Human Exposure, 0 to 3 kHz.

Rosemonde Mandeville, *Biophage, Inc., Montréal, Québec, Canada*

Dr. Mandeville is president and chief executive officer of Biophage, Inc. For Dr. Mandeville, the creation of Biophage is the culmination of a distinguished career spanning over 25 years of research in oncology, immunology and bioelectromagnetism. Dr. Mandeville sits on the board of directors of Investissement Quebec, Garantie Quebec, the Cancer Research Society, and la Fondation Armand-Frappier. Dr. Mandeville received her medical degree from the University of Alexandria, Egypt and her PhD from the University of Manitoba. She is the author of 64 publications and 180 scientific communications in peer reviewed international journals, has participated in more than 100 international meetings, and is the author of six books. Dr. Mandeville has supervised 27 master's degree and PhD students, 13 postdoctoral fellows, and 36 undergraduate students. Among Dr. Mandeville's notable scientific achievements is the development of a portable kit for the detection and identification of trichotecenes (allegedly used in biological warfare) for the Canadian Department of National Defense. Among the prestigious awards and distinctions bestowed

on Dr. Mandeville over the years are the "Dame de Mérite"—one of the world's most ancient decorations—given in 1989 by the Sovereign Order of St. John of Jerusalem (the Knights of Malta); named in 1996 among the 25 most promising scientists in Quebec; and selected by the Musée de la Civilisation in Quebec City in 1996 as the most valuable scientist in the medical field who has enriched the Quebec society by her work. Le "Salon de la femme" chose her the scientist of the century in April 1997.

Mary McBride, *Cancer Control Research Unit, British Columbia Cancer Agency, Vancouver, British Columbia, Canada*

Mary McBride has been an epidemiologist at the British Columbia Cancer Agency since 1980. She is active in the agency's Paediatric Tumour Group, cochairs the Etiology Working Group of the Canadian Childhood Cancer Surveillance and Control Programme (CCCSCP) of Health Canada, and is a part of the Management Committee of that program. Additionally, she is a member of the Children's Cancer Group, a North America-wide research group for childhood cancer. She is currently acting director of the BC Cancer Registry, and a member of the Board of the North American Association of Central Cancer Registries. Her interests relate either to childhood cancers, cancer control research, or both. She is a co-principal investigator of a large epidemiologic investigation into risk factors, including power-frequency electric and magnetic fields, for development of childhood leukemia.

Frank Prato, *Lawson Research Institute and Imaging Sciences Division, Department of Diagnostic Radiology and Nuclear Medicine, St. Joseph's Health Centre, London, Ontario, Canada*

Dr. Prato received his MSc in nuclear physics in 1971 and a PhD in medical biophysics in 1976, both from the University of Toronto. In 1980, he was elected to Fellowship in the Canadian College of Physicists in Medicine and in 1991 received certification in the American Board of Medical Physics. He is presently associate scientific director of the Lawson Research Institute and chair of the Imaging Sciences Division, Department of Diagnostic Radiology and Nuclear Medicine. Dr. Prato has an active research program in medical imaging, including the areas of cardiac magnetic resonance imaging and nuclear medicine brain imaging. Also, since 1982, he has been investigating nonthermal effects of magnetic fields from magnetic resonance imaging systems.

Donald Weaver, *Department of Chemistry, Faculty of Medicine, Queen's University, Kingston, Ontario, Canada*

Dr. Weaver received his MD in 1981 and PhD in 1986, both from Queen's University. He also completed a residency in clinical neurology at Dalhousie University receiving his FRCP(C) in 1989. In 1987 he was elected to Fellowship in the Chemical Institute of Canada. Presently he is

professor of chemistry and professor of medicine (neurology) at Queen's University, Kingston. Dr. Weaver currently has an active research program concerning the applications of quantum pharmacology calculations to the design and synthesis of molecules for the treatment of dementia and epilepsy.