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TECHNICAL REPORT

Carcinogenic Properties of Ionizing and Non-ionizing Radiation

Volume II - Microwave and Radiofrequency Radiation

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health

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A CURRENT LITERATURE REPORT ON THE CARCINOGENIC PROPERTIES OF IONIZING AND NON-IONIZING RADIATION

II. Microwave and Radiofrequency Radiation

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PREFACE

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and safety of workers exposed to an ever-increasing number of potential hazards at their workplace. To provide relevant data from which valid criteria and effective standards can be deduced, the Division of Biomedical and Behavioral Science of the National Institute for Occupational Safety and Health conducts a formal program of research and information dissemination. The users of this information include basic and clinical researchers, legislators, research and biohazards administrators, occupational safety and health professionals, teachers, and students.

In keeping with its mandate, the Division of Biomedical and Behavioral Science requested The Franklin Institute Research Laboratories' Science Information Services to review the world's biomedical literature and to prepare a general reference document on the known or potential carcinogenic hazards of occupational exposure to ionizing and non-ionizing radiation. The purpose of the study was 4-fold:

1. to identify and document radiation types which have been shown to be actual or potential carcinogens;
2. to review recent findings, regarding (a) current substantive issues and (b) impressions of distinguished investigators regarding the types of cancer induced by radiation, carcinogenic dose-response relationships, radiocarcinogenic mechanisms, and synergistic (co-carcinogenic) effects;
3. to predict the expected excess of cancers (or, for potentially carcinogenic types of radiation, the potential risk of cancer) either under commonly encountered conditions of occupational exposure or at the currently accepted maximum permissible dose limits; and
4. to identify specific gaps in the present knowledge of radiation carcinogenesis, and to recommend specific areas in need of further investigation.

In the course of the Franklin Institute study, five types of radiation were examined: ionizing, ultraviolet, visible, infrared, and microwave/radiofrequency radiation. The range of energies, frequencies, and wavelengths for each of these is as follows:

Type of Radiation	Energy Range	Frequency Range	Wavelength Range
Ionizing	above 12.4 eV	above 3,000 THz	below 100 nm

Type of Radiation	Energy Range	Frequency Range	Wavelength Range
Ultraviolet	6.15-3.08 eV	1,500-750 THz	200-400 nm
Visible	3.08-1.76 eV	750-428 THz	400-700 nm
Infrared	1.76 eV-1.24 meV	428 THz-300 GHz	700 nm-1 mm
Microwave	1.24 meV-1.24 μeV	300 GHz-300 MHz	1 mm - 1 m
Radiofrequency	1.24 μeV-1.24 neV	300 MHz-300 kHz	1 m - 1 km

Due to the volume of material, the study was limited to literature published since 1970, with only brief supplemental use of older materials when needed. The study is being published in three volumes:

I. Optical Radiation (Ultraviolet, Visible, and Infrared);
II. Microwave and Radiofrequency Radiation; and
III. Ionizing Radiation.

The present volume documents the current status of knowledge regarding the potential carcinogenic hazards of occupational exposure to radiofrequency (RF) and microwave (MW) radiation. A subclassification of the different regions of RF/MW radiation is given below.

	Energy Range	Frequency Range	Wavelength Range
Microwaves	1.2 meV-1.2 μeV	300 GHz-300 MHz	1 mm - 1 m
EHF	1.2 meV-100 μeV	300-30 GHz	1 mm - 10 mm
SHF	100 μeV-12 μeV	30-3 GHz	10 mm - 100 mm
UHF	12 μeV-1.2 μeV	3 GHz-300 MHz	100 mm - 1 m
Radar	200 μeV-900 neV	56 GHz-220 MHz	5.4 mm - 1.3 m
Radiofrequency	1.2 μeV-1.2 neV	300 MHz-300 KHz	1 m - 1 km

The information reported has been gathered from the original literature, from the proceedings of international symposia, and from reviews by distinguished investigators in the field. The authors' intent is to present a general non-technical overview with selective follow-ups. Since the bulk of the literature dealing directly with RF/MW-induced cancer contains unconfirmed and unscientifically reported allegations (generally published in non-technical or popular journals), an interpretive approach has been followed throughout the present volume. A general review of the biological effects of occupational exposure to RF/MW radiation has also been included from the point of view of identifying those effects which might enhance an already carcinogenic or potentially carcinogenic situation.

Throughout the present volume, the power density of distant RF/MW fields is reported in milliwatts/square centimeter (mW/cm^2). A distant or far field is defined as one in which the distance between the source and absorber exceeds $2a^2/\lambda$, where a is the greatest distance between points in the source (the reflector diameter in reflector antennas) and λ is the wavelength of RF/MW radiation. In near RF/MW fields, the size and geometry of the source are critical, and the electric and magnetic field strengths of the incident radiation are reported independently, when given. The units of measurement for these latter quantities are volts/meter (V/m) and amperes/meter (A/m).

Were the power absorbed by biological materials dependent solely on the field strengths of external RF/MW fields, the latter quantity could also be used as a measure of the biological dose. However, the amount of RF/MW radiation absorbed by biological materials depends on many factors, including the frequency, the material's degree of hydration, and its dielectric constant (ε), magnetic permeability, and electrical conductivity. The absorber's physical dimensions, its geometry, and its angle with respect to the incident radiation are also important since the combination of curved surfaces and high ε can sharply focus RF/MW radiation (McRee, 1972; Romero-Sierra et al., 1974; and Baird et al., 1974). Goldstein & Sisko (1974) have measured absorbed dose rates of 14-40 W/kg in rabbit heads exposed to 7-20 mW/cm^2 external MW fields. For materials with similar dielectric properties, such as experimental animals, the size of the animal relative to the wavelength is the primary factor governing RF/MW power absorption. The maximum absorption occurs at approximately 70 MHz in humans and 7-9 GHz in mice.

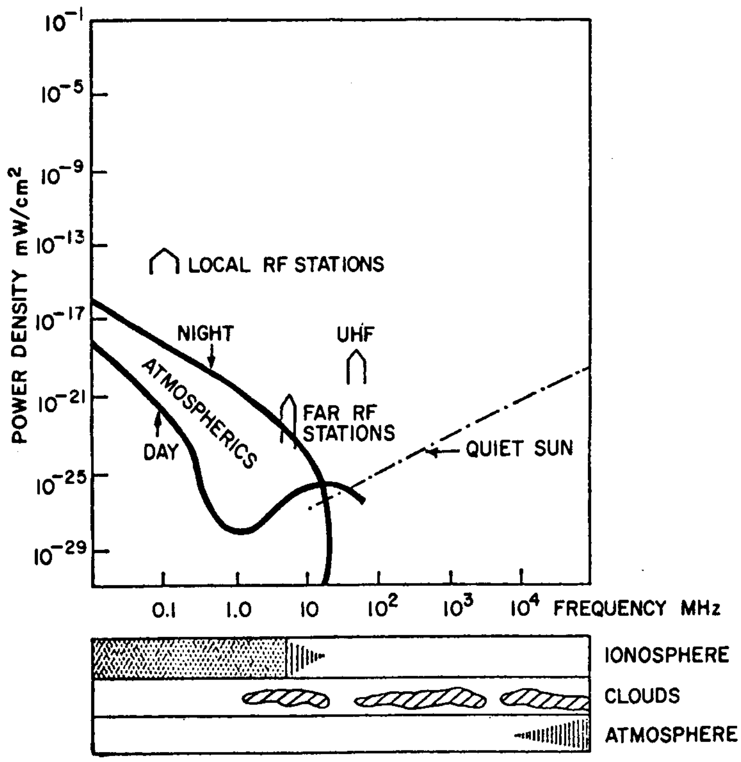
The biological effects of RF/MW radiation are usually designated as thermal or nonthermal in nature. Thermal effects result from the heating of body tissues by RF/MW radiation. The heating effect is similar to that produced by conventional thermal techniques although the exact distribution of hyperthermia in the body can not be duplicated exactly. Nonthermal effects involve minute temperature changes and are less clearly understood. They appear to result from a direct interaction between the electromagnetic field and biological materials. Experimentally, the distinction between the two types of effects (thermal vs. nonthermal) is often made on the basis of the power density of the external RF/MW field. In 1973, an International Symposium on the Biologic Effects and Health Hazards of Microwave Radiation was held in Warsaw, Poland (see Czerski et al., 1974), and the following external field intensity ranges were adopted:

Effect	Range
Thermal, heating	> 10 mW/cm^2
Thermal, non-heating	1-10 mW/cm^2
Non-thermal	< 1 mW/cm^2

These differ only slightly from the ranges proposed by Romero-Sierra et al. (1974) and at a 1972 meeting at the New York Academy of Sciences (Liboff & Rinaldi, 1974), at which the lower limit for the more subtle thermal, non-healing effects was taken as 0.1 mW/cm^2. Such figures, however, can be misleading since the true criterion is the power absorbed.

The current maximum occupational exposure recommendation within American industry is 10 mW/cm^2 over any possible 0.1 hour period (ANSI, 1975). However, no specific standard exists in the U.S. for the exposure of the general population to RF/MW radiation. The current standard for home MW ovens has been set by HEW's Bureau of Radiological Health in accord with Public Law 90-602. The maximum permissible leakage at a distance of 5 cm from an oven containing 274 ml water in a 600 ml beaker is 1 mW/cm^2 at the factory and 5 mW/cm^2 during the oven's lifetime. The average background level of RF/MW radiation is depicted below as a point of comparison (adapted from Czerski, 1977).

Average background levels of RF/MW radiation.



Internationally, there is much debate over the maximum recommended occupational exposure to RF/MW radiation. The U.S., United Kingdom, France and West Germany have generally accepted the ANSI power density exposure level of 10 mW/cm^2. The USSR and Poland specify a maximum level of 0.01 mW/cm^2, a factor of 1000 less than that recommended in western countries. Czechoslovakia has proposed a level of 0.025 mW/cm^2 for an average working day's exposure. At the heart of this controversy is the difference in importance attributed to the small thermal loads induced by RF/MW fields. In the Western hemisphere, thermoregulatory responses such as small increases in respiratory rate, heart rate, and basal metabolic rate are expected physiological responses and not considered to be RF/MW-induced damage. In Eastern countries, however, such changes are regarded as CNS induced responses having potentially deleterious effects on the exposed organism.

The present volume was prepared by Michael J. Dwyer, Group Manager for Biomedical Resources, The Franklin Institute Research Laboratories' Science Information Services, in consultation with Dennis B. Leeper, Ph.D., Director of the Thomas Jefferson University Hospital's Laboratory of Experimental Radiation Oncology. Every effort has been made to assure the accuracy and completeness of the information reported, and the first draft of this report was reviewed by the following outside consultants:

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ABSTRACT

This report presents a general overview of the current status of knowledge regarding the possible carcinogenic hazards of occupational exposure to radiofrequency (RF) and microwave (MW) radiation based on a review of the literature published since 1970. Recent findings are reported, and current substantive issues and impressions are discussed from the point of view of identifying those effects which might enhance an already carcinogenic or potentially carcinogenic situation. Specific gaps in the present knowledge of radiation carcinogenesis are identified, and specific areas in need of further investigation are recommended.

This report is part of a larger survey of the carcinogenic properties of ionizing and non-ionizing radiation. It was submitted in partial fulfillment of Contract No. 210-76-0145 by The Franklin Institute Research Laboratories under the sponsorship of the National Institute for Occupational Safety and Health.

CONTENTS

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THE NORTH KARELIAN CONNECTION

There is little scientific or medical literature relating directly to actual or possible carcinogenic effects of RF/MW radiation. The strongest evidence comes from a recent World Health Organization (WHO) study, the North Karelian Project (Zaret, 1976). The evidence is circumstantial, consisting of little more than a possible correlation between an RF/MW-induced increase in cardiovascular disease and a rise in the incidence of cancer, and the conclusions are disputed by some investigators. Furthermore, the reported correlation is only indirectly relevant to the more typical occupational situation.

The North Karelian Project was triggered by an earlier Soviet study of 100 cases of MW sickness (Sadcikova, 1974) which had revealed 71 patients with cardiovascular symptoms. Of these, 49/71 had experienced continuing chronic exposure to MW for 5-15 years and 22/71 had been exposed for shorter periods. None of the 22 patients, whose occupational exposure to MW had ceased, recovered. Twenty stabilized, and 2/22 continued to worsen. The conclusion was that MW had been a contributing if not the precipitating factor in these cases.

To test the Soviet hypothesis, the WHO sponsored an epidemiologic survey of the population of North Karelia, a region of Finland bordering the USSR, which has experienced an unusual increase in the incidence of fatal heart attacks and a shift towards a younger age of onset. The increased incidence of heart disease has also been compounded by an unexpected and so far unexplained increase in the incidence of cancer. Among other things, the survey showed a correlation between the North Karelian health problem and the installation of the Russian early warning radar system.

North Karelia lies opposite Lake Ladoga and directly on the principal axis for the air defense of Moscow against intercontinental ballistic missiles launched from sites in the U.S. Midwest. The major components of the Soviet early warning system include high powered troposcopic scatter units, which must be situated near large bodies of water so that their beams can be formed efficiently with a minimum of interfering multipath reflections and be directed over a flat surface tangentially to the Earth's curvature. As a result, the North Karelians are continuously exposed to high levels both of ground waves and of scatter radiation. Several additional observations are also relevant. The incidence of sudden death from heart disease increases in a geographic pattern leading to the Soviet border opposite Lake Ladoga. Furthermore, the increased incidence of heart disease among the North Karelians first appeared well after World War II. As with other delayed energy effects in man, the North Karelian health problem exhibited latency and did not become manifest until after the Soviet networks had become operational.

Herein lies the North Karelian connection. The increased incidence of cardiovascular disease has been compounded by an unexpected and so far unexplained increase in the incidence of cancer. (Quantitative data were not given.) Interestingly, the highest rates of carcinogenesis were reportedly found in two hamlets, Koitsanlahti and Parikkala. Both hamlets are adjacent to one another, and both face the Soviet border opposite Lake Ladoga.

Beyond this, little data has been found which directly implicates RF and MW as potential carcinogenic agents per se. There have been unconfirmed and unscientifically reported allegations of RF/MW-induced cancer in one incident at Philco-Ford (Electronics, 1971), at the U.S. Embassy in Moscow (Berkley, 1976), and at the Boeing Corporation; and Prausnitz & Susskind (1962) have reported (without follow-up) an increased incidence of leucosis and leukemia in chronically irradiated, Swiss albino mice. The biomedical literature, on the other hand, reports a variety of other problems, including behavioral, neurological, biochemical, hematologic, genetic, developmental, and degenerative disorders, and cellular transformations. Although these latter effects do not directly relate to cancer, the possibility of carcinogenicity at very high cumulative doses and the possible enhancement of already carcinogenic or potentially carcinogenic situations by occupational exposure to RF/MW radiation should be closely examined.

BIOLOGICAL EFFECTS

The thermal effects of RF/MW radiation have been widely studied. MW of frequencies >10,000 MHz cause only surface heating since they do not penetrate beyond the skin. Between 1,000 and 10,000 MHz, the organs most readily damaged by RF/MW are the testicles and the eyes. In man, testicular damage includes degeneration of the epithelium lining of the seminiferous tubules followed by a sharp reduction in the number of maturing spermatocytes (McRee, 1972; McLees & Finch, 1973). Ocular damage in laboratory animals consists chiefly in cataractogenesis and at the metabolic level, in an inability to synthesize ascorbic acid within the lens (McLees & Finch, 1973). Below 1,000 MHz, few biological studies have been done.

At nonthermal intensities, the brain and central nervous system (CNS) appear to be particularly susceptible to RF/MW induced damage. The bulk of significant clinical findings pertain to CNS disorders. An outline of these findings is given in Tables 1-4. In a study of operant conditioned motor-food reflexes in rabbits, Lobanova (1974) has ascribed these effects to altered cortico-subcortical relations involving the hypothalamus, hippocampus, and sensorimotor complex. Studies by Baranski & Edelwejn (1974) have also implicated subcortical sites, especially the reticular formation. In this regard, occupational exposure to 20 kHz and 10 GHz radiation has been alleged to have resulted in one death from astrocytoma, a rare form of brain cancer (Electronics, 1971). However, a check with local regulatory agencies (the Pennsylvania Environmental Resources Department and OSHA) failed to uncover any record of substantiating findings, and the absence of further mention in the literature is interpreted accordingly.

Closely related to the above neurological effects are the various biochemical effects of low frequency non-ionizing radiation. Among 40 patients exposed to radiation in the centimeter band, Klimkova-Deutschova (1974) found increased levels of fasting blood sugar in 74%, depressed creatinine excretion in 60%, and depressed serum levels of pyruvate and lactate. In patients (average age 45.5 years) who were exposed to 30-800 MHz radiation, increases in serum levels of protein (75%), cholestrol (40.9%), 17-ketosteroids, and β-lipoproteins were noted. Elevated γ-globulin and total proteins have also been seen in 140 personnel from radio and TV transmitting stations in Eastern Europe who were exposed to 640 kHz-300 MHz near-field radiation at 10-50 V/m, 40.5 hr/wk for 10.4-16.8 years (Pazderova et al., 1974). Edelwejn et al. (1974) and others suggest that the above RF/MW-induced effects reflect regulatory imbalances possibly related to the neurological effects of low frequency non-ionizing radiation. These imbalances may be significant since hormonal imbalances have been linked to oncogenesis in tissues (mammary, cervical, prostatic, etc.) dependent on hormonal balance for their maintenance. Some tumors are also hormone-dependent, that is, their rate of growth may be accelerated or reduced by specific hormones. However, Skidmore & Baum (1974) have noted no increase in the incidence of mammary tumors in pulsed MW-irradiated female Sprague-Dawley rats.

Table 1

Subjective Effects on Persons working in RF Fields*

Headaches
Eyestrain
Fatigue
Dizziness
Disturbed sleep at night
Sleepiness in daytime
Moodiness
Irritability
Unsociability
Hypochondriac reactions
Feelings of fear
Nervous tension
Mental depression
Memory impairment
Pulling sensation in the scalp and brow
Loss of hair
Pain in muscles and heart region
Breathing difficulties
Increased perspiration of extremities
Difficulty with sex life

* After data by Marha et al. (1970) as quoted by McRee (1972).

Table 2

Occurrence of Some Symptoms in Humans Exposed Occupationally to High Frequency Electromagnetic Fields (750 kHz-200 MHz)*

Symptoms	Length of Employment: 1-6 years (average 4.3) (73 persons)		Length of Employment: 7-16 years (average 9.6) (73 persons)	
	percent of cases	number of cases	percent of cases	number of cases
Headache	20.5	15	32.9	24
Disturbance of sleep	13.7	10	23.3	17
Fatigue	12.3	9	17.8	13
General weakness	7.0	5	12.3	9
Disturbance of memory	5.5	4	8.2	6
Lowering of sexual potency	5.5	4	8.2	6
Drop in body weight	2.7	2	12.3	9
Disturbance of equilibration	5.5	4	11.0	8
Neurological symptoms	0.0	0	15.1	11
Changes in ECG	17.8	13	28.8	21

* After data by Minecki (1964) as quoted by McRee (1972).

Table 3

Clinical Manifestations of Chronic Occupational Exposure of 525 Workers to Microwave Radiation*

Symptomatology

Bradycardia
Disruption of the endocrine-humoral process
Hypotension
Intensification of the activity of thyroid gland
Exhausting influences on the central nervous system
Decrease in sensitivity to smell
Increase in histamine content of the blood

Subjective Complaints

Increased fatigability
Periodic or constant headaches
Extreme irritability
Sleepiness during work

* After data by Letavet & Gordon (1960).

Table 4

Effects of Electromagnetic Fields on the Central Nervous System of Animals*

Changes in the conditioned reflexes
Alterations in sensitivity to light, sound, and olfactory stimuli
Changes in structure of skin receptors of the digestive and blood carrying system
Alteration in the biocurrents of the cerebral cortex
Reversible, structural changes in the cerebral cortex and diencephalon
Appearance of various vegetative reactions.

* After data by Kholodov (1962) as quoted by McRee (1972).

Mechanistically, the nonthermal neurological effects of RF/MW radiation have been attributed, in part, to altered membrane potentials and radiation-induced biocurrents in the affected regions. However, more recent data indicate a thermal basis for altering membrane potentials. Kholodov (1962) observed altered brain waves following MW irradiation in rabbits with destroyed cochlea, severed optic nerves, and severed rhinencephalon. Prolonged desynchronization reactions were seen in 20% of the rabbits exposed to 2 or 10 mW/cm^2 at 2.5 GHz, and EEG measurements revealed an increased biopotential amplitude with decreasing frequency in 76%.

The nonthermal, excitatory, and inhibitory effects of RF/MW radiation may thus result from direct interactions between the electromagnetic field of these radiations and cellular membranes. In this regard, Adey et al. (1974) have invoked the "greater membrane" model of Schmidt & Samson. Adey et al. suggest that due to their strongly polyionic character and their ability to reversibly bind water and divalent cations like Ca^{++}, the surface layers of glycoproteins in the greater membrane may be the site of these interactions. Bawin et al. (1973, 1975) and Adey (1975), for instance, obtained neurological bioelectric disturbances accompanied by Ca^{++} efflux with 147 MHz radiation amplitude modulated at 9-16 Hz. The suggestion, then, is that RF/MW-induced membrane excitation involves small (frequency-dependent) Ca^{++} shifts. Adey et al. (1974) suggest that these shifts occur between closely adjoining binding sites on sheets of the neural membrane's surface macromolecules. Such phenomena, moreover, need not be limited to nerve cell membranes. Szmigielski et al. (1977) have found that when transmembrane ionic transport is impaired by digitonin or when the cell membrane is damaged by bacterial toxins like sphingomyelinase or phospholipase C, somatic cells in tissue culture are more susceptible to MW hyperthermia than to equal hyperthermia obtained in a hot chamber.

The ability of weak electromagnetic fields to interact with cellular membranes may also suggest a rationale for the mitotic and chromosomal anomalies induced by long-term exposure to RF/MW radiation (McRee, 1972). Cone (1971, 1974) has studied the control of DNA synthesis and mitosis in normal and malignant somatic cells and established a link between these latter phenomena and changes in ionic levels and fluxes accompanying altered membrane potentials. Though many of the results (see below) have been obtained in the thermal region (>10 mW/cm^2), most authors consider them to be at least partly non-thermal in origin.

The frequencies and intensities at which mitotic and chromosomal anomalies have been seen, are reviewed in Table 5. A partial list of chromosomal aberrations induced by RF/MW is given in Table 6. As noted by Heller & Teixeira-Pinto (1959), these effects seem to mimic those obtained with ionizing radiation and c-mitotic agents. They are suggestive of changes induced in interphasic nuclei (Stodolnik-Baranska, 1974), and appear dependent upon the frequency, pulse, power, length of exposure, and axis of the cells in the field (Heller & Teixeira-Pinto, 1959). The existence of specific repair mechanisms has also been inferred. Chen et al. (1974) have found a significant reduction in the number of chromosomal aberrations in Chinese hamster cells after 4 generations of radiation-free growth.

The appearance of RF/MW-induced mitotic and chromosomal anomalies is very suggestive from a carcinogenic point of view. Chronic myeloid leukemia has reportedly been linked to the appearance of certain chromosomal abnormalities (Chen et al., 1974). More importantly, such aberrations suggest the possibility of radiation-induced mutagenesis. The appearance of genetic mutations is widely held to be essential for the transition from benign to malignant growth.

Some of the currently known mutagenic and teratogenic effects of low frequency non-ionizing radiation are summarized in Table 7. Danilenko et al. (1974) have demonstrated a synergistic effect between chemical mutagens and pulsed MW radiation. Their suggestion (as yet unproven) is that irradiation-induced membrane effects render the cell wall more permeable to the chemical mutagens. Altered membrane permeability has been observed by other authors (see, for instance, Baranski et al., 1974). This again raises the possibility that under certain circumstances, RF/MW radiation might enhance an already carcinogenic or potentially carcinogenic situation.

Other tentative links are suggested by some of the known transformational, hematologic and developmental effects of low frequency non-ionizing radiation. These effects are outlined in Tables 8-10. The lymphoblastoid transformations outlined in Table 8 are of special interest in that they mimic those

Table 5

Effects of RF/MW Radiation on Mitosis and Chromosomal Structure

System	Frequency	Power	Mitotic Anomalies	Chromosomal Anomalies	Ref.
Garlic root tips	27 MHz (pulsed)	1,000–1,500 V/cm	X	X	Heller & Teixeira-Pinto (1959)
Stimulated lymphocytes, erythroblasts (guinea pigs, rabbits)	2950 MHz (pulsed)	7–20 mW/cm^2	X	X	Stodolnik-Baranska (1974)
Human lymphocytes stimulated with phytohemagglutinin					
Chinese hamster cells, Human amnion cells	2450 MHz	20–50 mW/cm^2		X	Chen et al. (1974)
Slime mold (Physarum polycephalum)	45, 60 70 Hz	2.0 G 0.7 V/m	X		Goodman et al. (1976)
Chinese hamsters (femur bone marrow)	2450 MHz	<200 mW/cm^2	X	X	Leach (1976)
Cultured human lymphocytes, Chinese hamster cells	15, 19, 21 & 25 MHz (pulsed)	30,000 V/cm		X	Mickey (1976)

Table 6

Chromosomal Anomalies Commonly Induced by RF/MW Radiation*

Effect (Reference)
Polyploidy (2,3)
Linear shortening of the Chromosomes (1,2)
Irregularities in the chromosomal envelope (1)
Abnormal bridges and stickiness (1, 2, 5)
Translocations (1, 3, 6)
Chromosomal breaks and gaps (3, 5, 6)
Chromatid breaks (2, 3, 6)
Deletions (3)
Acentric chromosomes (3)
Dicentric chromosomes (2, 3, 6)
Fragmentation (3, 4)
Ring chromosomes (6)

* From data by 1) Heller & Teixeira-Pinto (1959), 2) Stodolnik-Baranska (1974), 3) Chen et al. (1974), 4) Goodman et al. (1976), 5) Leach (1976) and 6) Mickey (1976).

Table 7

Mutagenic and Teratogenic Effects of RF/MW Radiation*

Effect	Frequency	Intensity	Reference
Hereditary changes in Drosophila germ cells.	5-40 MHz (pulsed)	N.R.	Mickey (1963)
Synergistic effect with mutagens (N-nitroso-N-methylurea and N-methyl-N-nitro-N-nitroguanidine) in increasing the number of his + mutants and morphological variants in histidine-dependent *Candida tropicalis*.	37,000 MHz (pulsed)	1 mW	Danilenko et al. (1974)
Increased incidence of heritable abnormalities in the pollen *Antirrhinum majus*.	200 MHz	1.5 V/m (near-field)	Harte (1975)
Congenital (teratogenic) abnormalities induced in rodent fetuses.	2450 MHz	107.4 mW/g	Rugh & McManaway (1976)

*N.R. = Not reported

Table 8

MW-Induced Blastoid Transformations

System/Effect	Frequency	Intensity	Reference
Cultured Human Lymphocytes: - appearance of lymphoblasts, macrophages, fragmented nuclei with vacuolization of the fragments, and abnormal bridging.	2950 MHz (pulsed)	7 or 20 mW/cm^2	Stodolnik-Baranska (1967, 1974)
Adult Male CWF Mice: - increased number of lymphoblasts in lymph node cells	"	0.5 ± 0.2 mW/cm^2 (2 hr/d for 6 or 12 wk)	Czerski (1975)
Rabbits: - increased rate of spontaneous lymphoblastoid transformations.	"	5 mW/cm^2	"
Purified Human Lymphocyte Suspensions: - Lymphoblastoid transformations and production of macrophage migration inhibitory factor.	"	variable	"

Table 9

Other Hematologic Effects of RF/MW Radiation*

Marked increase of exudate in marrow
Presence of neutral and acid mucopolysaccharides in exudate
Transient disappearance of fat cells from marrow
Destruction and disappearance of parenchymal cells in marrow
Complete aplastic marrow
Decrease in the number of erythrocytes in the peripheral blood
Decrease in the number of small lymphocytes in the peripheral blood
Increase in the number of large lymphocytes in the peripheral blood
Elevated levels of granulocytes and reticulocytes
K^+ efflux from washed rabbit erythrocytes
Hemoglobin efflux from washed rabbit erythrocytes
Increased osmotic fragility of erythrocytes
Acid phosphatase and lysozyme efflux from washed rabbit granulocytes

* Summarized from results by Yagi et al. (1974), Baranski (1971), Kitsovskaya (1964), Baranski & Czerski (1966) and Grant et al. (1974).

Table 10

Some Developmental Effects of MW Radiation

Effects	Frequency	Intensity	Reference
Delayed 1st division and subsequent course of development in tubifex embryos.	N.R. (pulsed)	250–300 G	Brandsch & Jitaru (1970)
Development of small internal bulges in Zebra fish eggs quickly followed by an explosion with all embryonic material flowing into the chorionic space. Results qualitatively differ from those obtained by thermal means.	2700 MHz (pulsed)	0.5 mW/egg (500 W/g in 6 μs)	Pyle et al. (1975)
Hemorrhage, resorption, stunting and fetal deaths in mice depending on the terato-genic stage at time of irradiation.	2450 MHz	7.37 W	Rugh et al. (1975)
Spectrum of neurocranial, tail, hand and palate malformations in fetal rats with the type of malformation corresponding directly to the teratogenic phase at time of irradia-tion and the frequency of occurrence to the intensity or rectal temperature.	27.12 MHz	55–100 W	Dietzel (1975)
Reduced body weight in CFI mice previously ex-posed *in utero* with a significant lowering of age of death.	2450 MHz	7.4 W	Rugh (1976)

N.R. = Not reported

seen in lymphomas and lymphoblastic leukemias. The main difference lies in the apparently non-malignant or non-invasive nature of the former, radiation-induced transformations. The possibility of concomitant chromosomal aberrations and genetic mutations and the possible synergistic effects of non-ionizing radiation deserve close attention in this regard. It is noteworthy that the transformations described in Table 8 have, for the most part, been obtained with external field intensities lower than those permitted in the U.S. So have the synergistic mutagenic effects observed by Danilenko et al. (1974) (see Table 7). Although, there have been no substantiated reports of RF/MW-induced cancer in man at levels within the currently recommended U.S. occupational safety limits, Prausnitz & Susskind (1962) have reported a 3-fold increase in the occurrence of monocytic leukosis and myeloid leukemia in male Swiss albino mice chronically exposed to pulsed 9 GHz MW radiation (100 mW/cm^2, 4.5 min/day for 59 wk).

The key to the possible role of RF/MW radiation in oncogenesis may rest in the epigenetic aspects of neoplastic transformations. The importance of epigenetics in carcinogenesis is illustrated by the recent work of Mintz & Illmensee (1975) and Illmensee & Mintz (1976) in which fetal tissue has undergone teratomatous growth when transplanted subcutaneously. When retransplanted in a uterine site, nuclei from these teratomas produce normal fetuses. In each case, the DNA is the same. What differs is the epigenetic context into which it is inserted.

Studies such as those by Mintz and Illmensee are reminiscent of Waddington's classical experiments in epigenetic adaptation and genetic assimilation (1957, 1960, 1971 and the references therein). Waddington has shown that prolonged environmental stress can destabilize developmental processes and alter the normal phenotypic expression of an underlying genotype. Subsequent offspring will produce the normal phenotype if the stress is removed. Breeding under continued stress, however, will select for mutations which enhance the ease of development of the novel phenotype under stress. Over a number of generations, this tendency can be set on an internal hair trigger. Once it has arisen, this hair trigger will act as a two-edged sword since it can be set off either by continued environmental stress or by a small genetic mutation. In short, the situation can arise in which an otherwise minor mutation will determine what was previously obtained only under the combined influence of the initial genotype and a specific environmental stress. The novel characteristic will be genetically assimilated, and will appear even when the outside stress is removed.

The implications for RF/MW radiation are potentially very serious. The long induction periods associated both with externally-induced tumors and with the transition from benign to malignant lesions are consistent with a process of epigenetic adaptation and genetic assimilation. So is the large variety of different factors which have been implicated in oncogenesis.

Recent studies with RF/MW radiation have revealed a high degree of biological activity, especially when pulsed. More importantly, many of the observed effects (Tables 1-10) occur simultaneously. Evtushenko et al. (1972) have reported the pulsed near-field irradiation of male albino rats for 90 or

180 minutes daily for 0.5-6.0 months at 7 kHz and 300 or 900 G. In these experiments, the animals' immunological reactivity, phagocytic index, WBC and neutrophil counts, and agglutinin and lysozyme titers were reduced while the lymphocyte count increased. Reductions in the rates of hepatic protein synthesis and hepatic, neural and cardiac metabolism were noted. An increase in the blood ammonia level was also noted. Other effect in Evtushenko's animals included a general disturbance in the blood and lymph circulation, reduced vascular membrane permeability, dystrophy of the parenchymous organs, protoplasmic swelling and vacuolization, reduction of the chromatin content of cell nuclei, karyorrhexis, pyknosis, loss of cytoplasmic glycogen and ribonucleoproteins, increased pyroninophilia and reduced succinate, malate, and isocitrate dehydrogenase activities in necrotic hepatocytes. The most pronounced histologic changes occurred in the livers of these animals. Also noted were the loss of the spermatogenic epithelium in the seminiferous tubules, atrophy and reduction of testicular size, and decreased RNA and DNA levels.

At present, the evidence linking RF/MW radiation to carcinogenesis is speculative and circumstantial. Only a few experimental studies have been performed, and the bulk of these have been negative. Skidmore & Baum (1974), for instance, found neither an increased incidence nor an earlier age of onset of cancer in MW-irradiated, leukemia prone AKR/J male mice; nor was any increase noted in the incidence of mammary tumors in irradiated female Sprague-Dawley rats. These results, however, are far from absolute. Furthermore, the possibility of synergistic effects (i.e. -- that RF/MW radiation might enhance already oncogenic or potentially oncogenic situations) has not yet been thoroughly explored. This possibility seems real and cannot be ruled out by the known data. Further quantitative work is required in this very important area of research.

DOSIMETRY, ENERGY DEPENDENCE AND ESTABLISHED SYNERGISTIC EFFECTS

From the point of view of carcinogenesis, there is little data to establish safe levels of exposure to RF/MW radiation. Even apart from the question of carcinogenesis there is little agreement over what constitutes the maximum safe level of exposure. Dose-response relationships, energy (frequency) dependence, and actual or potential synergism have yet to be fully established, and many authors find it difficult to compare even the studies listed in Tables 1-10 with one another.

The main difficulty in quantifying dose and energy-dependent relationships is the problem of accurately measuring the amount of energy dissipated within a given biological system. It is customary to measure the external field intensity. However, so many variables are involved that such measurements can often misrepresent the biological situation by several orders of magnitude (Baird et al., 1974).

As previously noted, the amount of RF/MW radiation absorbed by biological materials at a given frequency depends on the material's degree of hydration, its dielectric constant, magnetic permeability, and electrical conductivity. The absorber's physical dimensions relative to the wavelength of incident radiation, its geometry, its alignment within the field, and its ability to focus electromagnetic radiation by acting as a dielectric lens and/or reflector are also important. Gordon & Schwan (1974) thus recommend that the external field intensity ranges adopted at the 1973 International Symposium in Warsaw (Czerski et al., 1974) be replaced by separate scales for different tissues, organs, species, and stages of development. Baird et al. (1974) recommend measuring the square of the electric and magnetic field strength.

Additional quantitative difficulties are introduced by the use of internal electrodes and probes, and by external electronic equipment. Baird et al. (1974) point out that the sharp edges and points of internally placed metallic or other highly conducting probes tend to give rise to fringed fields. The result is an intense localization of absorbed radiation bringing about an artificial thermal gradient at the tip of the electrode. Guy (1974) also notes the effect of the leads and the amplifier. These latter components of the typical experimental situation serve as antennae to further focus RF/MW radiation at the electrode-tissue interface.

Baird et al. (1974) also point out the problem of external diffraction both in experimental and in occupational situations. At 1-3 GHz, the frequency range most often employed, the motion of animals or people gives rise to strong interference patterns in the external field. The experimenter can thus exert a profound effect on his results, especially when using hand-held probes. Overcrowding or, in an occupational setting, the use of mobile RF/MW sources can also result in non-uniform exposure to both near and far fields. In short, there is no reliable method of individual dosimetry even from the point of view of measuring exposure to external fields (Edelwejn et al., 1974).

The many uncertainties surrounding quantitative RF/MW studies offer a partial explanation for the often contradictory results. At the same time, they make it difficult to lightly dismiss the possibility that there may be particularly hazardous frequencies or dose levels (Czerski, 1977). Table 10, for instance, lists MW-induced developmental defects obtained at intensities as low as 0.5 mW. The hematologic effects noted in Table 9 were also induced at moderate intensities (1-40 mW/cm^2). Tables 5-7, in turn, list a number of mitotic, chromosomal, and mutational anomalies obtained at intensities reportedly below the recommended U.S. safety level of 10 mW/cm^2. McRee et al. (1975), on the other hand, have noted no significant developmental effects when irradiating Japanese quail eggs with 30 mW/cm^2 at 2450 MHz, nor have they observed any significant changes in the hematocrit, WBC count, RBC count, hemoglobin, differential WBC percentages, or overall weight of hatched quail. Mittler (1975), in turn, has seen no mitotic, chromosomal, or mutational effects when male Drosophila were placed for 1-12 hr directly on an antenna transmitting 146.34 MHz at 20W or 29 MHz at 300W.

Given the broad spectrum of experimental and clinical findings and the many uncertainties surrounding these results, it is difficult to clearly define quantitative relationships. There does, however, appear to be some evidence suggesting the existence of cumulative, frequency-dependent, and synergistic effects. Baillie (1974) has suggested on theoretical grounds that the existence of repair mechanisms such as those noted by Chen et al. (1974) implies the possibility of cumulative injury when the frequency of exposure exceeds the time needed for repair. Grant et al. (1974) suggest the possibility of progressive injury proceeding from the functional to the biochemical and structural levels. Carpenter et al. (1974) interpret their experiments in cataractogenesis as providing evidence for the existence of cumulative effects, and Rugh (1976) has found that 2-month-old CFI white mice have a significantly reduced tolerance to 2450 MHz radiation when previously irradiated in utero at 12 or 16 days gestation. According to Grant et al. (1974), these and earlier findings by Rugh provide presumptive evidence for the existence of cumulative effects. Similar remarks can be made regarding the frequency-dependence of RF/MW-induced effects. These effects are, in part, due to the differential absorption of electromagnetic radiation and to the frequency-dependence of dielectric focusing and reflection by curved surfaces (Baird et al., 1974) thus making comparison of studies on different species difficult. The existence of an energy-dependent relationship in cataractogenesis is illustrated in a qualitative way in Figure 1. The frequency-dependence of MW-induced chromosomal anomalies has also been noted by Stodolnik-Baranska (1974).

At the molecular level, there appears to be a relationship between the frequency of absorbed radiation and the conformational states of the absorbing macromolecules. Grant et al. (1974) stress in a qualitative way that the probability of resonant interactions between electromagnetic radiation and biological macromolecules decreases with the frequency of the field. Con-

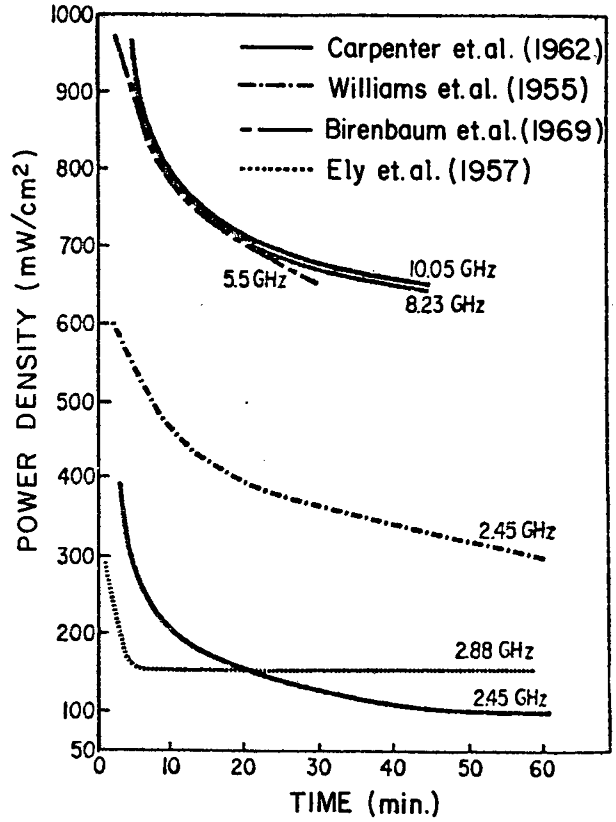

Figure 1. Energy-dependence of the apparent power density and time thresholds for the induction of opacities in the eyes of rabbits. (From McRee, 1972.)

versely, resonant interactions in molecular systems become more important at higher frequencies (mostly in the optical region). Molecular collisions are strongly diabatic with respect to rotation and translation, and strongly adiabatic with respect to electronic and vibrational states. Molecular interactions with electromagnetic radiation are thus relaxational below 3 MHz, resonant above 3 THz, and of an intermediate nature in the far-infrared region of the spectrum. As a result, RF/MW radiation is unlikely to cause molecular dissociations at in vivo temperatures unless the dielectric saturation level is exceeded by extremely high fields.

The dielectric behavior of many biological tissues is illustrated in Figure 2. Three relaxation regions (α, β, γ) of the dielectric constant appear, and these correspond to low, medium and very high frequency radiation. The postulated mechanism of these relaxational dispersions is given in Table 11. Figure 3 illustrates the variability of the characteristic frequency for the different mechanisms of Table 11. Blood cells, for instance, display a weak α-dispersion near 0.1 kHz (Schwan, 1974).

Gross Structure

α — Excited membrane?
    Intracellular structure?
β — Tissue structure (Maxwell-Wagner)
γ — Water

Fine structure

α_1 — Charge transfer (ion relaxation)
β_1 — Subcellular components, biologic macromolecules)
δ — Bound H_2O, side chain rotation, amino acids

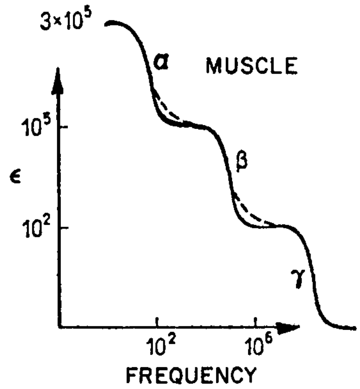

Figure 2. Gross and fine structural relaxation contribution to the dielectric constant of muscle tissue. Dashed lines indicate fine structural contributions. The data and various structural contributions are typical for all tissues of high water content. (From Schwan, 1974.)

Table 11

Electric Relaxation Mechanism*

Inhomogeneous Structure (Maxwell-Wagner)	β
Permanent Dipole Rotation (Debye)	γ, β tail
Counter-Ion Relaxation Electrophoretic Relaxation	α

* From Schwan (1974).

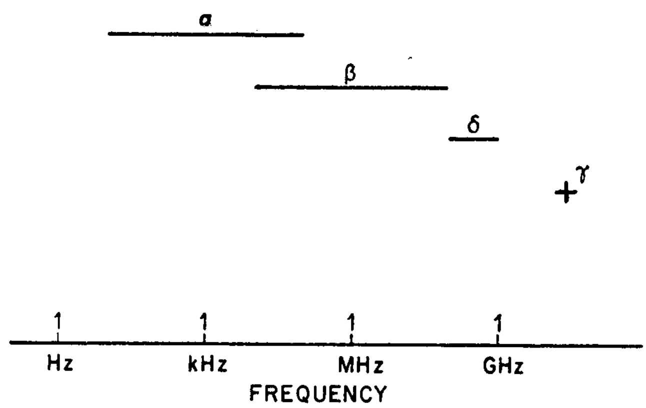

Figure 3. Ranges of characteristic frequencies for various biological systems. (From Schwan, 1974.)

In general, the dispersion characteristics of biological materials are given in Table 12. As noted by Grant (1974), most tissues have a high water content and, in the microwave region, the electrical properties of water dominate those of all other biomolecules. This situation is further illustrated in figure 4 where it is seen that in the MW region, the electrical conductivity of biological materials increases by 4 orders of magnitude while the permittivity decreases by a factor of about 15. These changes appear to result almost entirely from the γ-dispersion of water. The β-dispersion seems to be due to the presence of biomolecules, and the δ-dispersion is usually attributed either to bound water, to the side chains associated with macromolecules, or to a combination of both effects (Grant, 1974). However, the above-mentioned phenomena are very complex and further study is required.

Finally, with regard to synergism, the literature is sparse. Danilenko et al. (1974) have found a cooperative (i.e.-synergistic) relationship between pulsed MW irradiation and chemical mutagens within the recommended U.S. safety limit for occupational MW exposure (see Table 7 for details). Other authors (see, for instance, Baranski et al., 1974) have observed altered membrane permeability in MW-irradiated cells, and Hahn and Strande (1976) have shown that hyperthermia similar to that induced by MW enhances the effect of cytotoxic chemicals. This raises the strong but as yet unproven possibility that exposure to RF/MW radiation might have a synergistic effect in the presence of actual or potential chemical carcinogens.

Table 12

Dispersion Characteristics of Certain Biologic Materials*

Electrolytes	γ
<u>Biologic Macromolecules</u>:	
Amino Acids	$\delta + \gamma$
Proteins	$\beta + \delta + \gamma$
Nucleic Acids	$\alpha + \beta + \delta + \gamma$
<u>Cells, free of protein</u>:	$\beta + \gamma$
Charged	$\alpha + \beta + \gamma$
Excited membranes	$\alpha + \beta + \gamma$

* From Schwan (1974).

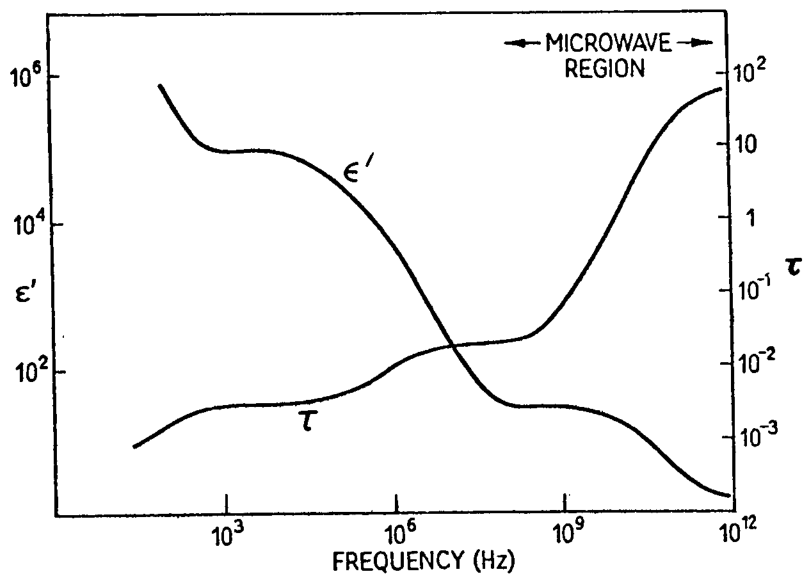

Figure 4. Fall of permittivity (ε') and increase in conductivity (τ) with increaseing frequency for a typical biological tissue. (From Grant, 1974.)

RECOMMENDATIONS FOR FURTHER INVESTIGATION

There is little scientific or medical literature relating directly to actual or possible carcinogenic effects of RF/MW radiation. The strongest epidemiologic evidence comes from the above-mentioned WHO study of the North Karelian health problem. Even here, the evidence is circumstantial, consisting of little more than a possible correlation between a demonstrable RF/MW-induced increase in cardiovascular disease and an alleged rise in the incidence of cancer. Furthermore, the North Karelian health problem is only indirectly relevant to the more typical occupational situation due to the intensity and duration of exposure.

Beyond this there is little published data. Several unconfirmed allegations have been made, and one positive experimental finding has been reported. The nature and variety of RF/MW-induced effects are very suggestive, but the current paucity of quantitative data prevents a reliable estimate of the situation. Since these data are not sufficiently quantitative, many of the abovementioned studies cannot demonstrate causal relationships. Furthermore, they cannot be rigorously intercompared. Hence, the most important recommendation is the need for further, careful quantitative research into the potential hazards of RF/MW radiation. What is needed is a more thorough quantification of results, adequate controls, and uniform standards for reporting the frequency, intensity, rate of exposure, length of exposure, total dose absorbed, and dose distribution to which the organism or the part was actually exposed.

More detailed information is also needed regarding both the mechanisms of RF/MW interactions with biological materials and the etiology of carcinogenesis. RF/MW radiation has been implicated in a variety of biological phenomena including altered transmembrane potentials, increased membrane permeability, hyperthermia, hormonal imbalances, chromosomal anomalies and mutagenesis. Although their exact roles are unknown, similar phenomena have been implicated in carcinogenesis. In the absence of more detailed quantitative data, it is impossible to adequately assess the potential carcinogenicity or synergistic properties of RF/MW radiation.

In conclusion, there is very little mention of cancer in the RF/MW literature. The experimental and clinical results raise more questions than answers. Though these questions (especially those from North Karelia) are both stimulating and suggestive, further quantitative research is required to critically assess the potential carcinogenic hazards of RF/MW radiation.

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