

RADIO FREQUENCY RADIATION OF MILLIMETER WAVE LENGTH: POTENTIAL OCCUPATIONAL SAFETY ISSUES RELATING TO SURFACE HEATING

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Abstract—Currently, technology is being developed that makes use of the millimeter wave (MMW) range (30–300 GHz) of the radio frequency region of the electromagnetic spectrum. As more and more systems come on line and are used in everyday applications, the possibility of inadvertent exposure of personnel to MMWs increases. To date, there has been no published discussion regarding the health effects of MMWs; this review attempts to fill that void. Because of the shallow depth of penetration, the energy and, therefore, heat associated with MMWs will be deposited within the first 1–2 mm of human skin. MMWs have been used in states of the former Soviet Union to provide therapeutic benefit in a number of diverse disease states, including skin disorders, gastric ulcers, heart disease and cancer. Conversely, the possibility exists that hazards might be associated with accidental overexposure to MMWs. This review attempts to critically analyze the likelihood of such acute effects as burn and eye damage, as well as potential long-term effects, including cancer. *Health Phys.* 78(2):170–181; 2000

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INTRODUCTION

THE RADIO frequency (RF) region of the electromagnetic spectrum is generally defined as including electromagnetic waves with frequencies in the range of 3 kHz to 300 GHz. Common applications of RF radiation include radar (e.g., weather, marine, air traffic control, military, and police traffic), communication and navigation equipment, medical devices, industrial heating devices, and microwave ovens (Cleveland 1994; WHO 1993). The millimeter wave (MMW) frequency range is a subset

within the RF region of the spectrum, comprising the frequency range from 30 to 300 GHz. Recently, hardware systems capable of generating MMWs have been developed and are increasingly being used for a number of applications, such as satellite communications, military radar, smart weapons, high speed data communications, automotive anticollision devices, weapons detection, and medical devices. Medical applications of MMWs began in the countries of the former Soviet Union (FSU) in the 1970's and have been in widespread usage since the mid-1980's (Rojavin and Ziskin 1998). The first part of this review will summarize clinical and experimental findings related to the use of MMWs for therapeutic purposes.

The second part attempts to summarize the available information on possible hazards resulting from accidental overexposure to MMWs. To date, there has been no published discussion of this issue. As the practicality of MMW-based technology increases, however, the possibility of inadvertent exposure to MMWs will also increase. This scenario has occurred in the past and is likely with the development of any new technology. For example, as microwave devices utilizing lower frequencies were developed and became available, accidental overexposures occurred (Table 1). It should be noted that some of the emerging MMW applications will require increasingly high power outputs; for example, communication with satellites orbiting the earth requires higher power outputs than communication over shorter distances. As these systems come "on-line," service and maintenance technicians will be required and the possibility of accidents occurring will increase. Currently, the maximum permissible exposure limit for frequencies between 30 GHz and 300 GHz varies from 5 mW cm^{-2} (ICNIRP 1998; NCRP 1986) to 10 mW cm^{-2} (ANSI/IEEE 1992). Averaging exposure time also varies from 10 s to 6 min depending on frequency. Although most systems operate at low powers, certain military and commercial applications operate at much higher powers, suggesting the possibility of accidental overexposure that might be harmful to personnel. This review thus critically evaluates the possibility of acute and long-term risks that might be associated with accidental overexposure to MMWs.

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Table 1. Microwave overexposure cases reported in the biomedical literature.

Reference	Application	Frequency
Nicholson et al. 1987	RF heat sealer	10 MHz
Ciano et al. 1981	RF heat sealer	27.12 MHz
Brodtkin and Bleiberg 1973	Microwave oven	2,450 MHz
Ciano et al. 1981	Microwave oven	2,450 MHz
Fleck 1983	Microwave oven	2,450 MHz
Tintinalli et al. 1983	Microwave oven	2,450 MHz
Dickason and Barutt 1984	Microwave oven	2,450 MHz
Zambrano and Boswick 1984	Microwave oven	2,450 MHz
Stein 1985	Microwave oven	2,450 MHz
Maley 1986	Microwave oven	2,450 MHz
Alexander et al. 1987	Microwave oven	2,450 MHz
Budd 1992	Microwave oven	2,450 MHz
Forman et al. 1982	Military radar	8–12 GHz
Williams and Webb 1980	Military radar	>10 GHz
Castillo and Quencer 1988	Military radar	Unreported

THERAPEUTIC APPLICATIONS OF MMWS: THE FSU EXPERIENCE

MMW therapy is a widely used therapeutic technique that has been officially approved by the Russian Ministry of Health. In fact, it has been reported that, as of 1995, more than 3 million people have received this therapy at over 1,000 MMW therapy centers in Russia. MMW therapy has been reported to be efficacious in the treatment of over 50 diseases and conditions (Pakhomov et al. 1998; Rojavin and Ziskin 1998). While this treatment is widespread in the FSU and some other European countries, it is not recognized in medical practice in the United States. Indeed, only three laboratories in the U.S. are currently performing research on the bioeffects of MMW exposure in general, and only one laboratory in the U.S. is actively investigating the biophysical and physiological mechanisms underlying MMW therapy (Alekseev and Ziskin 1995; Logani and Ziskin 1996; Rojavin and Ziskin 1997). This disparity in research effort in the FSU and the non-FSU is reflected in the number of publications pertaining to MMW (436 from the FSU vs. 261 from the rest of the world; Pakhomov et al. 1998).

The authors of two recent review articles have surveyed and translated the FSU literature pertaining to this subject, thereby making this database accessible to Western (non-FSU) investigators for the first time (Pakhomov et al. 1998; Rojavin and Ziskin 1998). Pakhomov and colleagues (1998) make several insightful and important points concerning the FSU literature. First, they note that the limited Western literature that exists concerning MMWs is driven by concerns for public safety, whereas the FSU literature is predominantly concerned with medical applications. Hence, the FSU literature is replete with individual case studies regarding this therapy. Many clinical studies have also been performed; some of these conform to conventional quality criteria (double-blind protocol, proper control groups, placebo treatment, etc.), while others do not. Of those studies that do conform to proper criteria, Pakhamov et al. (1998)

note that independent groups of clinical investigators have produced remarkably similar results, suggesting that the therapy may indeed be effective. Finally, there are many fewer experimental animal studies reported in the FSU literature than clinical studies, and these animal studies did not necessarily precede the clinical use of MMW, as if the animal experiments were performed to justify the clinical phenomena reported.

It is not the intent of this review to provide detailed information on the FSU literature; for an in-depth review of this literature, we refer the reader to the excellent papers mentioned previously (Pakhomov et al. 1998; Rojavin and Ziskin 1998). Because this literature describes potential human bioeffects that are not well understood, we offer a brief synopsis of the research using MMW therapy.

What is MMW therapy? Basically, MMW therapy consists of exposure of certain areas of the skin to low intensity RF energy in the 30–300 GHz frequency range. The penetration depth of MMWs is less than 1 mm (Erwin and Hurt 1981; Gandhi and Riazzi 1986). This means that essentially all of the energy deposition and, therefore, heat deposition, will occur within the skin. RF energy in this frequency range is typically applied at a low average incident power density ($<20 \text{ mW cm}^{-2}$), which produces skin temperature increases of $<1^\circ\text{C}$ (Rojavin and Ziskin 1998). There are now more than 100 models of medical MMW devices available in the FSU and some European countries that operate using these parameters (Rojavin and Ziskin 1998).

The most common diseases or conditions that are treated using MMW therapy are gastric and duodenal ulcers, cardiovascular diseases (including angina pectoris, hypertension, and myocardial infarction), respiratory illnesses (including tuberculosis, bronchitis, and asthma), and skin diseases (including wounds, burns, psoriasis, and atopic dermatitis). This therapy has also been used in cancer patients to alleviate toxic side effects of chemotherapy (Pakhomov et al. 1998; Rojavin and Ziskin 1998). Furthermore, there are isolated case reports of the successful treatment with MMW therapy of a variety of other ailments. In light of the shallow penetration depth of MMWs, it is interesting to note that this therapy is apparently efficacious at diseased organs that are distal from the site of irradiation. This raises an important question: How does MMW therapy act to alleviate gastric ulcers, for example, when the energy does not penetrate past the level of the skin? A number of mechanisms have been proposed to explain such events (e.g., "resonance" phenomena, irradiation of acupuncture points, stimulation of peripheral receptors, humoral events), but there is little experimental evidence offered to substantiate these postulates. Until a physiologically feasible mechanism is characterized and established empirically, Western medicine must react skeptically and treat such claims of improvement at distal sites as a phenomenon rather than a scientifically-based therapy.

The ability of MMW therapy to provide benefit in the treatment of superficial skin lesions appears more

plausible, and is supported by more experimental evidence. MMW therapy has been reported to promote healing of both aseptic wounds and those made septic by infection with *Staphylococcus* in rabbits (Korpan et al. 1994; Pakhomov et al. 1998) and rats (Pakhomov et al. 1998). Data from these studies lead to different conclusions regarding the function of the immune system in this beneficial effect; Korpan and his colleagues (1994) suggest that the immune system is stimulated while Detlavs and his colleagues (as discussed in Pakhomov et al. 1998) suggest that the immune system is suppressed. In a double-blind controlled study, Korpan and Saradeth (1995) provide evidence that MMW therapy significantly increased the rate of wound healing of postoperative patients with septic wounds. Taken together, these data indicate that MMW therapy may be effective to promote healing of skin wounding, which appears reasonable considering the penetration depth of MMWs. Interestingly, tissue regeneration of underlying nerves and bones has also been reported (Kolossova et al. 1996; Pakhomov et al. 1998), once again requiring the presence of a physiological mediator to transduce MMW effects from the skin to deeper tissues.

In summary, MMWs are currently being employed for therapeutic benefit in the FSU and other European states. The efficacy of this therapy in treating diverse symptoms of such disparate etiologies raises more questions than answers. Because the treatment does appear to have therapeutic value under some conditions, we agree with Pakhomov et al. (1998) and Rojavin and Ziskin (1998) that more research is necessary. This should include well-performed, double-blind clinical studies to eliminate a "placebo" effect or other artifact, and experimental studies to determine biophysical and physiological mechanisms underlying the putative therapeutic effect. What is clear, however, is that the widespread use of this therapy in the FSU has not proved harmful, in that the incidence of reported side effects is quite small in comparison to the total number of patients treated (Pakhomov et al. 1998; Rojavin and Ziskin 1998).

OVERVIEW OF ACCIDENTAL MICROWAVE OVEREXPOSURE

Until the recent development of MMW systems, most RF devices produced frequencies in the microwave range (10 MHz–30 GHz). Thus, all reports of human overexposure in the biomedical literature concern these lower frequency ranges. A few essential differences between lower-frequency microwaves and MMWs are notable, however, when one begins to analyze the relevance of these case studies to potential risks from MMWs.

The amount of RF energy absorbed by an organism depends on several factors, including frequency, intensity of the RF radiation, and duration of exposure (Durney et al. 1986). Quite clearly, RF radiation produces heating in living tissue when the rate of energy absorption is relatively high. The specific absorption rate

(SAR) is a measure of the rate of energy absorption per unit mass (watts kg^{-1}). As SAR increases, the potential for heating and, thus, tissue damage also rises. The whole-body SAR for a given organism will be highest within a certain resonant frequency range, which is dependent on the size of the organism being irradiated and its orientation relative to the electric and magnetic field vectors and the direction of wave propagation. For an average man, for example, the peak whole-body SAR occurs in a frequency range of 60–80 MHz, while the resonant frequency for a laboratory rat is about 600 MHz (Durney et al. 1986). In each case, the height of the man (175 cm) and length of the rat (20 cm) is 0.4 times the resonant wavelength when the electric field vector is parallel to the long axis of the man or rat, respectively (Gandhi 1974). Above resonant frequency, however, the depth of penetration of the RF waves varies inversely with the frequency; that is, the higher the frequency, the more shallow the depth of energy and, therefore, heating. Indeed, the depth of penetration of 35 GHz and 94 GHz into human skin has been calculated to be less than 0.75 mm and 0.35 mm, respectively (Erwin and Hurt 1981; Gandhi and Riazi 1986), while the depth of penetration of 2,450 MHz (the frequency of the standard microwave oven) is approximately 2.5 cm (Durney et al. 1986).

What does this mean in terms of possible thermal injury from inadvertent exposure? Because most of the MMW energy is absorbed in the first millimeter of cutaneous tissue, it is likely that accidental overexposure will produce damage to superficial layers; that is, one might expect that injury would be confined to the skin. Accidental overexposure to microwave energy of lower frequency, however, might be expected to produce deeper injury. Such injuries or symptoms have occasionally been reported (Table 1). In many of these cases, exposure occurred when the safety devices on the microwave ovens (operating at 2,450 MHz) failed (Brodkin and Bleiberg 1973; Ciano et al. 1981; Fleck 1983; Tintinalli et al. 1983; Dickason and Barutt 1984), although this has been questioned in some cases (Osepchuk 1984; Budd 1992). In any event, microwave-induced thermal injury has typically been characterized by involvement of deeper tissue without immediate observable skin injury or pain sensation (Budd 1985; Surrell et al. 1987). For example, the appearance of skin burns in dogs exposed to 2,800 MHz may be delayed by as much as 6 d following exposure and, upon appearance, develop without the blisters characteristic of thermal burns induced by more familiar modalities (Michaelson et al. 1967).

POSSIBLE ACUTE EFFECTS OF OVEREXPOSURE TO MMWS: SKIN

The thickness of adult human skin varies across the body, from approximately 1.3 mm on the scalp to 4 mm on the back (Snyder et al. 1975). Because MMWs penetrate <0.8 mm (Erwin and Hurt 1981; Gandhi and Riazi 1986), it is thus clear that the energy deposited by

MMW exposure will be absorbed within the skin. Indeed, by using computer-modeling algorithms, it has been shown that 95% of the temperature increase produced by exposure to 94 GHz RF energy will occur in the first 1.2 mm of the skin.^{||} Accidental overexposure to the extent of thermal injury is thus expected to produce superficial burns not unlike those produced by other modalities (e.g., contact with heated object or flame). In other words, it is anticipated that MMW-induced burns will produce blistering and local inflammatory responses, as in conventional burns, rather than the deep-tissue thermal injury characteristic of overexposure to lower frequencies.

What degree of overexposure would be necessary to elicit such burns? Currently, there is no literature on the threshold for skin damage in response to MMWs. Additionally, no cases of accidental overexposure to MMWs have been reported in the biomedical literature to date. In order to answer this question, we must therefore make the assumptions that the basic effect of MMW exposure is to increase the skin temperature and that such exposure will produce conventional burning. In light of the shallow penetration depth of MMWs, these appear to be reasonable conjectures. By making these assumptions, we can use the literature defining thresholds for burn injury to approximate the degree of MMW-induced heating necessary to produce thermal injury. In their classic paper, Moritz and Henriques (1947) applied hot objects to the skin of both pigs and humans to determine the temperature-duration relationships necessary to produce varying levels of thermal injury. For example, it was found that a "first degree" reaction (i.e., hyperemia without epidermal loss) could be induced by application of 45°C for 2 h, 48°C for 15 min, or 53°C for 30 s. Furthermore, production of "second and third degree reactions" (i.e., complete epidermal necrosis) required application of 48°C for 18 min, 51°C for 4 min, and 60°C for 5 s. If application of heat via MMW exposure and hot objects is roughly equivalent (an untested assumption), then temperature-duration relationships for thermal injury for each situation should be roughly equivalent. Until these assumptions are tested, such approximations are the only relevant information available.

What is the likelihood that inadvertent MMW exposure might increase skin temperature to the point that thermal injury ensues? If the power level to which the individual is exposed is extremely high, it is possible that such temperatures could be reached before the individual senses warmth and removes himself from the field. Again, it must be emphasized that this would occur only when the power level is extremely high and the critical temperature increase is reached within a few seconds after the onset of exposure. It should be noted, however, that the elevated temperatures required to produce damage within a reasonable time (minutes) are well above threshold values for warmth detection of MMWs. Blick et al. (1997) determined threshold levels (in mW cm⁻²)

of MMW exposure sufficient to sense warmth in human volunteers. Mathematical modeling based on these empirical data demonstrates that the MMW-induced temperature increase at the skin surface required to elicit the sense of warmth is 0.07°C (Riu et al. 1996). Thus, human skin is sensitive to less than a 0.1°C increase in skin temperature, meaning that MMW exposure will be sensed almost immediately at the onset of exposure (to levels high enough to increase temperature). It should also be noted that temperature receptors are sensitive to both absolute temperatures as well as the rate that temperature increases (Pierau 1996); that is, rapid warming produces greater responses from thermoreceptors than slower warming, a consideration that would conceivably further decrease response time (or increase sensitivity) to higher levels of MMW exposure. Furthermore, MMW exposure at levels greater than the maximal permissible level might be expected to increase skin temperature above the threshold for pain detection, which is 43–45°C for conventional heating (Hardy et al. 1952). Preliminary results indicate that the pain threshold for 35 GHz and 94 GHz exposure is also approximately 45°C (Blick et al. 1998). Lawrence and Bull (1976) have demonstrated that the threshold levels for pain sensation are much below the threshold levels for skin damage resulting from contact with hot objects. Considering the temperature-duration relationships derived by Moritz and Henriques (1947) and Lawrence and Bull (1976), an individual would have to remain in a painful RF field for a relatively long (considering the pain) duration before thermal damage would be likely to occur. Taken together, these results suggest that, in the event of accidental exposure to moderate power levels of MMWs, humans will sense warmth and, possibly, pain; this "warning system" will allow them to move out of the field before burning occurs.

In summary, a plausible acute effect of MMW exposure on skin is that of superficial burning. Unless people are accidentally exposed to extremely high power levels, however, it is likely that they will take action to remove themselves from the area of irradiation before thermal damage occurs.

POSSIBLE ACUTE EFFECTS OF OVEREXPOSURE TO MMWS: EYES

Exposure of the eye to microwave or MMW radiation can lead to a temperature rise sufficient to damage tissues. This will, of course, depend on the intensity of the irradiation and how well the deposited energy is removed. As with the skin, lower frequency microwaves will be deposited deeper in the eye, while MMWs will be absorbed in the cornea on the front surface of the eye. The eyes of mammals do not efficiently remove heat that is deposited internally. A primary avenue of heat removal is blood flow in the retina. Other than conduction through the sclera and convection and radiation from the surface of the cornea, heat removal is poor compared to other tissues. Many investigators have postulated that the poor

^{||} Personal communication, R. Medina, AFRL/HEDB, Brooks AFB, TX 78235; September 1998.

heat dissipation from within the eye of humans and other animals may lead to heat buildup and subsequent thermal damage (Al-Badwaihy and Youssef 1976).

Early investigations of microwave effects on the eye focused on the parameters of power density and duration of exposure needed to produce cataracts in the lens of the eye. The majority of these studies were conducted at frequencies below 6 GHz and dealt with only acute exposure damage to the lens. Cataracts are an opacification or clouding of the lens that may occur during the normal aging process or are associated with several disease processes. They are also thought to result from excessive heating that accompanies microwave irradiation. For example, Guy et al. (1975) exposed rabbits with a near field applicator at 2,450 MHz and determined that 150 mW cm^{-2} was required for 100 min to produce a cataract. The maximum SAR for this exposure was 138 W kg^{-1} . Kramar et al. (1978) found nearly the same threshold (180 mW cm^{-2} for 140 min) for rabbits exposed to 2,450 MHz radiation. Interestingly, they found that similar exposures at much higher power densities (500 mW cm^{-2} for 60 min) could not produce a cataract in rhesus monkeys. They attributed this to less heating because of poorer microwave absorption in the monkeys' eyes due to the shape of the skull compared with rabbits. Reviews of the literature of microwave-induced cataracts are available (Tengroth 1983; Elder 1984).

MMWs, on the other hand, will be absorbed in the surface layers of the cornea. The resulting damage will also depend on the duration and intensity of exposure which, together with cooling, determine the temperature rise. If exposures are intense enough, reflexive eye blink and head aversion will limit temperature rise and associated pain. It is known that reflex eyelid closure often protects the eyes during facial burns (Lipshy et al. 1996). The extent of any damage that may occur will depend on eyelid closure, the MMW frequency, its penetration depth and the resultant temperature rise in the different layers of the cornea. At infrared wavelengths, which are absorbed at the very surface of the cornea, absorption of $1,000 \text{ mW cm}^{-2}$ can produce a temperature increase of 10°C , which elicits a pain response in humans in a fraction of a second (Sliney and Wolbarsht 1980). Damage limited to the corneal epithelium will undergo a normal repair process within 24 to 48 h. Damage to the underlying stromal layer, however, may be longer lasting and result in the development of corneal opacities. Thus, it is expected that reflexive eyelid closure would also limit corneal damage at MMW frequencies.

Very little research exists on eye damage due to MMW exposure. One research study has shown that stromal layer damage occurs at MMW frequencies and depends on the wavelength. Rosenthal et al. (1976) irradiated anesthetized rabbits and found that, at 40 mW cm^{-2} , extensive epithelial damage was observed at 35 GHz and 107 GHz. Stromal injury was observed only for the deeper penetrating energy of 35 GHz irradiation. They reported longer lasting damage to rabbit eyes for 35

GHz but a lower threshold for damage at 107 GHz. Damage at 107 GHz usually disappeared the next day. It may be important to note that the threshold levels reported by Rosenthal et al. (1976) were determined under anesthesia. The corneas were therefore deprived of their normal convective cooling as no blinking occurred during irradiation. As the authors reported, their data pertained only to acute exposures.

Recently, Chalfin et al. (1998) reported thresholds for corneal damage at 94 GHz in rhesus monkeys. They used much higher power densities (2 W cm^{-2}) and shorter exposure durations (1 to 4 s) than the rabbit study. Five juvenile rhesus monkeys were given baseline eye exams using slit lamp examination, corneal topography, specular microscopy, and pachymetry. Anesthetized monkeys were then exposed in one eye to pulsed 94 GHz microwaves at different intensities and exposure durations with the other eye serving as a control. The fluence necessary to produce a threshold corneal lesion (faint epithelial edema and fluorescein staining) at 94 GHz was 6 J cm^{-2} (3-s exposure to 2 W cm^{-2}).

Kues et al. (1998) reported chronic exposures of rabbits and rhesus monkeys to 60 GHz MMWs at an incident power density of 10 mW cm^{-2} . They used a variety of diagnostic tests including slit lamp examination, specular microscopy, and iris angiography before and after exposure to MMWs to assess damage in each subject. Following single 8-h or five separate 4-h exposures, no damage to the exposed eye of rabbits and monkeys was observed. Light and transmission electron microscopy of eye tissues failed to reveal any damage from the chronic exposures to MMWs.

POSSIBLE CHRONIC EFFECTS OF OVEREXPOSURE TO MMWS

Skin cancer from MMW exposure?

The controversy over whether RF radiation might initiate or promote cancer continues to receive a great deal of attention, both in the popular press and in the biomedical literature (e.g., Jauchem 1991, 1993, 1995; Goldsmith 1997; Repacholi 1997, 1998; Valberg 1997; Brusick et al. 1998; Verschaeve and Maes 1998). In order to understand the RF literature on this issue, it is first necessary to understand the current experimental model of cancer development. Cellular and molecular events leading to cancer development are operationally divided into 3 major stages: initiation, promotion, and progression (Boutwell 1989; DiGiovanni 1992; Slaga et al. 1995). These stages were first defined and are most well-understood in animal models of skin carcinogenesis, so we will discuss these stages in relation to the skin. The initiation event occurs as a result of interaction of a carcinogen with the DNA of the epidermal cell, resulting in mutations. As an example, a single application of a chemical carcinogen to the skin may cause alterations in the DNA of the cell that are essentially irreversible. Cancer will not develop, however, unless a promoting agent is repeatedly present following initiation. The

process of tumor promotion is believed to involve the selective expansion of initiated cells into visible outgrowths (tumors) on the skin. Tumor progression, by definition, involves the conversion of benign outgrowths to malignant tumors (Boutwell 1989; DiGiovanni 1992; Slaga et al. 1995).

It is now well-accepted that RF radiation *per se* cannot be mutagenic, inasmuch as the energy which the electromagnetic waves carries is insufficient to break chemical bonds (Repacholi 1997, 1998; Brusick et al. 1998; Verschaeve and Maes 1998). Furthermore, extensive reviews of the database fail to reveal RF-induced effects on DNA in the absence of hyperthermia (Brusick et al. 1998; Verschaeve and Maes 1998). More specifically, mutagenic effects of MMWs have not been observed in the absence of hyperthermia (Dardalhon et al. 1979, 1981; Gandhi 1983). Thus, it is clear that RF radiation is not genotoxic and therefore cannot initiate cancer.

Studies investigating the carcinogenic potential of RF radiation have thus focussed on promotion or co-promotion (i.e., the ability to enhance the effects of a chemical promoter). Again, studies performed to date have been limited to microwave frequencies below 30 GHz. Without going into detail (since these frequencies are not the subject of this review), the majority of such studies have shown that chronic exposure of animals to RF in the range of 435 to 2,450 MHz did not significantly alter the development of tumors in a number of animal cancer models (Table 2). It should be noted, however, that some earlier studies have found a significant acceleration of the tumorigenesis process with chronic microwave exposure (Table 2).

To date, there have been no laboratory studies that address the specific issue of whether MMW exposure might promote cancer development. Because applications of RF energy in the MMW range are so novel, there is also no epidemiological work addressing this question. Because MMW energy is absorbed in the skin, it would be expected that any long-term detrimental health effects would most likely be manifest in the skin. Again, the only information available on the ability of RF energy to promote skin cancer comes from two studies (performed

in the same laboratory) using 2,450-MHz RF radiation. In these studies, exposure to RF, either prior to or during initiation and promotion of skin tumorigenesis with benzopyrene, accelerated the development of skin cancer and, consequently, decreased animal survival time (Szmigielski et al. 1982; Szudzinski et al. 1982). It was also observed, however, that the same acceleration of skin cancer development and reduction in survival occurred in animals exposed to chronic confinement stress in the absence of RF exposure, suggesting that the RF effect could possibly be due to a nonspecific stress reaction (Szmigielski et al. 1982). In the context of potential artifacts, it should also be noted that hyperthermia produced by non-RF sources (warm water bath) can either serve as an antipromoter (Mitchel et al. 1986) or as a promoter (Mitchel et al. 1988), depending on application regimens.

Anecdotally, it is also interesting to note that repeated exposure to extreme hyperthermia has been shown to result in skin cancer. In several cultures, the repeated use of heating devices placed directly on the skin has resulted in induction of skin cancer. For example, the Kashmir Mission Hospital in India recorded more than 2,000 cases of squamous cell carcinomas between 1881 and 1924 that were directly associated with the use of the "kangri" heating device, an earthenware bowl heated with charcoal placed directly in contact with the skin (as discussed in Treves and Pack 1930). Skin temperatures under these conditions reached 65–93°C. A further report of kangri burns in Kashmiris has recently been published (Chowdri and Darzi 1996). In Japan, older women attending temples of worship tie a "kairo" around their waist for heat. The "kairo" is a light tin box heated with charcoal that provides heat for about 3 h, but is often reignited repeatedly throughout the day. The use of this device has been associated with squamous cell carcinoma (Treves and Pack 1930; Bartle et al. 1990). The "kang" cancer of northwestern China has also been attributed to the artificial warming of beds (Bartle et al. 1990). In all of these cases, skin cancer has resulted from the chronic thermal dermatitis associated with these heating devices. In some of these cases, the cancer has arisen from burn scars produced by the use of these

Table 2. Studies of chronic exposure to microwaves in specific animal models of cancer development.

Species	Cancer model	Frequency	Effect on cancer development	Reference
C3H/HeJ mice	Mammary tumors	435 MHz	None	Toler et al. 1997
E μ -Pim1 mice	Lymphoma	900 MHz	Increased tumor incidence	Repacholi et al. 1997
Fischer 344 rats with implanted glioma cells	Brain glioma	915 MHz	None	Salford et al. 1993, 1997
C3H/HeA mice	Mammary tumors	2,450 MHz	Decreased latency to tumor development	Szmigielski et al. 1982
Balb/c mice painted with 3,4-benzopyrene	Skin cancer	2,450 MHz	Decreased latency to tumor development	Szmigielski et al. 1982; Szudzinski et al. 1982
C57/6J mice with B16 melanoma	Skin cancer	2,450 MHz	None	Santini et al. 1988
Balb/c mice injected with dimethylhydrazine	Colon cancer	2,450 MHz	None	Wu et al. 1994
C3H/HeJ mice	Mammary tumors	2,450 MHz	None	Frei et al. 1998a, 1998b

devices, making it difficult to determine whether the cancer has arisen from the repeated hyperthermic episodes themselves or from processes within the scar tissue (as discussed in a subsequent section). There is, however, one case report of skin cancer arising in the absence of burn scars in a patient who was "in the habit for many years of sitting in her rocking chair with a hot water bottle resting on top of her hands" (Denham 1982). As mentioned before, a few animal studies have indicated that repeated episodes of hyperthermia may promote but does not initiate carcinogenesis in skin (Urano 1981; Mitchel et al. 1986, 1987, 1988; Baker et al. 1988; Sminia et al. 1996).

Hypertrophic scarring or keloid formation from MMW exposure?

In a previous section, we discussed the possibility that exposure to MMWs might produce superficial skin burns. Although such an occurrence is unlikely because of the pain "warning system," the possibility exists that sudden, acute overexposure to MMWs could produce thermal injury. Could such injury produce subsequent health problems? Because there have been no published reports of MMW overexposures that have produced burns in humans, there is no information available to specifically address this issue. There are two issues, however, that immediately suggest themselves for further consideration. The first is the possibility that such MMW-induced burns might result in hypertrophic scarring or keloid formation. The second possibility to be considered is whether skin cancer may later arise from the conventional burn scar (to be discussed in the subsequent section).

Hypertrophic scars and keloids are excessive tissue responses that may occur following trauma, inflammation, surgery, or burns in predisposed individuals (Murray 1993; Nemeth 1993). Keloid formation is much more common in darker-skinned races than in lighter-skinned races (Kelly 1988; Sahl and Clever 1994 a,b; Thomas et al. 1994), and runs in families, implying a genetic basis (Nemeth, 1994; Thomas et al. 1994; O'Sullivan et al. 1996; Tredget et al. 1997). Both keloids and hypertrophic scars are benign fibrous growths that disfigure and may be a cosmetic issue but do not eventuate in malignant disease (Nemeth 1993; Murray 1993). Although treatment presents a clinical challenge, there are a number of well-accepted treatment modalities now being used to both prevent and to treat keloids (Sherris et al. 1995; McCauley and Hollyoak 1996; O'Sullivan et al. 1996; Tredget et al. 1997).

It is thus clear that the possibility of keloid formation and hypertrophic scarring must be considered in a discussion of occupational overexposure to MMWs, as they would with any agent that has the potential to produce irritation or injury of the skin. Again, it should be emphasized that the likelihood of overexposure to the point of inducing thermal injury appears to be small because of the pain "warning system." If an individual genetically predisposed to keloid formation is accidentally exposed to levels sufficient to produce thermal

injury, however, it is necessary that the clinician treating the burn be apprised of his family history in order that proper avenues of treatment may be pursued to minimize the likelihood of keloid formation. It should also be emphasized that this is not a life-threatening condition but rather a cosmetic issue for which appropriate treatments exist.

Skin cancer from burn scars?

The second issue that must be considered is whether cancer might later arise in a superficial burn scar resulting from inadvertent overexposure to MMWs. Again, there is no information available in the literature that specifically relates to this issue. There have been, however, a number of case reports of skin cancer arising from scars, including burn scars (Table 3). Is the development of skin cancer in scar tissue restricted to that produced by burns? What kind of skin cancer arises from such scars? How likely is this to occur with burn scars? Are burn scars any more likely to result in cancer than other physical scars (e.g., from traumatic injury)?

At the present time, 1 in 7 Americans will develop some form of skin cancer in their lifetime, making it the most prevalent form of cancer (Am. Society for Dermatologic Surgery 1997; National Cancer Institute 1998). Skin cancer is also the most treatable of cancers; approximately 90% of all skin cancers may be cured if detected and treated in time. The term "skin cancer" actually refers to 3 forms of cancer. The first, basal cell carcinoma (BCC), is the most common type of skin cancer. BCC refers to an epithelial tumor that seldom metastasizes but may cause considerable damage through direct growth and invasion of local tissue. Approximately 300,000–400,000 persons in the U.S. are diagnosed with BCC

Table 3. Types of scars (other than those from burn) that have later developed into skin cancer.

Type of scar	Reference
Chronic stasis ulcers	Arons et al. 1965; Barr and Menard 1983
Tattoos	Kirsch 1969
Smallpox vaccination sites	Marmelzat 1968
Hair transplantation sites	Sahl and Clever 1994a, b
Osteomyelitis	Bowers and Young 1960; Arons et al. 1965
Lupus rash	Ryan et al. 1981
Chronic dermatitis	Stromberg et al. 1977
Blisters or pimples	Stromberg et al. 1977
Urinary fistula	Arons et al. 1965; Steffen 1984
Frostbite	Coburn 1976
Blunt or crush injury	Swanbeck and Hillstrom 1969, 1970; Barr and Menard 1983; Hill et al. 1996
Gunshot wounds	Sharlit 1938; Arons et al. 1965; Barr and Menard 1983
Puncture wounds	Sharlit 1938; Arons et al. 1965; Barr and Menard 1983
Amputation	Arons et al. 1965
Open fracture	Barr and Menard 1983
Dog bite	Barr and Menard 1983

each year, but it is easily treatable using surgical techniques (including cryosurgery) or by topical chemotherapy. Squamous cell carcinoma (SCC) is also a cancer of epithelial tissue, but SCC has a greater potential to metastasize. SCC will be diagnosed in 80,000–100,000 persons/year, but it again is readily treatable when detected in early stages. If detected after metastasis, SCC can be lethal and results in approximately 2,000 deaths/year. The third kind of skin cancer, malignant melanoma (MM), is not as common as either BCC or SCC, but is much more serious because of its ready ability to metastasize early. MM is diagnosed in approximately 38,000 Americans each year; over the last 20 y, the incidence of MM has risen 4% each year. MM has an 85% survival rate (5 y from diagnosis), though, because it is usually detected at an early stage. It is now well-established that exposure to the sun and sunburn are causally linked to all of these forms of skin cancer (Am. Society for Dermatologic Surgery 1997; National Cancer Institute 1998).

It has been known for many years that skin cancer may arise within the boundaries of scars, including those produced by burn. Indeed, Celsus first described this phenomenon as early as the first century A.D. (Bartle et al. 1990; Fleming et al. 1990). The term “Marjolin’s ulcer” was later coined to describe malignant transformation in scars after the French physician Jean-Nicolas Marjolin described the condition in 1828 (Treves and Pack 1930; Bartle et al. 1990; Fleming et al. 1990).

Although Marjolin’s ulcer is most commonly thought of in reference to burn scars, it is important to realize that any cutaneous scar has an increased potential to degenerate into malignancy (Glover and Kiehn 1949; Fishman and Parker 1991). Skin cancer has thus been described in many types of scarring (Table 3). Why does skin cancer arise in scars of such disparate etiologies? Several postulates have been put forward to explain this phenomenon, but there is no definitive answer at the present time. It is known that chronic local infection or irritation of the scar site, delayed healing of the original wound, and a prolonged latent period (up to 70 y) often precede the development of malignancy (Glover and Kiehn 1949; Horton et al. 1958; Fishman and Parker 1991). Virchow originally suggested that chronic irritation is a factor in the initiation of carcinoma (as discussed in Horton et al. 1958) and, in support of this hypothesis, it is notable that many scars which have given rise to cancer lie within flexion creases of the extremities (Giblin et al. 1965; Fishman and Parker 1991). Other hypotheses, however, have also been put forward (Bartle et al. 1990; Fleming et al. 1990).

It is clear, then, that the possibility exists that skin cancer might later arise in cutaneous scar tissue, including that produced by burns. Because the focus of this review is the possibility of malignancy arising in MMW-induced burns, subsequent discussion will be restricted to burn scars. As with other forms of scarring, burn scars that are at risk for later developing malignancies are

those that have prolonged healing periods and are chronically irritated. It is important to note that, in the vast majority of malignancy cases reported in the literature, the original burn was either not treated with skin grafting techniques or was not adequately grafted (Horton et al. 1958; Bartle et al. 1990; Fleming et al. 1990; Fishman and Parker 1991). Because the latency period for the development of malignancy may be as long as 70 y, several of the recent reports involve patients who sustained their burn injuries as children 40–50 y earlier (Ikeda et al. 1995; Alconchel et al. 1997; Akiyama et al. 1997; Phillips et al. 1998), when skin grafting was not common. This is not an uncommon occurrence; Lawrence (1952) first noted that there is an inverse relationship between the age of the patient at the time of the burn and the latent period before development of malignancy, and this concept has been widely accepted (Abbas and Beecham 1988; Bartle et al. 1990; Fishman and Parker 1991; Phillips et al. 1998). Because of the development of skin grafting techniques and better treatment regimens, it has been predicted that the incidence of Marjolin’s ulcer from burn scars will decrease as more initial burn injuries are treated in a fashion that minimizes healing time and chronic ulceration problems (Edwards et al. 1989).

What kinds of skin cancer arise from burn scars? Clearly, the most common form of skin cancer seen in relation to burn scars is SCC (Treves and Pack 1930; Lawrence 1952; Bowers and Young 1960; Bartle et al. 1990; Fleming et al. 1990; Fishman and Parker 1991). The second most common neoplasm is BCC, which generally arises in scars produced by more superficial (i.e., partial-thickness) burns that spare hair follicles (Treves and Pack 1930; Lawrence 1952; Fishman and Parker 1991; Koga and Sawada 1997). In their classic study, Treves and Pack (1930) determined the etiology of SCC (in 1,091 patients) and BCC (in 1,374 patients) treated over a 12-y period. They found that previous thermal injury scars accounted for approximately 2% and 0.3% of the cases of SCC and BCC, respectively. Although MM in burn scars has been reported, the incidence of this disease is quite rare; Alconchel et al. reported in 1997 that only 17 recorded cases of MM arising from burn scars exist in the literature (one case has been reported since; Akiyama et al. 1997). Occasionally, isolated cases of sarcomas have been reported (Fleming and Rezek 1941; Gargan et al. 1988; Nishimoto et al. 1996; Can et al. 1998).

What is the likelihood that a burn scar will develop skin cancer? This is an important question in terms of assessing potential long-term health effects of MMW exposure. To date, there has been no study to determine the later incidence of skin cancer in burn patients (Novick et al. 1977). Furthermore, only a few animal studies have been performed that address this question. In 1940, des Ligneris subjected 150 mice to scalding 3 times per week for 3 mo without the development of either benign or malignant skin tumors. Furthermore, this scalding protocol did not accelerate the production of

skin tumors that were chemically initiated (des Ligneris 1940). In contrast, a single burn initiated tumorigenesis in 2 of 30 (7%) mice, and promoted the development of tumors in animals treated with croton oil (Saffiotti and Shubik 1956). In a larger study, only 2 cases of SCC (0.4%) were observed in 480 animals that were subjected to either a single burn or multiple burns followed by intermittent abrasion of the burned area (Arons et al. 1966). From these few animal studies, it would thus appear that the likelihood is quite small, although it should be emphasized that this postulate is based on a very limited database. This question will remain unanswered unless a definitive retrospective study evaluating the later development of skin cancer in burn patients is performed.

Thus, the possibility that burn scars induced by accidental overexposure to MMWs might develop into skin cancers cannot be totally eliminated. Based on the available evidence, however, the likelihood that this will occur must be considered small. Assuming that treatment of such burns is prompt and proper, this likelihood may be decreased even further.

SUMMARY

In summary, MMWs comprise a subset of the RF spectrum that are only recently being exploited for practical applications. One such application is their use in MMW therapy in states of the FSU, an application that is new to Western nations. At this point, the biophysical and physiological mechanisms mediating the putative effects of this therapy are unknown but are worthy of further research. As the use of MMWs increase, the possibility exists that personnel might be inadvertently exposed, perhaps leading to injury. Because of the shallow penetration depth of MMWs, thermal injury to the eye and the skin are most likely. However, irradiation of both the eyes and the skin are, for the most part, self-limiting in that the exposure will be sensed and avoided before thermal injury is incurred. Low-level exposure of MMWs is not known to be carcinogenic; the majority of animal experiments performed to date have failed to demonstrate carcinogenic potential of microwaves at lower frequencies than MMWs. Finally, in the event of an accidental exposure to MMWs of sufficient power to produce thermal injury, there is an extremely low possibility that scars derived from such exposure might later become cancerous. With proper wound management, this possibility decreases even further, as does the risk of hypertrophic scarring/keloid formation.

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