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DEFINITION OF PROCEDURES FOR CHRONIC EXPOSURE OF CANCER-PRONE MICE TO LOW-LEVEL 2,450-MHz RADIOFREQUENCY RADIATION

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The animals involved in this study were procured, maintained, and used in accordance with the Animal Welfare Act and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources - National Research Council.

The Office of Public Affairs has reviewed this report, and it is releasable to the National Technical Information Service, where it will be available to the general public, including foreign nationals.

This report has been reviewed and is approved for publication.

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13. ABSTRACT *(Maximum 200 words)*

Several published reports have implied that long-term, low-level exposure to radio-frequency radiation (RFR) may influence the growth and/or differentiation of mammalian cells in vivo. Specifically, the issue involves whether or not such RFR exposure can cause cells to differentiate into an invasive form (tumor induction) or can act as a promoter of tumor expression. To address this issue, the United States Air Force sponsors a project involving long-term exposure of tumor-prone mice to low-level 435-MHz RFR. An earlier onset, greater incidence, or faster growth rate of tumors in the irradiated group, as compared to sham irradiated controls, would suggest an enhanced tumor promotion potential. This investigation is essentially a parallel study to that being conducted at 435 MHz. The critical difference is the exposure frequency; this study will be conducted at 2,450 MHz, which is near the resonant frequency for mice. Knowledge gained from this study will contribute to the ongoing evaluation of safety standards for human exposure to RFR which is essential to the protection of military operational personnel and the general public.

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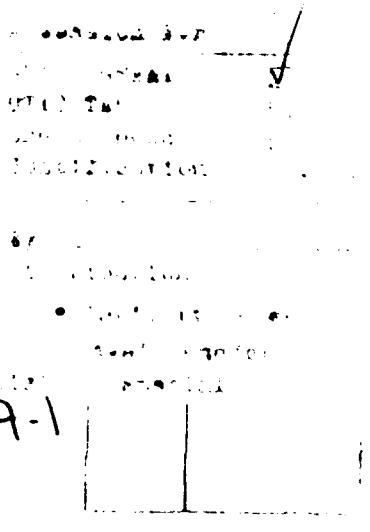

DEFINITION OF PROCEDURES FOR CHRONIC EXPOSURE OF CANCER-PRONE MICE TO LOW-LEVEL 2,450-MHZ RADIOFREQUENCY RADIATION

INTRODUCTION

A long-standing controversy, that has received considerable attention recently, concerns whether or not nonthermal exposure to radiofrequency radiation (RFR) induces or promotes tumorigenesis in mammals. Several in vitro studies (Akamine et al., 1985; Phillips and Winters, 1987; Phillips et al., 1986a; Phillips et al., 1986b; Stodolnik-Baranska, 1973) have indicated elevated growth rates in animal tumor-cell cultures following exposure to electromagnetic energy. Retrospective epidemiological studies (Savitz, 1985; Wertheimer and Leeper, 1979, 1982) have also claimed to suggest a positive causal relationship between low-level exposure to electromagnetic energy and various forms of cancer. Results of these two types of studies (in vitro and epidemiological) have been difficult to evaluate due to inadequate controls, lack of proper dosimetry, and a variety of potential confounding factors not evaluated.

Limited data have been derived from in vivo studies of this question. In 1962, Prausnitz and Susskind repeatedly (5 day/wk, 4.5 min/day) exposed mice to 9,270-MHz pulsed RFR for 59 weeks at power densities that caused a significant increase (2-5 °C) in rectal temperature. They reported an increased incidence of "leucosis" and leukemia in the irradiated mice. These abnormalities were described as monocytic or lymphocytic "leucosis" and lymphocytic or myeloid leukemia; however, "leucosis" was not defined. In 1982, Roberts and Michaelson submitted that the Prausnitz and Susskind report did not support a correlation between exposure to RFR and development of neoplasia, and should not be cited as suggestive of such a

correlation. Factors such as a lack of definition or characterization of "leucosis," an intercurrent epidemic of pneumonitis, and the significant number of animals that were not necropsied or subjected to histopathology, formed the basis of this suggestion. In an evaluation of the data for the Environmental Protection Agency (EPA), Kirk (1984) criticized both the statistical procedures and the experimental methods used in the Prausnitz and Susskind study.

If, on the other hand, there was legitimate neoplasia elevation in the irradiated animals, the probable cause was thermally induced stress. There is no doubt that these mice were thermally stressed, as evidenced by testicular degeneration. In fact, the stated rectal (actually colonic) temperature increase was very likely a gross understatement of the temperature extremes that existed in certain body areas, such as the skin. For example, in a recent study by Frei et al. (1989a), in which rats were exposed to 9.3-GHz RFR to produce a 1 °C colonic temperature increase, subcutaneous temperature was seen to increase by 4-5 °C, due to the poorly penetrating nature of high-frequency RFR.

In 1971, Spalding et al. exposed mice to unmodulated 800-MHz RFR for 2 h/day, 5 day/wk, for 35 weeks, at an average power density of 43 mW/cm^2. Controls were sham exposed. Upon completion of the study, no significant differences in red and white blood cell counts, hematocrit, hemoglobin level, activity, body weight, and survival time were seen between irradiated and sham-irradiated controls. The only hints of a difference were that the irradiated animals survived slightly longer and that aged exposed animals weighed slightly more than did the controls.

In a study by Szmigielski et al. (1982) mammary tumor-prone mice (C3H/HeA) and Balb/c mice, some of which were treated with benzopyrene (which causes skin

cancer), were irradiated with 2,450-MHz RFR at 5 or 15 mW/cm^2 for 2 h/day, 6 day/wk, for periods ranging from 1 to 10.5 months. Controls consisted of sham-irradiated animals, and a group exposed to chronic stress by confinement.

Irradiation for 3 months at 5 or 15 mW/cm^2 resulted in a significant lowering of antineoplastic resistance (unspecified number of mice) as determined by a lung cancer colony assay. Irradiated C3H/HeA mice developed mammary tumors earlier than sham-irradiated controls, and the onset of skin cancer in exposed animals was similarly accelerated. The decreased latency period for cancer development and the lowering of antineoplastic resistance were similar between mice exposed to 5 mW/cm^2 and those chronically stressed by confinement, but both conditions differed significantly from animals irradiated at 15 mW/cm^2.

From the data presented, one can only agree that there was a relationship between irradiation and cancer expression, and between irradiation and lowered resistance. However, the cause of this relationship is unclear. The most obvious cause is that the effects are related to lowered resistance due to chronic stress, a condition that has been reported to be related to cancer expression. This condition is stated by the authors as a possible cause, and is borne out by the similarities between the effects of low-level irradiation and confinement. A probable mechanism involves the production of adrenal steroids that depress normal function of the immune system. Unfortunately, corticosterone levels were not measured in this study.

If indeed, chronic stress was the cause, what caused the stress in irradiated animals? As is the case with many studies that have claimed nonthermal effects of RFR, little attention was paid to careful determination of the radiation dose being delivered and absorbed. The exposure parameters to be delivered were based on the results of irradiation of a single carcass. These results were then calculated and

extrapolated to arrive at what the authors refer to as a "rough estimate" of the energy absorbed during in vivo experimentation. In support of their estimation, the authors state that there were no increases in rectal (actually colonic) temperature during exposure at either 5 or 15 mW/cm^2, although the methods of arriving at this conclusion are not mentioned. If the absorbed energy "markedly exceeded" the basal metabolic rate (as stated by the authors), such an observation is questionable. The authors do suggest the possibility of significant "hot spots" during irradiation at the higher power density. Concerning this possibility, D'Andrea et al. (1985,1987) and Frei et al. (1989b) have shown that such hot spots do exist due to nonuniform absorption of RFR energy. Thus, as was the case with the Prausnitz and Susskind study, thermally induced stress was the probable cause of the effects noted.

In the most recently completed long-term study performed by Guy et al. at the University of Washington, 100 Spraque-Dawley rats were exposed to pulsed 2,450-MHz at specific absorption rates (SARs) ranging from 0.1 to 0.4 W/kg (depending on size) for 21.5 h/day, 7 day/wk, for 25 months, and 100 were sham irradiated.

Measurements of motor activity, corticosterone levels, immune competence, blood chemistry, hematologic profiles, body weight, food and water consumption (although both irradiated and control animals consumed approximately 2x normal amounts of food), organ weights (tumored adrenals were heavier), metabolic rate (young control animals showed increased O_2 consumption at night, presumably due to increased metabolism in the 21 °C environment), and causes of death, showed no significant difference between controls and irradiated animals.

The original pathology report (Kunz et al., 1985) showed that if one combined all malignant tumors into a group, the irradiated animals had a higher tumor incidence than did controls. However, if one included benign tumors as well, the difference disappeared, and at no particular site was there a difference in numbers

of tumors. The authors concluded that the higher overall incidence of malignant tumors was of "questionable biological significance."

In 1987, McGaughy, of the EPA (OPEA), saw a need for a more detailed description of the survival and histopathologic findings than was provided in published reports. Upon request, Kunz, pathologist for the study, provided a more detailed description of his findings, which was subsequently reanalyzed by McGaughy.

The EPA's reevaluation of Guy et al.'s work yielded two positive correlations between microwave exposure and cancer: (1) The incidence of benign pheochromocytomas of the adrenal medulla was significantly higher in the microwave-exposed group than in controls, and (2) the incidence of malignant tumors of the glandular organs (as a group) was significantly higher in the microwave-exposed group.

In mid 1990, a team of research scientists from the Radiation Sciences Division at the United States Air Force (USAF) School of Aerospace Medicine (now, the Directed Energy Division, Armstrong Laboratory), Brooks AFB, Texas, reviewed McGaughy's conclusions. Concerning the long-term animal studies, it was concluded (based on inappropriate statistical treatment of data, lack of reproducibility, and rampant use of postulation and speculation) that the existing experimentally derived data do not support the EPA's assertions that RFR, per se, induces or promotes carcinogenesis. Thus, after approximately 20 years of observation and sporadic experimentation, there is no unified consensus of opinion as to whether or not there is a definite link between exposure to electromagnetic energy and cancer incidence.

The objective of the present study is to determine whether or not chronic, low-level exposure of mammary tumor-prone mice to 2,450-MHz microwaves promotes an earlier onset, a greater incidence, or a faster growth rate of tumors.

EXPERIMENTAL METHODS

Animal Model

The mammary tumor-prone mouse (C3H/HeJ) was selected as the model for studying the effects of chronic, low-level radiofrequency irradiation on growth and differentiation of mammalian cells in vivo. This model was selected for a number of reasons. (1) C3H mouse mammary tumors are among the most frequently studied spontaneously occurring neoplasms, and the incidence and latency to onset are well documented (Outzen et al. 1985). (2) Taking into account the physical limitations of the existing exposure facility, use of mice allows study of a relatively large number of animals, thereby strengthening the statistical power. (3) Using the C3H model, Szmigielski et al. (1982) showed that irradiated female mice developed mammary tumors earlier than sham-irradiated controls and in slightly greater numbers. (4) The currently on-going USAF-sponsored chronic exposure series being performed by Toler et al. at the Georgia Institute of Technology also employs the C3H/HeJ mouse model. Although the frequencies, power densities, and exposure regimen were varied in these studies, use of the same animal model in the present study will provide some uniformity and continuity to the research efforts.

Animal Facility

The circular-waveguide (CWG) facility consists of two rooms in Bldg 1187 of the Radiofrequency Radiation Facility at Brooks AFB, TX. The waveguides occupy an 18 ft x 18 ft (5.49 m x 5.49 m) room that has its own source of temperature control, humidity control, and ventilation. The airflow is approximately 10 exchanges per hour. Room temperature will be maintained at 24 ± 1 °C, and relative humidity will be kept at 50 ± 5%. A time-controlled lighting system will provide a 12h/12h light/dark cycle (lights on at 0600). Illumination levels of approximately 30 ft-candles at 1.0 m above the floor will be provided by fluorescent fixtures.

Animal Housing

The circular waveguide system to be used in this study is a modified version of the system used in the University of Washington study (Guy et al., 1983). The cages, which were originally designed to house a single rat, were modified to house 2 mice, allowing both mice free access to food and water. Modified cages were tested for adequacy by comparing mouse growth rates with controls housed in standard "shoebox" cages (2/cage). Analysis of variance showed no significant differences in growth rates between the 2 groups (n = 15/group) although the individually housed mice exhibited a slightly greater growth rate.

The cages are constructed of Plexiglas material with the floor made of 5.0 mm Plexiglas rods spaced 0.75 cm apart. This spacing provides adequate animal support and allows feces and urine to fall into a disposal tray beneath the cage. Plexiglas is virtually transparent to RFR at 2,450 MHz and permits visual inspection and observation of the animals. In addition, Plexiglas can be conveniently sanitized in a commercial cage washer. The cages provide a floor area of 143 cm^2 per animal which is significantly greater than required by the Guide for the Care and Use of Laboratory Animals (NIH Publication 86-23).

Animal Procurement and Identification

Two hundred (plus sentinel animals) weanling C3H/HeJ mice will be obtained from the same colony of a commercial vendor (Jackson Labs, Bar Harbor, ME). When procured, the mice will be approximately 3-4 weeks of age. The mice will be randomly assigned to 2 groups (irradiated and control), marked for identification (toe clip method employed by Toler et al.), and quarantined for 2 weeks. The mice will be introduced into the exposure regimen at approximately 6 weeks of age.

Animal Husbandry

Mice will be housed individually (1/cage) within the circular waveguide. Purina Certified Rodent Chow will be available ad libitum. The water source will be the Brooks AFB Water System. Animals will have free access to fresh water from anti-shock bottles. There will be no evaluation of food or water consumption during this project.

Mice will be removed from the waveguide cages for a weekly inspection and weighing after which they will be returned to clean cages with clean water bottles and sipper tubes. Dirty cages and watering devices will be transported to Bldg 1004 where they will be washed in a commercial cage and bottle washer (wash and rinse cycles > 82.2 ^{o}C (180 ^{o}F)).

During the experimental period, animals will be visually inspected twice daily; once between 0730 and 0830 and again between 1600 and 1700.

Exposure Duration

Using the C3H/HeJ substrain maintained under standard rodent colony conditions by Jackson Laboratory, Outzen et al. (1982) found that the average time required for 50% mammary tumor incidence was 61 weeks. However, preliminary reports on the Toler et al. study indicate that when mice are housed individually, the latency period for tumor onset is considerably lengthened.

Mice will be introduced into the exposure regimen at approximately 6 weeks of age. The exposure schedule will be maintained for the period of time such that 90% tumor incidence occurs. We anticipate that this criterion will be met after 18 to 20 months of experimentation.

Exposure Fields

Exposure Equipment

For this study we will use the circular waveguide system described by Guy et al. (1983). The exposed group will be irradiated with 2,450-MHz RFR. The signal will be generated by a Hewlett Packard Signal Generator, Model 8616A. The signal will be amplified by a MCL 1-KW S-band Amplifier, Model 10704. The RFR power level of the MCL Amplifier will be monitored continuously at the output terminal. On a rotating basis, output of RF studs to individual waveguides will also be monitored; a different waveguide will be monitored each day. A Boonton RF Powermeter (Model 4300) will be used for all power level monitoring. Signals will be fed to the system computer (Zenith 248) via an IEEE 488 bus.

Dosimetry

Meaningful research on the bioeffects of RFR exposure depends on accurate determination of radiation dose levels. Otherwise, accurate relationships between experimental results and absorbed energy levels cannot be established and certainly cannot be replicated. It is also impossible to extrapolate results obtained using experimental animals to equivalent human models unless the energy deposition during experimentation is reliably determined.

The responses of animals exposed to RFR are clearly related to the SAR rather than to the incident power density or the field intensity. The SAR determination for the irradiated mice will be obtained in two ways. The first method will be used before starting the experiment and will be used to validate results of the second technique. The SARs will first be determined calorimetrically by placing mouse carcasses in the CWG with the appropriate cage, water bottle, etc., turning on the RFR to obtain a temperature rise, and then placing the carcasses in calorimeters to determine the amount of energy absorbed [method of Padilla and Bixby (1986)].

Carcasses of various weights, representative of the weight range expected during the exposure period, will be irradiated in this manner. Additionally, carcasses will be placed in various positions within the cages in order to quantify any power absorption differences due to changes in orientation within the CWG.

The second method, based on differential power measurements will be used to determine SAR during the course of experimentation. In this method, power going into, reflected from, and absorbed by the CWG will be measured. From this measurement, the amount of energy absorbed may be calculated (technique of Guy et al., 1983). Initially, the 2 techniques will be performed simultaneously to verify the validity of the differential power technique.

Irradiation Levels

In the current Georgia Institute of Technology chronic-exposure project, the irradiated animals are receiving RFR at an average whole-body SAR of 0.32 W/kg. This dose rate was determined experimentally using medium-sized mouse carcasses. We propose that the transmitter and amplifier in the present study be adjusted to provide power densities to each experimental CWG that will yield a SAR of 0.3 W/kg in a medium-sized mouse. After establishing the required power levels, the status of generator, amplifier and CWGs (on a rotating basis) will be constantly monitored by the system computer.

Study Logistics

Preparatory

The initial 6 months of the study will be devoted to preparations for initiation of the RFR exposure. During this period, the following steps will be accomplished:

- Preparation of protocol
- Preparation of standard operating procedures (SOPs) to be used during the study

- Completion of CWG dosimetry
- Calorimetric determination of SAR and comparison with SARs determined by differential power measurement
- Development of software and interface to allow computerized data acquisition of:
    - Up to 16 channels of RFR data, such as forward and reflected power, AC voltage, transmitter status, etc.
    - Environmental conditions, such as relative humidity and ambient temperature.
- Development of animal growth monitoring system
    - Subject body weight database
    - Integrated statistical analyses
- Development of animal health status database
    - Tumor onset and growth rates
    - Annotated daily health check
    - Integrated statistical analyses
- Debugging - Equipment stress test - hardware/software/human factors integrity testing
- Training in techniques of necropsy and tissue preparation

Pre-Exposure Animal Logistics

When the preparatory tasks are completed, 250 female C3H/HeJ mice will be ordered from a suitable commercial vendor (Jackson Laboratory, Bar Harbor, ME). Upon receipt, 240 of the animals will be weighed and randomly assigned numbers. Animals will be numbered by toe clips. The remaining 10 mice (sentinel animals) will be euthanized by a CO_2 inhalation and necropsied as part of the necropsy training program provided by Pathology Associates, Inc. (PAI). The necropsy results will

be used to characterize the health status of the animals and will provide the baseline against which results of subsequent necropsies will be compared.

These preliminary tasks will be followed by a 2-week trial period, during which the SOPs will be followed with respect to daily animal observations, record keeping, weighings, cage washing, cleaning and changing soil trays, etc. During this period, the day/night cycle for the animals will be established. Any needed revisions will be incorporated into the applicable SOPs.

One day prior to initiation of RFR exposure, a second group (5) of sentinel animals will be necropsied under the supervision of a PAI representative (Dr. Stedham). A final pre-exposure health status examination will also be performed.

Logistics of RFR Exposure and Data Acquisition

Radiation exposure will begin at 1200 hours on a Monday (Time Point 0). The transmitter will be energized and adjusted such that the field delivered to each CWG will result in an average SAR of approximately 0.3 W/kg/animal. Exposure will continue for 20 h; the transmitter will be de-energized at 0800. This exposure schedule will be maintained 7 days per week for 72 to 80 weeks. During the 0800 to 1200 period each day, routine facility cleaning, animal inspection, and transmitter maintenance will be accomplished in accordance with the SOPs. Twenty cages will be changed every day during the normal work week (M through F). On any day, 40 mice will be removed from their cages, weighed, palpated, visually inspected, and returned to clean cages. Soil trays beneath all cages will be changed every other day (M-F).

At Time Point 6 months (6 months after exposure initiation), Dr. Stedham will return to supervise the third scheduled sentinel animal necropsy. At this time, he will inspect all animals.

At Time Point 12 months, the procedures of Time Point 6 months will be repeated.

The RFR exposure will be terminated at Time Point 18-20 months. At this time all remaining animals (those that did not die spontaneously or became moribund and were euthanized) will be euthanized and necropsied. This final necropsy will be performed by Dr. Stedham and his team of prosectors from PAI.

Following completion of the final necropsy, all specimens will be inventoried, and returned to the PAI laboratory for processing. All protocol-specified tissues and gross lesions will be evaluated blindly. Microscopic findings will be entered into the PAI-LABCAT automated pathology data system and a report formulated. The list of tissues for complete histologic evaluation has been published elsewhere (Toler and Bonasera, 1987).

The PAI Quality Assurance Division will monitor all phases of tissue preparation, evaluation, and report formulation. A Quality Assurance Certification Statement will accompany the final Pathology Report.

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