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Biological Effects of Microwave Radiation: A White Paper

The White Paper reproduced below was written by Dr. Cletus Kanavy, the chief of the biological effects group of the Phillips Laboratory's Electromagnetic Effects Division at Kirtland Air Force Base, NM, in October 1992. The references at the end of Kanavy's paper are omitted here.

The biological effects of microwave radiation on living organisms have been the subject of extensive research for the past four decades. The most comprehensive programs were conducted by the Soviet and Eastern Bloc nations. The U.S. has lagged behind badly in this area of research. Initially, the principal concern for human exposure to microwave radiation was that of thermal heating of the tissues. Permissive exposure limits were based on such criteria. Since the 1970s this limit has been progressively set at lower levels of average field power density for the classical six-minute time average period. These limits, which are published as the American National Standards Institute (ANSI) microwave standards, are actually derived by the Institute of Electrical and Electronics Engineers (IEEE). Under IEEE, a blue-ribbon panel of experts periodically reviews the research database and assesses the need to revise the standards. Until 1991, these standards did not consider the possible biological effects of "pulsed" microwaves. The 1991 standards do address the pulse condition (rather shabbily, I believe), place restrictions on the number of pulses per six-minute time period as a function of pulse width, and continue to use the continuous wave time averaging technique for thermal criteria. The existence of nonthermal effects is essentially denied by omission.

The U.S. research community was aware of the Soviet findings of deleterious biological effects at exposures well below the ANSI standards. The Soviet findings were rejected for various reasons. The principal reason was that U.S. attempts to duplicate the Soviet results were reportedly not successful. It was not until the mid-1980s that U.S. researchers began to successfully duplicate Soviet experimental results and began a research program to expand upon and further test the Soviet nonthermal theories.

Since March 1991, we have been conducting a comprehensive search of worldwide literature on the results of experimentation regarding biological effects produced by microwave radiation. The results of this search have been consolidated into a computerized database which we have shared with the Armed Forces Medical Intelligence Center and the Central Intelligence Agency. We attempted to share the database with the Armstrong Laboratory. A list of the holdings in the database was presented to Dr. Dave Erwin of Armstrong who proceeded to "line-out" the publications of researchers he believed not to be credible. These were researchers who were reporting the positive existence of nonthermal effects.

The literature published in the late 1980s is abundant with information on nonthermal effects which are produced at levels below the ANSI standards. These are essentially chronic exposure effects at low levels of average field power densities. Researchers stress the chronic, nonthermal nature of these effects as opposed to acute exposure thermal effects. Ample experimental evidence exists from credible researchers from well-established and highly regarded institutions, both government and university, to justify a national research program into the full spectrum of biological effects of electromagnetic radiation.

The principal electromagnetic biological effects of greatest concern are behavioral aberrations, neural network perturbations, fetal (embryonic) tissue damage (inducing birth defect), cataractogenesis, altered blood chemistry, metabolic changes and suppression of the endocrine and immune systems. The verification of blood–brain barrier suppression should have a high priority. The passage of normal blood-borne toxins into the brain could explain some previously observed early behavioral aberrations, loss of physical endurance and functional central nervous system and perceptual changes. A large amount of data exists, both animal experimental and human clinical evidence, to support the existence of chronic, nonthermal effects. The Soviet studies of humans under occupational conditions report marked functional changes, sometimes accompanied by histological and biochemical changes, under the chronic influence of microwaves at power densities ranging from fractions of microwatts to a few milliwatts per square centimeter. Research to date has concentrated on determining the psychological/physiological effects (changes) produced by electromagnetic fields of various power densities, carrier frequencies and modulation rates. These results are the macroscopic part of the issue. The microscopic part of the issue urgently needs to be addressed—namely the physical mechanisms behind the various observed biological effects. Various theories and interaction models exist to explain, in a limited way, some of these physical mechanisms for specific effects. None have yet been positively verified. This is believed to be a key issue which needs to be addressed as soon as possible....

Other areas of concern center on the uninvestigated human response to high peak, low average power, moderate to high pulse repetition frequency microwave fields. The relationships between these variables and specific human responses should be of prime importance to the directed energy weapon (DEW) development programs. The ability of certain modulation frequencies imposed on various carrier frequencies to affect (lock onto) circadian rhythms poses a formidable research problem. A principal question raised is the existence of "frequency windows" and resonances associated with certain physiological and psychological responses. The past several issues of *Bioelectromagnetics* have contained many articles by prominent U.S. researchers which report nonthermal effects. New concerns are also forthcoming, i.e., bioeffects of ELF and electromagnetic fields in close proximity to high voltage power lines and transformer banks. Thus the entire issue of human interaction with electromagnetic (RF & microwave) radiation is pushing forward as a major national population health concern.

search program is to monitor the health of Kirtland employees exposed to RF/MW radiation. Erwin, however, rejects this idea. In his January letter to Godfrey, Erwin appended four different memos—one from an epidemiologist, one from a lawyer and two from members of his research group—to counter Kanavy's arguments for a long-term health monitoring program of high-power microwave workers at the Phillips Lab. He concluded that, "The consensus opinion is that such a limited program would yield no legal or scientific benefit to the Air Force and might even have a negative impact."

Despite all the criticisms, Erwin's plan to consolidate all Department of Defense research on non-ionizing radiation is proceeding. The microwave lab at WRAIR has closed down and the equipment has been shipped to the Armstrong Lab. The Naval Aerospace Medical Research Lab in Pensacola, FL, is scheduled to move to San Antonio next summer.

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POTENTIAL PUBLIC HEALTH RISKS FROM WIRELESS TECHNOLOGY

RISK EVALUATION RESEARCH:
PROGRESS, PRIORITIES, AND REQUEST FOR PROPOSALS

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1.0 INTRODUCTION

1.1 Research Agenda

In early 1993, questions regarding the safety of hand-held portable cellular telephones were raised publicly in a Florida lawsuit in which a man claimed that his wife's brain tumor was a result of her cellular telephone use. Subsequently, the cellular telephone industry, including manufacturers of telephones, manufacturers of the telecommunications infrastructure, and cellular telephone carriers, pledged their support for a major research initiative to facilitate science-based decisionmaking regarding the safety of current and future wireless technology. [1]

An independent Scientific Advisory Group (SAG) (now Wireless Technology Research, L.L.C.) was commissioned and given the task of managing an independent, comprehensive, and rigorous research program to develop a scientific database upon which public health decisions could be made. The Wireless Technology Research, L.L.C. (WTR) was further charged with presenting advice and recommendations to the industry regarding both the presence of any public health risks posed by wireless communication instruments and strategies for the mitigation of those risks.

Among the initial functions of the WTR were to collect, review, and assess available research on the potential effects of radiofrequency radiation (RFR), define the areas for which information is needed, and develop a research plan. In August of 1994, the SAG published "Potential Public Health Risks from Wireless Technology: Research Agenda for the Development of Data for

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[1]The history and evolution of the research program is detailed in a number of publications available through the WTR. It is strongly recommended that investigators interested in applying to the program for funding read through the following at a minimum: "Potential Public Health Risks from Wireless Technology: Research Agenda for the Development of Data for Science-Based Decisionmaking"; *Wireless Technology Update*, Volumes 1, 2 and 3; Information Packet on Wireless Technology Research, L.L.C.; "Interim Status Report: Potential Public Health Risks from Wireless Technology: Development of Data for Risk Management Decisionmaking"; "Report on Phase One: Laying the Foundation."

Science-Based Decisionmaking" (Research Agenda). The Research Agenda was 15 months in the making including a seven-month peer review period. More than 150 scientists from academia, private laboratories, government agencies, and industry provided informed input. The Research Agenda, therefore, stands as the template against which all work under the program is to be judged. The research agenda was subjected to intensive scientific peer review by a Peer Review Board. The Harvard University School of Public Health, Center for Risk Analysis is coordinating scientific peer review under the program. All aspects of the WTR research program are subject to ongoing peer review.

A straightforward public health paradigm was described in the Research Agenda. Four operating questions were used to define the scope of the program:

- Is there a public health risk posed by wireless communication instruments?
- If yes, what are the characteristics of that public health risk?
- What are the appropriate interventions to mitigate that public health risk?
- What is the appropriate implementation strategy for those interventions?

The WTR in its efforts to develop answers to question one above supports an ongoing surveillance program to assess current information and identify new areas of research and sponsors research required to fill data gaps identified as part of the surveillance program. Four general principles laid out in the research agenda guide the research effort.

- The research program is limited to studies directly relevant to the public health impact of cellular telephones and other wireless communication instruments.
- The research program includes only studies conducted in accordance with Good Laboratory Practices (GLPs), Good Epidemiology Practices (GEPs) and Good Clinical Practices (GCPs).
- Investigators funded through the program are required to submit their work for publication in the peer-reviewed scientific literature.

- The risk evaluation research program encompasses a tiered approach to both developing information and placing appropriate weight on specific scientific findings.

The three-tiered system incorporates a hierarchy regarding the importance/weight given to different elements of the research program. Since cellular telephones are already in relatively wide use, a high quality database integrating both animal and epidemiological data is essential in order to provide a scientific foundation for determining the potential for health risk, as a reference for possible post-market surveillance, and as a health perspective benchmark for the evolution of cellular telephone products.

Tier I studies involve the development of RFR exposure systems relevant to wireless communication instruments including cellular telephones and conduct of toxicology studies in accordance with standard approaches to product safety evaluation.

RFR exposures resulting from the use of wireless communication instruments are unique; therefore, central to the conduct of toxicological tests is the development of appropriately designed exposure systems. Experimental exposure systems are being developed by the WTR that appropriately represent actual human exposure conditions. These systems will be applicable to *in vivo* or *in vitro* experimental situations and will be standardized across investigations. Once appropriate exposure systems have been developed, these will be made available to investigators supported by the WTR or other interested parties.

Toxicology research sponsored by the WTR involves a series of studies using *in vivo* and *in vitro* systems to assess potential genotoxic effects of cellular phones. From a scientific point of view and a regulatory perspective, *in vivo* and *in vitro* genotoxicity studies are considered to be helpful in determining carcinogenic potential. Lifetime chronic studies in rodents are the standard method of assessing carcinogenic potential and are accepted by regulatory agencies.

Tier II studies encompass epidemiological evaluations and longitudinal surveillance of cellular telephone users, employing appropriate measures of real-life exposures. A series of

epidemiology studies of appropriate designs (e.g., cohort, case-control, cross-sectional) will assess the potential health risks derived from exposures to RFR waves from cellular telephone usage. No epidemiology studies have been conducted on cellular telephone users. Different study designs (cohort, case-control, etc.) are necessary to fully evaluate possible causal associations. Cohort studies allow for evaluation of a wide range of health outcomes, while case-control studies are most useful for the study of disease-specific hypotheses.

Tier III studies will address mechanistic issues arising from studies conducted under Tiers I and II which are suggestive of a public health risk. *In vitro* or *in vivo* mechanistic studies will be conducted, as needed, to assist in the interpretation of results from Tier I and Tier II studies to make relevant scientific judgements as to their human health implications.

The WTR research program creates a nexus through which the WTR can identify appropriate public health concerns and possible interventions as rapidly as possible. The information collected as a result of this research program will provide the basis for prompt actions by government and industry to correct identified public health problems through implementation of interventions identified by this program.

1.2 Progress Since Publication of the Research Agenda

As described above, the Research Agenda laid out the general structure and goals for the WTR's research program. In addition, areas in which relevant information were lacking were identified pertaining to dosimetry, toxicology and epidemiology. Accumulation of information needed to fill knowledge gaps identified in the Research Agenda was considered a prerequisite for the formulation of rational decisions concerning specific research program goals and priorities. The reader is referred to "Report on Phase One: Laying the Foundation" for a complete overview of the WTR's efforts since the publication of the Research Agenda.

1.3 Purpose of This Document

This document is meant to assist potential investigators and other interested parties by presenting the following information:

- a detailed description of progress in the development of the WTR's risk evaluation research program;
- an outline of the rationale on the development of research priorities based on the information gathered during and subsequent to the preparation of the Research Agenda;
- a listing of the current research priorities in the areas of dosimetry, toxicology, epidemiology, clinical studies and areas of research identified as part of the WTR's surveillance program; and
- specific requests for proposals in response to the identified research priorities.

In addition, other items covered in this document include: details regarding the current status of development of WTR's *in vitro* exposure system, a description of quality assurance and GLP/GEP/GCP standards required of investigators interested in participating in this program, and information pertaining to proposal review procedures and estimated deadlines for selected events.

2.0 TIER I - EXPOSURE SYSTEM DEVELOPMENT

Central to the conduct of Tier I studies is the development of exposure systems that appropriately represent actual human exposure conditions. These must be applicable to *in vivo* or *in vitro* experimental situations, and to the degree possible, be standardized across investigations. Exposures from wireless communication instruments are unique in comparison to exposures typically studied in the past. Instruments such as portable cellular telephones generate low and localized exposure to the head and hand, with extremely low, even negligible exposure to the rest of the body. Appropriate exposure systems designs must address biological

scaling concerns and must allow for incorporating a range of exposures reflecting the use of wireless technology communication.

The exposure systems and dosimetry techniques used for WTR-funded research will be developed in-house through the help of the Dosimetry Working Group, originally organized to address cellular telephone certification issues. Since this group also has considerable expertise in exposure system development and RF dosimetry, additional members were added to address the exposure and dosimetry issues. The rationale for this decision is three-fold: 1) discussion within the Working Group, conduct of workshops (see below), and consultations with experts in the field made clear the complexity of achieving the exposure system design requirements of this program; 2) important information, such as accurate and detailed specific absorption rate (SAR) characterization in the rat head under appropriate exposure conditions were unavailable and therefore need to be produced by WTR-sponsored research; 3) many of the proposals submitted in response to the WTR's initial request for proposal (RFP) (*Wireless Technology Update*, Vol. 1, No. 3) involved the use of inappropriate whole-body exposure techniques.

2.1 Progress to Date

2.1.1 WTR Workshop on Dosimetry

In December 1994, WTR held a workshop[2] to discuss, debate, and attempt to reach a consensus on appropriate directions for development of *in vivo* and *in vitro* exposure systems. Topics of discussion and areas of consensus developed during this meeting are outlined below.

Relevant exposures for this research program will most likely demand a novel, head-only exposure system for *in vivo* experiments. An accurate characterization of SAR distribution in animal and human models will be crucial in defining *in vivo* dosimetric parameters and in

[2]Radiofrequency Exposure and Dosimetry Workshop: Small animal and *in vitro* exposure systems, 2-3 December 1994, Los Angeles, CA.

assessing epidemiology studies (see Garn and Gabriel, 1995; Anderson and Joyner, 1995). Assurance of uniform SAR distribution and control of thermal effects were identified as important considerations in the selection and design of relevant *in vitro* exposure systems.

2.1.2 Exposure Parameters

In designing toxicology studies involving RFR, definition and selection of exposure parameters are critical. RFR exposure parameters to be considered are frequency, modulation, polarization, scaling, and intermittent versus continuous exposures. Dose should be considered the product of dose rate and time of exposure. The selection of relevant doses will require the characterization of SAR through completion of *in vivo* modeling studies and/or setting a defined limit based on current exposure guidelines. Time of exposure will require integration of epidemiological findings with general guidelines for conduct of *in vitro* and *in vivo* toxicology studies.

2.1.3 Frequency and Modulation

One of the most fundamental requirements for system and experimental design for both *in vitro* and *in vivo* experiments is the selection of relevant exposure frequencies. Wireless communications currently use frequencies in the 800-900 MHz band, while next-generation technologies will use higher frequencies (1800-2200 MHz). The use of specific frequencies representative of current and future technologies would simplify system and experimental design. However, without information as to the effects of different frequencies it will be difficult to determine the appropriate frequency to use. Studies conducted at multiple frequencies would establish coherence of the frequency band and address concerns about frequency-specific effects. Broadband exposures would be useful, since moving between frequencies within the cellular band would be a more realistic approximation of human exposure. The limitations for multiple types of exposure, however, are the introduction of considerable expense and the inability to pinpoint frequency-specific effects, if they occur.

Current-generation wireless technology uses either simple frequency modulation (analog systems) or more complex time- or code-division modulation (digital systems). Personal Communication Systems (PCS) and some digital technologies are expected to involve amplitude modulations. Evaluation of the effects of various types of modulations will be an important parameter to test.

2.1.4 Polarization

Cellular telephone antennas in use at this time are monopole antennas with the polarization predominantly vertical (parallel with the axis of the antenna). Thus, the head of a cellular telephone user is subject to exposure with polarization varying from vertical to about 45 degrees from vertical. In keeping with duplicating human exposure as closely as possible with *in vivo* exposures, animals should be exposed to the same polarization with respect to brain anatomy.

For *in vitro* exposures, polarization considerations will be important in designing exposure systems that will provide the most uniform SAR throughout the medium. As for the human or animal body, the medium in the flask has three specific axes, long, medium, and short. When the radiation is polarized with the electric (E) field vector parallel to the long axis, the direction of propagation (K-vector) parallel to the medium axis, and the magnetic (H) field vector parallel to the short axis (called EKH polarization) maximum SAR is produced. However, the distribution is very non-uniform over the flat surface of the medium due to maximum constructive and destructive interference between E-field and H-field induced currents. When the radiation is polarized with the K-vector parallel with the long axis, the E-field parallel with the medium axis and the H-vector parallel with the short axis (called KEH polarization) the SAR is lower than that for EKH polarization but is still non-uniform since the long and medium axes of a typical flask are of similar dimensions. The most uniform SAR for an exposed flask occurs when the H-field is parallel with either the long or medium axis and the K-vector is parallel with the medium or long axis respectively, and the E-field is parallel with the short axis (HKE or KHE polarizations). SAR is most uniform for this configuration since there is very little interference

between the relatively uniform E-field and H-field induced currents. However, the energy coupling efficiency and the SAR are very low.

2.1.5 Specific Absorption Rate

The SAR is defined as the rate at which energy is absorbed by an incremental mass of an exposed object divided by that mass and is expressed in watts per kilogram. SAR is a quantitative dosimetric quantity that can be used to determine temperature increase, internal electric-field strength, and induced current density. SAR is, therefore, the appropriate dosimetric parameter for quantifying both the peak and average values for the internal fields and current densities. Both experimental (e.g., temperature probe measurements) and computer numerical methods can be employed to calculate SAR distributions in an exposed object. The advantage of numerical methods is the ability to deal with non-homogeneous objects given that the dielectric properties of the various sections of the object (i.e., tissues) are known. One mathematical model called the finite-difference time-domain (FD-TD) method has been used to evaluate SAR distributions both for whole-body and partial-body exposures from far- or near-fields.

In keeping with the goal of mimicking as closely as possible the exposure of human cells from use of wireless communication technology during *in vitro* studies, peak SAR in cells of the human head exposed to RFR during use of wireless communication technology will need to be defined. Though a large amount of data is becoming available from theoretical calculations and experimental measurements of SAR in models of the human head, there is a great deal of disagreement over reported values. Peak values of SAR are usually expressed in averages over a gram of tissue in the shape of a cube, averages over a voxel in a computer model, or averages over the volume occupied by a field sensor. None of these truly provide the SAR as averaged over a single cell, which is needed to form a basis for specifying maximum *in vitro* exposure levels. The peak values of SAR associated with the smallest voxels (2mm x 2mm x 3mm) used for theoretical FD-TD studies of the exposed human head model will probably provide the most accurate estimate of peak SAR associated with cell exposure.

Studies of realistic human models have reported peak SAR values ranging from 1.06 to 1.99 W/kg in brain tissue and as high as 4.8 W/kg in other tissues. Though these numbers result from an average over a volume much larger than a cell, at the wavelengths used by cellular telephones and PCS, there cannot be much variation of SAR throughout a typical 12 mm^3 volume of tissue represented by a single computer model voxel. Therefore, based on the highest reported SAR averaged over a voxel, we would expect that single cell exposure could be as high as 2 W/kg in the brain and as high as 5 W/kg in other tissues. Rigid temperature control throughout the cell medium will be necessary to eliminate thermal effects. This is especially important for SARs necessary to produce exposures that are multiples of theoretical peaks which are likely to ensure a robust test for potential effects of wireless communication technology.

2.1.6 Temperature Control And Thermal Effects

The importance of temperature control in the interpretation of results from research on effects of RFR on cells was noted by Moressi more than 30 years ago:

> "One may critically question the role of unrecognized temperature discrepancies in many of the previously reported studies in which gross results seemed to indicate the presence of a non-thermal factor. Temperature regulation is thus a major concern in investigations concerned with the effects of high frequency electromagnetic irradiation on biological systems, especially when some form of cellular destruction is involved."

At very high SARs a significant temperature gradient exists between the cooling wall and the middle of the cell suspension. This gradient may be responsible for the induction of convection currents which can result in movement of cells, leading to non-uniform SAR over time. Control of temperature presumably will allow for separation of thermal (heat-related) effects from non-thermal effects (effects due to frequency or modulation, for example). Thermodynamic analysis for the exposure system might provide useful information regarding the potential for significant cell culture heating.

Consideration of thermal and non-thermal effects, thresholds, and mechanisms will be important in designing appropriate exposure systems and toxicology tests. Several reviews of biological

effects of RFR including discussions of thermal and non-thermal effects are available (including NCRP, 1986; WHO, 1993; Elder, 1994). Thermal effects are related, for the most part, to interaction of RFR with water molecules. Thus, tissues with high water content absorb more RF energy for a given electric field in the tissue. For *in vitro* exposures this means that, at least for thermal effects, cells can be treated as a part of the medium. No definitive mechanism has been demonstrated for non-thermal effects. At the cellular level, membrane effects have received the most attention (for more details see references listed above). In most studies, differentiating between potential thermal or non-thermal effects has not been possible, since at low SAR, thermal responses may occur without temperature changes as measured by standard equipment. On the other hand, at SARs which clearly induce thermal stress and/or measurable temperature increases, effects potentially due to non-thermal mechanisms may be masked by thermal effects. For *in vitro* experiments there is no clear method for determining temperature increases at the cellular level so that initial work will depend on demonstrating a uniform SAR distribution in media at a power level below the thermal threshold.

2.2 *In vitro* Exposure Systems

The pros and cons of several types of *in vitro* exposure systems have been considered by the WTR, including the following:

1) Exposure in a Transverse Electromagnetic (TEM) Cell in Air or Liquid

TEM cells provide exposure conditions most similar to the free-space environment and have thus been used widely in the past. Since the TEM cell simulates free space radiation conditions, polarization effects for free space radiation apply. The height and width of the TEM cell should be less than one-half wavelength of the highest frequency to be used. For example, at 837 MHz a half wavelength is 17.9 centimeters. However, with careful design, a relatively pure TEM wave may be maintained in a larger TEM cell if no discontinuities are introduced to excite the higher order modes.

2) Exposure in a Radial Waveguide

The radial waveguide, like the TEM cell, also propagates a wave approaching that of a TEM cell at sufficient distance. The major difference is that in a TEM cell the energy is contained and propagates in a structure of uniform cross section over its useful length without any appreciable attenuation. The energy in a radial waveguide spreads out directly in proportion to the radial distance from the energy excitation probe, at the center of two parallel plates. Close to the feed point, the energy is non-uniform in the radial direction but uniform in the vertical and circumferential directions. However, at large radial distances compared with the size of the exposed object, there should be negligible radial variation, and the resultant SARs will have the same characteristics and exposure polarization as TEM cells. An advantage of the radial waveguide system is its capacity to hold larger and more flasks than the TEM cell, but it is also subject to the excitation of higher order modes for plate separations greater than ½ wavelength or at locations beyond $\frac{1}{2}\pi$ wavelength from the excitation probe. The former can support field variations in the vertical direction and the latter can support circumferential variations. The exposed flasks can be arranged in number and order to minimize the excitation of the modes that produce circumferential variations.

2.3 *In vivo* Exposure Systems

Laboratory animal exposure and dosimetry considerations for evaluating possible health effects of human exposure to cellular phones are quite a bit different than those related to typical exposures to the radio sources in the environment. Typical exposures to radio transmitting antennas, microwave dishes, mobile radios, small boat radars, and marine radios involve whole-body illumination at a distance from the source. In such cases, RF energy is absorbed at all locations of the body with peak variation in the order of ±20 times the whole-body average. In fact most general population exposure standards are based on limiting whole-body energy specific absorption rate (SAR) to 0.08 W/kg and peak SAR to 1.6 W/kg as averaged over a gram of tissue. These values are based on whole-body exposure of laboratory animals. Cellular phone exposures result in a relatively low whole-body SAR of less than 0.004 W/kg at a much higher

0.3 to 4.0 W/kg average peak SAR in the head of the user, a ratio as high as 1000:1. Thus, the research results from whole-body animal exposures are not relevant to the assessment of cellular telephone safety. New research directed toward the assessment of health hazards of cellular telephones and personal wireless equipment exposure should not be based on the older whole-body exposure paradigms but on exposures of laboratory animals that truly duplicate human exposures, that is, producing whole-body average SAR or better yet, whole-head average SAR and peak SARs as near as possible to those related to human exposure to cellular phones or wireless instruments.

2.4 Biological Parameters

Exposure system designs for conduct of *in vitro* tests will require consideration of biological or experimental parameters as well as dosimetric parameters. Biological parameters include types of cells and flasks to be used and will require input both from the experts in test design and individuals directly involved in exposure system design. From the viewpoint of *in vitro* test battery design, the following are obvious considerations: culture vessel shape and number, requirements for constant culture conditions, suspension versus attached cultures, inclusion of appropriate negative controls, and temperature control and monitoring.

One of the major considerations in the design and conduct of *in vivo* studies with animals using RFR exposure systems is the control of confounding factors. For example, a limited restraint or position apparatus would permit more precise control over RFR exposure parameters, but may lead to confounding stress-related effects. It is well established that some types of animal restraint systems induce stress leading to altered endocrine function, which can effect tumor rates and other critical endpoints. In fact, the RFR literature (see Research Agenda) contains references to the confounding effects of stress. For this reason, the WTR is currently evaluating whether a restraint or controlled position device can be incorporated without the introduction of stress in the development of *in vivo* exposure systems. Using non-restrained animals exposed in a free-living cage system is also being actively considered. A further confounding factor is the

influence of RFR-induced temperature rises on biological outcomes as discussed above; the exposure systems being developed by WTR will control this potential source of confounding.

2.5 Exposure System Design Strategy

A wide variety of different systems has been employed in previous *in vivo* and *in vitro* studies serving to confound interpretation of the results. Exposure systems delivering RFR at frequencies (824-849 MHz, 1800-2200 MHz) and modulations (FM, complex) of cellular telephones are necessary so that relevant study designs can be developed, and the results obtained can be extrapolated to human exposure during use of wireless communication instruments. Other exposure variables, such as exposure duration and telephone antenna design, will also be addressed as appropriate. WTR-sponsored toxicology studies will simulate, to the extent possible, the characteristics of actual human exposure (e.g., intermittent exposure, appropriate frequencies, power levels and modulations, etc.).

Based on a characterization of the SAR distribution using the FD-TD method, the following strategy was adopted for developing *in vitro* and *in vivo* exposure systems for short-term toxicology experiments using analog, digital, or PCS wireless communication technology. Since dosimetry considerations apply equally to low frequency analog and digital data, the same exposure systems will be suitable for experiments on either. PCS, however, due to the higher frequency band width, may require an exposure system of different dimensions and design. The following strategies, therefore, are grouped as to their appropriateness for current analog/digital or PCS wireless technologies.

For analog and digital technologies, SAR will be characterized for different systems (cell culture, animal, or partial animal) at 837 MHz. The TEM cell, while somewhat less efficient than other types of apparatus, will likely provide the most useful exposure system for *in vitro* experiments at this frequency.

For PCS technology, SAR will be characterized at the level of the test system (culture, animal, or partial animal) over the bandwidth of 1.8 to 2.2 GHz. Various arrangements of the test system and the exposure apparatus will be evaluated to optimize efficiency. The TEM cell may be inappropriate for either *in vivo* or *in vitro* experiments involving PCS exposures. Standard (rectangular, commercially available), radial, or circular wave guides may be used for *in vitro* experiments. For *in vitro* experiments, the best location and orientation for a particular culture flask will depend somewhat upon its size and shape and will, therefore, have to be determined for each type of flask to be used. For *in vivo* experiments, the apparatus will be designed for head-only exposure using a loop-dipole or slot antenna. The SAR for the exposed head will be characterized for each frequency.

The WTR is currently involved in direct research related to various aspects of *in vivo* exposure system design and is funding the development of RFR exposure systems for *in vivo* experimentation which mimics as closely as possible exposures sustained by humans using wireless technologies. When the WTR publishes *in vivo* RFPs, position statements describing the progress and results of decision making in the area of *in vivo* exposure and dosing will be included.

Through its surveillance program and thorough consultation with experts in toxicology and RF physics, the WTR is aware of a variety of possible exposure systems for use in RFR studies (see section 2.0). In assessing possible *in vitro* exposure systems, two plans have been considered, independent investigator-developed exposure sites or the development of a central exposure site by the WTR. The WTR's DNA/Genotoxicity Expert Panel addressed this question and reported their recommendations and rationale concerning exposure system development to the WTR (see section 3.1.3). After careful consideration of dosimetric, technical, and logistical factors, the WTR has chosen to use a single-site exposure facility for all *in vitro* studies to be conducted as part of the WTR risk evaluation research program. The site chosen will include "wet lab" facilities (culture facilities, etc.) and an exposure facility (the exposure facility will be staffed by WTR representatives who will conduct all exposures and maintain the facility). Researchers

chosen through the peer review process will be expected to supply staff and equipment necessary to conduct appropriate studies.

The use of a consistent and well-controlled exposure system is crucial to the conduct and interpretation of studies involving RFR. Use of a single exposure site, independent of any particular researcher, will simplify exposure system characterization and control. In addition, use of a single site will assure consistency across experiments, investigators, and endpoints, and reduce costs related to construction of exposure facilities. It is anticipated that this facility will become a useful resource for a variety of investigators, including those not directly part of the WTR program.

Exposure systems capable of generating the following exposure scenarios will be developed for conduct of *in vitro* and *in vivo* toxicology studies. Initial exposure system development will involve the use of commercially available wireless communication instruments for the generation of appropriate frequencies and modulations. If feasible, this should be the simplest and most efficient method for assuring that the RFR exposures are identical to those most commonly experienced during use of such instruments by humans. The initial exposure matrix for *in vitro* genotoxicity tests and short-term animal studies will utilize available digital time division multiple access (TDMA), code division multiple access (CDMA), as well as common analog and newly developed PCS technologies (see Table 1).

TABLE 1: *In vitro* and *In vivo* Exposure Scenarios

	WIRELESS TECHNOLOGY			
VARIABLE	**DIGITAL**	**DIGITAL**	**ANALOG**	**PCS**
Modulation	TDMA (AM)	CDMA (AM)	FM	DIGITAL (AM)
Frequency	837 MHz	837 MHz	837 MHz	1880 MHz

For *in vitro* experiments, systems capable of generating SARs of at least 10 W/kg will be required. Based on a review of the literature of RFR effects on cells *in vitro*, the

DNA/Genotoxicity Expert Panel agreed that two hours represents the maximum time necessary for duration of exposure. Therefore, initial *in vitro* experiments will involve three dose rates of varying SAR level maintaining a constant time. To control for confounding effects of gross temperature increases, *in vitro* exposure systems will be capable of limiting media temperature variation to ±0.8°C. Unless effects are observed during one of these scenarios, only experiments involving a single exposure will be conducted. If effects are observed at SARs below which thermal influences can be substantiated, these will be investigated further. For these experiments, the effective SAR will be tested at varying time increments and the relevance to human exposures will be determined. *In vivo* experiments will be conducted at SARs determined to be appropriate from human modeling and epidemiology studies.

3. 0 TIER I - TOXICOLOGY RESEARCH

The central focus of the WTR toxicology risk evaluation research program is the assessment of potential carcinogenicity of exposure to RFR as a result of human use of wireless communication instruments. The research paradigm to be used is the same as commonly used for regulatory assessment of the safety of chemical agents and mechanical or electronic devices. The tests used to evaluate the potential carcinogenicity of RFR from wireless communication instruments will involve standardized short-term tests for genotoxicity, and various long-term animal studies. The WTR is, however, committed to a complete evaluation of all potential adverse health effects. When warranted by the needs of the research program or as the result of research identified through the WTR's surveillance program, the toxicology research program has and will be expanded to encompass areas of interest. In this way, the WTR toxicology research program will serve the WTR in its commitment to a rapid evaluation and assessment of new areas of research relevant to the overall assessment of potential adverse health effects of RFR.

3. 1 Progress to Date

Background information presented here is intended to bring potential investigators up to date on the latest WTR priorities on a range of research topics. The WTR recognizes the complexity of assessing the potential health risks of wireless communication technology and recognizes the need for a multidimensional approach embodied by the three-tiered research program. The WTR places a high value on the multi-disciplinary approach. The WTR has embraced a weight-of-evidence approach where consistency of findings across study designs and between disciplines plays an important role in interpretation of results in the context of public health risk. Accordingly, the WTR research program has been designed to facilitate simultaneous identification of relevant research results, risk evaluation research on potential health effects and the development of strategies and tools to mitigate or to manage any identified health risks.

3. 1. 1 DNA Investigations Strategy

As part of the WTR's ongoing surveillance program, published literature and ongoing studies involving RFR are reviewed and evaluated for their relevance to the toxicology research program. Through this mechanism, preliminary and published findings involving the alterations of DNA structure which were judged to be potentially relevant to RFR toxicology were identified (Fairbairn and O'Neill, 1994; Sarkar et al., 1994; Lai and Singh, 1995). In response to these findings, the following action plan was developed to assess the extent to which studies of potential effects of RFR on DNA should become part of the WTR toxicology research program.

1) Establishment of the DNA/Genotoxicity Expert Panel with the following mandate:
   - Assist in the critical review of the literature on possible effects of RFR on DNA;
   - Assist in the consideration of DNA damage assays; and
   - Advise on development of *in vitro* and *in vivo* test batteries.

2) Establishment of the Single Cell Gel (SCG) Expert Panel with the following mandate:

- Advise on the strengths, limitations, and usefulness of the SCG assay as a test for genotoxicity; and
- Consideration of possible experimental designs for *in vivo* studies using the SCG assay.

3) Issuance of Requests for Proposals to address investigations of potential genotoxicity of RFR.

3.1.2 Report of the SCG Expert Panel

In October of 1994, the WTR convened an Expert Panel on the SCG Assay. The Panel advised the WTR on the status of the SCG DNA assay regarding its use for genetic toxicology evaluations in general and for the study of the biological effects of RFR specifically. The panelists' direct experience with this assay was discussed, as well as general results in the field of DNA damage and repair. In addition, several data sets were discussed, with particular emphasis on the studies listed above. The Expert Panel reported the following conclusions and recommendations to the WTR:

- RFR has insufficient energy to cause direct damage to DNA, although possible indirect effects cannot be ruled out;
- Based on the available studies no conclusion as to the potential for RFR to induce DNA strand breaks can be drawn;
- The SCG assay was considered, due to its sensitivity, to be an appropriate assay for the assessment of potential effects of RFR on DNA structure; and
- The available information warrants the conduct of SCG studies using exposure parameters relevant to wireless communication technologies.

3.1.3 Report of the DNA/Genotoxicity Expert Panel

The DNA/Genotoxicity Expert Panel met in May 1995 and was asked to address the following:

- What can be concluded regarding potential genotoxicity of RFR?
- What information is available directly relevant to the assessment of potential genotoxicity of radiation from current wireless communication instruments?
- What *in vitro* genotoxicity tests should be conducted to fill data gaps identified above?
- What *in vivo* genotoxicity tests should be conducted to fill data gaps identified above?

The Panel presented the WTR with the following conclusions and recommendations based on an assessment of currently available literature:

- Using a weight-of-evidence approach, the existing data suggest that there is no clear evidence for a genetic hazard associated with RFR;
- Few studies have been conducted in the frequency range of current wireless communication instruments, and they were largely negative;
- The *in vitro* battery should include microbial and mammalian mutations assays, and a chromosome aberrations assay using human lymphocytes;
- Selection of an *in vivo* battery should await completion of *in vitro* studies and consideration of the availability of standardized tests using brain tissue; and
- All *in vitro* studies, including those involving the SCG assay, should be conducted at a central exposure facility.

The Panel review of literature relevant to the potential genotoxicity of RFR was considered preliminary, a final report will be completed shortly and submitted for publication in a peer-reviewed journal.

3.2 Sub-chronic and Chronic Animal Studies

Conduct of a long-term animal bioassay is both complex and expensive. In addition, exposure system development for use in this study will involve the manufacture and validation of a unique head-focused apparatus (see section 2.5) which will introduce logistical and practical constraints on this study. Finally, the WTR is committed to the study of current and future wireless technologies including the evaluation of important dosimetric parameters, such as frequency and modulation. A basic exposure matrix is described in Table 1 (see page 19), which if evaluated completely would involve the conduct of at least 16 studies (four exposure variations, both sexes, two species). The WTR *in vivo* toxicology program will, therefore, make use of sub-chronic (30-day) studies to evaluate both the exposure system and a variety of exposure parameters. The WTR is developing endpoints for these sub-chronic studies, and the RFPs will be published at a later date.

3.3 Tumor Promotion

In January of 1995 the WTR established the Tumor Promotion Expert Panel made up of experts in carcinogenesis, experimental tumor promotion, and RF physics. The WTR was aware of a number of studies, both *in vitro* and *in vivo*, related to the question of potential promoting activities of RFR. In addition, given that there is minimal evidence of RFR related non-thermal genotoxic effects, tumor promotion must be considered as a possible mechanism of action. Tumor promotion, for the purposes of this document, is defined as the production of tumors in experimental animal systems by a treatment regimen involving a single exposure to a carcinogen (initiator) followed by repeated treatment to a non-carcinogenic agent (promoter). Neither the single exposure to the initiator or the repeated exposures to the promoter alone result in increased tumor incidence. Tumor promoters are generally considered non-genotoxic, result in tissue-specific effects, and produce toxicity in the sensitive tissue visible in short-term studies

The Panel conducted a thorough review of the relevant literature focusing on experimental design and interpretation of results. In addition, the Panel considered the relevance of animal

tumor promotion studies to the scientific and regulatory evaluation of potential carcinogenic effects of wireless communication instrument use by humans. Specifically the Panel addressed the following questions:

- What conclusions can be gained from a critical review of current literature as to the potential effects on or possible mechanisms of tumor promotion by RFR?
- What factors should be considered by the WTR in evaluating the relevance of tumor promotion and *in vitro* transformation studies to risk evaluation research on RFR?
- What biological mechanisms might be operative for tumor promotion by RFR?

The Panel has prepared a comprehensive report which evaluates models of tumor promotion and the relevance of experimental promotion studies to human health risk assessment. This report will be published in a peer-reviewed journal late in 1995. A preliminary report of the Panel was presented at the annual meeting of the Bioelectromagnetics Society (Boston, 1995). The following preliminary conclusions were presented:

- The available data do not indicate that RFR is tumorigenic in long-term animal bioassays.
- The available data do not indicate a tumor promotion effect of RFR using *in vitro* or *in vivo* modeling systems.
- Animal tumor promotion models may have only general mechanistic relevance to the assessment of potential affects of RFR in humans and should not be used for human health risk assessment.
- An experimental program in tumor promotion is premature without clear evidence of a causal relationship between RFR and biological effects related to tumor promotion.

3.4 Extrapolation

To design and interpret animal studies relevant to human exposure to wireless communication instruments, there is a need to understand dosimetric scaling and extrapolation of *in vivo* and *in vitro* experimental results to humans. A WTR Working Group on Extrapolation has been