CSIRO AUSTRALIA
Division of Radiophysics

Status of Research on BIOLOGICAL EFFECTS AND SAFETY OF ELECTROMAGNETIC RADIATION Telecommunications Frequencies.

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Spectrum Management Authority, **1994**

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OVERVIEW

Written by Stewart Fist

This publication is also known as the "Barnett Report". It was officially 'published' in 1994 after Dr Stan Barnett of the Radiophysics Department of the CSIRO (Commonwealth Scientific and Industrial Research Organisation) delivered his final report to the (then) Spectrum Management Authority, which in turn delivered it to Michael Lee, the then Minister for Communications in the Australian Labor Government.

Nothing more was heard of it, despite government promises that it would be made public.

Like many Australian journalists I tried to get a copy, but after many futile attempts I gave up. However, nearly a year later in talking to a parliamentary librarian, I discovered that the library had a copy. It then transpired that the report had been "officially published" by the government and "made available to the press and public nearly six months before" ... probably on the office copy machine.

I then contacted the Minister's office, and the spokesman expressed surprise that I hadn't received a copy since it had "been made public"; he suggested I contact the Spectrum Management Authority since the Minister's office didn't have any. The SMA initially denied that the report had been publically released, then after checking with the Minister's office they informed me that, yes, it was a public document, but unfortunately there were no copies available. After a lot of pressure, they finally released a copy.

The report was then privately copied and circulated, and eventually when requests began to pile up the SMA did print and circulate some themselves. They've now run out, and don't have copies available. So once again, I've decided to assist them in their public duty of informing the Australian public by releasing this on-line. It has been costing me a fortune in photocopying.

Be warned. It has been scanned in and OCR'd, so there may be a few mistakes. We have diligently proof-read it, but we can't be sure every mistake has been corrected.

PREFACE

The CSIRO Report presents the current status of research on health effects of electro-magnetic radiation at frequencies relevant to telecommunications.

Because of constraints on time and resources, this report does not claim to be a comprehensive evaluation of the many hundreds of published papers and conference reports on the subject of biological effects of EMR. Rather than attempt to cover every aspect of biological effects research that has been published, it highlights what are considered to be important issues relative to human health. Because of the uncertainties in dosimetry and experimental procedures in many early studies this report has focused on relatively recent (within 10-15 years) studies to improve the chance of achieving consistency. There are a number of review articles that deal with pre-1980 research.

The CSIRO Report has been prepared in a way that will allow it to be read and understood as a single entity. Thus, it includes supporting information (in text and table format) for the summary statements thereby obviating the need to refer to other reference texts except for detailed information. The bibliography is provided as a means of identifying sources of information and a data base is being compiled. However, it should not be taken that this list is either comprehensive, or that every report has been scrutinised for its scientific validity. It was considered to be ethically appropriate to make comment on issues and to try to avoid overt criticism of publications that have presumably already passed some scientific peer-review process. Much of the recent data that was presented at the BEMS conference is not published in peer review journals and was not reviewed for acceptance at the conference. The relevance of certain fields of study has been questioned in some instances.

This CSIRO Report on the status of research on biological effects and safety of electromagnetic radiation was prepared by the Division of Radiophysics. A contribution to the cost of this project was provided by Spectrum Management Agency.

SCOPE OF REPORT

The possible adverse effects on human health of exposure to radiofrequency (RF) and microwave electromagnetic fields and radiation are of public concern. As the ambient electromagnetic environment continues to intensify (e.g. cellular and portable phones, wireless communications, LANs, PCNs) the effects of exposure from cumulative sources and prolonged exposure to low levels needs to be addressed. Advice is based on the assessment of risks to health resulting from these exposures as derived from studies on the effects of RF radiation on animals and volunteers and from epidemiological studies of exposed populations. This review considers RF and microwave radiation above 100 kHz. It is acknowledged that there are several possible areas of biological interaction which have health implications and about which current knowledge is limited.

The CSIRO Report draws information from: major reviews by scientific bodies (EPA 1984; NCRP 1986; NRPB 1991; NRPB 1992; NRPB 1993; WHO 1993), and the extensive scientific literature; interviews with prominent scientists in the USA, UK, Europe and Australia; interviews with government agency representatives in the USA and UK. Information was also obtained through attendance at the conference of the Bioelectromagnetic Society, 1994. The CSIRO Division of Radiophysics research program includes investigation of the biological effects and safety of microwave radiation. The CSIRO Report was prepared with support and resources provided by the Division of Radiophysics and a financial contribution from Spectrum Management Agency. Contributions from the Australian Radiation Laboratory constitute sections 11 and 12 of the report on dosimetry and epidemiology.

Because of the lack of information on the responsible mechanisms it is difficult to ignore the effects at low frequencies when reviewing the literature on frequencies used for telecommunications. However, this is beyond the scope of this report.

Microwave and Radiofrequency Radiation

This report refers to microwave and RF radiation. Microwave radiation borders on the optical part of the non-ionizing electromagnetic spectrum, ranging in wavelength between 1 mm (300 GHz) and 1 metre (30 MHz). Most of the animal experiments have been carried out at commonly used frequencies such as 27, 915, or 2450 MHz. Exposure are often carried out in the far-field (at distances greater than one wavelength from the antenna), where the magnetic and electric components of the radiation are in-phase. Assessment of applied dosimetry is relatively straightforward compared to near-field conditions (as applied in the use of cellular telephones) although in situ tissue dosimetry is not fully understood. Radiofrequency radiation encompasses the microwave region and additionally extends to ELF frequencies where pulse modulation systems are employed.

Sources of human exposure to RF and microwave radiation include microwave communication links, radar, radio and TV transmitters and domestic microwave ovens. The strongest RF fields likely to be encountered by members of the public are those used in clinical magnetic resonance diagnosis which may involve patient exposure for short periods (less than 1 h) at whole-body SARs of up to about 4.0 W/kg.

RF and microwave radiation emits a waveform as oscillating electric fields (measured in volts per metre, V/m) and magnetic fields (amperes per metre, A/m). The intensity (or power flux density) of a beam of radiation is expressed in watts per square metre (W/m2), equal to the product of the electric and magnetic field strengths. The rate of absorption of energy by biological tissue in animals or humans is conventionally described in terms of the specific energy absorption rate (SAR) expressed in watts per kilogram (W/kg) for the whole body or parts of the body. The time-integral of this (watts multiplied by seconds, per kilogram) gives the specific energy absorption in joules per kilogram (J/kg).

1.0 INTRODUCTION

A by-product of technological development is the recent rapid increase in environmental exposure to electromagnetic radiation, whether in the home, or in the workplace, or in public areas. The polluting signs of industrial development are visibly obvious air-borne or water-borne particles that obscure the air and clearly damage the environment. Electromagnetic radiation is even more pervasive and is unseen and unrecognised. Public concern is easily activated by a fear of the unknown. Terms such as “electromagnetic smog” have been coined which express concerns about its potentially polluting effects. Because of public community awareness and industry concern of the risk of litigation there is an apparent urgency to provide an answer to the question of safety of handheld mobile and cellular telephones . The use of these devices is unique in that the power transmitter is held against the head of the user. Media attention has focused on the legal claims for damages due to alleged cause of brain tumours. Public concern is aggravated by the appearance of multitudes of cellular transmitter antennas on towers adjacent to school playgrounds and on office buildings. Electromagnetic interference is already recognised as an important problem and work has begun to address issues on compatibility of electronic equipment. There are vital health issues associated with EM interference of medical equipment, but these are outside the scope of this document.

Issues that are critical for an assessment of human health effects are: teratogenic, mutagenic, carcinogenic/tumour production, ophthalmic, immunologic and neurologic effects.

There have been suggestions, based on some epidemiological studies at low (power line) frequencies that chronic exposure to EM fields may increase the risk of developing certain types of cancer. Although there has been no epidemiological study completed specifically addressing the higher frequency range used for telecommunications there have been some reports of increased incidence of tumours in animals exposed to microwaves together with a known carcinogen. However, there was a recent report of increased breast cancer in a very small group of female radio-operators on Norwegian ships (Tynes et al 1994) who were exposed to a combination of ELF and RF radiation. The recent legal claims in the USA that brain tumours may be caused by the use of digital cellular telephones has focussed the debate on the 450-915 MHz frequency.

For the development of cancer to be a significant issue it requires critical changes in development of certain cells that can be detected with appropriate tests. There are two aspects to cancer development; the production of aberrant cells and the depression of the body’s natural immunological defences. Abnormal cell growth and behaviour may be detected as altered enzymatic activity, altered gene expression, peculiar growth patterns and changes in the ability of transformed cells to form colonies with in vitro tests. In cell biology, calcium plays an important role as a biochemical regulator that helps to relay signals from the cell surface (receptor site) to its interior. One effect of altered calcium function may be the increased activity of growth enzymes leading to uncontrolled cell proliferation and cancer. Therefore, research has focussed on this issue.

Cells that are actively dividing are at the greatest risk of induced abnormalities, hence the bone marrow and blood-forming system and the developing central nervous system are considered to be the most sensitive targets. Claims of cancers in these biological systems have been associated with most forms of energy deposition. High rates of cell division occur in the development of sperm cells and effects could produce either tumours or abnormal cells with subsequent impairment of normal fertilization processes.

The normal status of circulating lymphocytes, natural killer cells and macrophages is important in the control of disease processes, in general. Therefore, a number of studies has been directed towards the possible interference in the haematopoietic and immunologic systems by exposure to electromagnetic radiation. The cell membrane is considered to be sensitive to EMR interaction and, therefore, one would expect to see bioeffects in the immune response and gene expression.

Research methodologies in medical and biological sciences have gradually evolved from studies of entire organisms or organ systems and tissues, cells and the molecules that comprise living tissue. The move away from reporting phenomenological effects on a gross scale in living tissues has presented a far greater challenge to scientists to understand the chemistry of molecular and sub-molecular composition and interactions. This has led to the emergence of a new field of science, bio-electromagnetics, that proposes that biological organisation is based on physical processes at the atomic level that regulate the products of biochemical reactions.

Cells grown in culture exhibit characteristic abnormal behaviours and appearance that can be readily identified. The use of in vitro test systems allows manipulation of the environmental conditions in which the cells grow and provides an accepted vehicle for investigation of the mechanisms responsible for physiological and morphological abnormality. Animal models are also frequently used to identify potential carcinogens. The disadvantages of animal studies are that they are long-term, expensive, and results can be influenced by species or strain sensitivity to certain tumours. Mapping the in situ dosimetry in whole animals is far more complex than for in vitro exposures in radiation transparent cell chambers. The importance of animal studies is that they provide a complete biological system with which to evaluate the overall effect of subtle changes observed in cell systems. They allow closer relationship to the human's whole organism physiology with the advantage that their environmental conditions can be controlled to isolate the effects of an individual physical or chemical agent.

Clearly no single biological system will provide the answer to a problem as complex as the possible development of cancer from exposure to EMR. Any report, whether positive or negative, needs to be independently verified in a laboratory with similar scientific credentials before the result can become part of a reliable data base. Phenomenological approaches that report cause-and-effect events have limited usefulness. Predictions about safety can only be made with confidence when the responsible mechanisms are understood and demonstrated. The issue of safety of EMR in telecommunications is extremely important, socially and economically, however, it would be unrealistic to expect a definitive answer in the short term.

The purpose of this CSIRO Report is to review the existing literature and identify issues that are directly relevant to human health. It includes conclusions on the current status of international research and make recommendations on the direction of future research.

2.0 SUMMARY OF STATUS OF RESEARCH ON HEALTH EFFECTS OF EMR

2.1 EXECUTIVE SUMMARY

Key Points:

- Despite rapidly developing markets, there has been little funding for research on safety
- Accepted thermal effects above 1°C temperature rise
- Increasing evidence of non-thermal effects
- Cancer related effects are emotive issues
- Other important issues are corneal lesions, impaired memory function, and altered blood-brain barrier
- Dosimetry is uncertain, but numerical techniques are improving
- Past research lacks direction and the general standard of publications is not high
- Concerns over the suitability of the ANSI Safety Standard
- Lack of confidence in the value of epidemiology surveys

While this report deals with a wide range of frequencies relevant to telecommunications, it is obvious that there is a considerable emphasis on safety issues relating specifically to cellular telephones.

Digital technology has allowed unexpectedly rapid growth in the cellular telephone industry world-wide. According to Motorola (BEMS 1994) the number of subscribers worldwide increased from 25 million in 1992 to more than 34 million by 1993. Research on biological effects and development of safety standards always lags many years behind technological development, due to the limited availability of funding. However, public acceptance can be easily damaged if the safety issues are not satisfactorily resolved. A small proportion of the massive manufacturing benefits would fund substantial research programs.

To answer the question of safety of CT is a tall order. The vast majority of the research on EMR has addressed power line frequencies because it is an area of continuing public concern and has huge investment capital. Work in the microwave field has experienced bursts of activity mostly with the development of microwave ovens, radar and radio communications. Generally, exposures used continuous wave. Data from ELF work shows that for many biological responses the waveform needs to be pulse-or amplitude-modulated. Subtle cellular effects of RF and microwave exposures are often dependent on pulsing and the presence of an ELF component in the waveform.

The main topic of concern seems to be whether or not a real risk exists for the development of cancer. This is doubtlessly due to the continuing uncertainty about power line frequency. Some evidence has been given for an association of leukemias and tumours with ELF fields and a recent report of increased breast cancer in female radio-telegraph operators. Many laboratory studies show abnormal cell growth and gene expression when exposed to ELF or RF modulated with an ELF component. The lay-press ignores any distinction of effects across the radiation

frequency spectrum and implies a cancer link. From the perspective of human health implications, the key issues are whether there is any association with teratogenic, immunologic, neurologic, or mutagenic effects. There is a strong chance that the pre-occupation with cancer-related effects will drain much of the research resources in animal and epidemiological studies, without settling the debate. In the meantime there are other important areas of study that may be overlooked.

In the present climate of scientific uncertainty it is difficult to see how the situation can be suitably resolved in the near future. There is no scientific basis to support initiation of cancer by RF radiation and most human cancers take many years to develop. The latency factor is an important issue. Meaningful animal studies require exposure throughout the normal lifetime and therefore require many years to properly plan, exercise and evaluate. There is no evidence that low levels of electromagnetic radiation at frequencies up to 300 GHz can directly alter the DNA genetic material of cells and initiate cancer. However, there is some evidence that EMR alters enzyme synthesis in ways similar to known chemical cancer promoters.

The thermal mechanism is most commonly accepted, and there is a tendency to assume that physiological effects cannot occur in conditions where the expected temperature increase is less than 1°C. Reports of teratogenicity, altered behavioural responses, and lens cataracts are usually associated with a significant increase in tissue temperature caused by high SARs. There are some reports of synergism between different radiations. The attitude of physical scientists is, generally, to disregard reports of effects for which a known physical mechanism cannot be readily attributed. However, the mechanisms are inadequate to explain all of the observed biological responses. Radiation biologists have reported a number of changes in various biological systems following exposure to EMR that produces insignificant or undetectable, temperature increase. These effects range from alteration of ion concentration in cells, increased rate of DNA synthesis to enhancement of the rate of tumour growth in experimental animals. The effects have been reported over a range of frequencies from ELF to RF. Mechanisms for many of these biological effects have not been identified or proposed and this lack of scientific explanation has, not surprisingly, led to a reluctance to accept the effects as “real”. The difficulty is compounded by the fact that as there is limited research activity, particularly at RF, much of the work has not been replicated in independent laboratories. There is often no attempt to establish a dose-response for reported effects. This is difficult to explain or justify.

Whilst researching the scientific data base in the preparation of this report it has become evident that subtle changes in cell structure and biochemistry have been frequently reported at exposure levels where gross thermal change could not be attributed as a cause. The effects involve a number of phenomena from cell membrane permeability to altered gene expression. For a cellular alteration to be permanent requires alteration of the DNA or synthesis or activation of specific genes. Epigenetic postulates have been developed for cancer induction as alternates to the existing DNA breakage mechanism in mutagenesis. Cell membrane receptors mediate transmembrane ion flow and signal a cascade of intra-cellular biochemical events that culminate in altered gene expression and erratic growth patterns.

A number of effects have been reported from reliable research groups of in vivo effects resulting from exposure to pulsed microwave radiation. Reported low level in vivo effects that have received little notice involve the impairment of short-term memory function in rats exposed to 2.45 GHz at 1 mW/cm^2 or whole body SAR 0.6 W/kg for 45 min. The effect was produced with both c.w. and pulsed waveforms and is thought to be due to microwaves activating endogenous opiods in the brain thereby causing a decrease in cholinergic activity in the hippocampus. The effect is similar to that caused by stressors.

Degenerative changes have been reported in ocular tissues in primates exposed to pulsed (1.25 - 2.45 GHz) microwaves where SAR 2.6 W/kg has produced lesions in the cornea and iris. Application of the glaucoma drug timolol maleate reduced the threshold for microwave induced damage to 0.26 W/kg (below the ANSI Safety Standard). In the latest extension of this study the pulse shape was found to be critical where a sharp rise-time was more effective in creating lesions irreversible in the retinal endothelium. The electroretinogram response to light stimulation was also depressed by microwave radiation which typically involved 4 h exposures on three consecutive days.

SAR measurements in human tissue phantoms in the brain and cheek have been shown to exceed the ANSI uncontrolled safe exposure levels. Furthermore, modelling studies have shown that for cellular telephones operating at the level of occupational standard the SAR in the pregnant fetus has been shown to exceed the uncontrolled level.

Problems in studies of human populations published to date include imprecise estimates of exposure. As a result such epidemiological studies may underestimate any real risk. The likelihood of epidemiological studies providing useful information is questionable, particularly if the biological endpoint cannot be predicted. Its value in the short term (< 10 years) must be negligible unless there was an enormous increase in the rate of cancer growth. Interestingly, the incidence of brain tumours in the EC countries has increased substantially in recent years. This fact has not escaped the attention of the media and implications of a possible connection with EMR were given in a recent commentary on television in the UK (June 1994).

Safety of RF radiation cannot be assessed in the absence of reported serious effects when so little research has been aimed at the problem. It is somewhat surprising and rather disappointing, to find that although the literature contains many hundreds of publications, there are very few areas of consensus. Where very high power outputs are emitted there are predictable effects related to tissue heating. The magnitude of effect, and hence the threshold in terms of SAR, varies according to the size of the animal so that considerably lower values apply to humans compared with rodents. At low levels the absence of clear thresholds and presence of intensity and frequency windows has created questions rather than provided answers.

The equivocal nature of much of the literature is of concern. Following discussions with a number of prominent researchers insight into the situation has been somewhat clarified. It seems that in the past the subject of EMR bioeffects has suffered from; (a) lack of direction, (b) poor dosimetry (as the resolution of current numerical techniques were not available, (c) research studies based largely on the

availability of equipment and biological systems within a particular organisation, i.e. no real attempt to predict a mechanism of interaction and match dosimetry, frequency and biological endpoint, (d) poorly described techniques, (e) obviously poor standard of peer-review, if any.

In many respects, the effects of exposure to RF from cellular telephones should be relatively easy to determine because the radiation is emitted from the antenna close to the skull. Although the field becomes complicated due to interference by the head, numerical methods to estimate local SAR are improving. Values for the maximum power outputs are available and a number of studies are investigating the SAR levels expected in various adjacent tissues. In situ SAR values on the order of 3 W/kg averaged over 10 gm of tissue have been estimated in brain tissue close to a cellular telephone operating at 900 MHz and maximum output. Under the same conditions the maximum SAR value averaged over 10 gm of tissue was 4.6 W/kg at 1.8 GHz.

It is difficult to envisage an epidemiological survey that would effectively discriminate amongst the other environmental variables, including the many forms of EMR that exist in addition to cellular telephone or telecommunications frequencies. As a number of cellular responses have been associated with low level (50-60 Hz) mains frequency, this may also be a potential confounding variable. The development of cancer is a slow process taking many years before it is positively diagnosed in humans. The latency factor is very important in evaluating cancer development. It is most unlikely that retrospective studies will provide any useful information for recently developed technology, such as cellular telephones. Prospective studies will have negligible chance of showing any effect, if present, in less than 10-20 years (Coleman 1994).

Concern over the lack of appropriate research was voiced by Frey (1988) in a chapter on evolution of research with low intensity ionizing radiation. At that time he somewhat outspokenly claimed that, “the significant research, that which does not use high intensities and is not thermoregulatory oriented, has been largely squeezed out for reasons unrelated to science.” His concern was that while there is no doubt that there is a diversity of biological effects of low intensity RF radiation the research to evaluate and understand these processes is not being undertaken, at least in the USA.

There is no doubt that the interpretation of bioeffects data has been clouded by a pre-occupation with thermally-mediated processes. In fact, development of the ANSI/IEEE standard is based only on well established thermal effects, and ignores the more subtle non-thermal processes that are more difficult to interpret and apply to human health. The inappropriate exemption from standards by the 7W exclusion clause is due to be removed from the ICNIRP standard.

2.1.1 Implications

Because of its equivocal nature, the data base for RF emissions has limited value. It may be dangerous to make general statements on safety based on lack of evidence of harmful effects when so little relevant research has been carried out. The enhancement of ocular effects including corneal lesions by the simultaneous

application of the glaucoma drug and very low SAR is a surprising finding. This has important implications to human health, and research into the mechanism of action is essential.

A common thread throughout much of the literature is the potential development of cancers. From a public health perspective, it would be appropriate that the main goals of such a study would be to identify mechanisms and demonstrate their capability to create biochemical/biomolecular changes that lead to altered gene expression. Studies that do not address the issue of mechanisms have a limited use for assessment of human health effects. However, bioeffects studies, per se, are necessary to establish threshold levels for interactions.

There are two approaches that can be taken to answer the problem of whether or not EMR can be linked with cancer or tumour promotion. A simplistic engineering response would be to take the view that any biological changes that cannot be explained by known mechanisms cannot be significant. The alternative view is to adopt the notion that existing knowledge on biological processes is inadequate and to work towards understanding these events and the potential risk with abnormal cellular development.

Currently a few laboratories are addressing the issue of signal transduction pathways from the cell membrane to the nucleus and the ultimate expression of altered genes. The role of highly reactive free radicals in carcinogenesis is under examination. The hormone melatonin is a potent antioxidant and, therefore, could protect DNA against damage and potential cancer promoting actions of free radicals. It has been shown that during EMR exposure melatonin secretion can be suppressed and the life of free radicals is significantly extended. Furthermore, free radicals are usually produced during the intracellular signal transduction process that follows response to EMR exposure.

Cancer related phenomena require long term studies, and only parts of the signal cascade of events are understood (or in most cases theorised). The solution to the problem will not be achieved in the short term. Research on the mechanism for cancer production has been extensively funded for decades without elucidating an answer. In contrast, research on effects of EMR on cell membrane and gene expression are carried out under limited funding.

2.2 RECOMMENDED RESEARCH

There is an urgent need for an orchestrated research effort to combine rigorous animal experimentation and specialised bioeffects/mechanistic studies at the cellular and molecular level. It is essential that the biological aspects of EMR are thoroughly investigated to establish whether a mechanism exists by which carcinogenesis or cancer promotion may occur.

An effective research program will establish threshold levels for the onset of biologically significant events, from the level of molecular biology to whole organ systems and whole-being physiological reactions. Only when a solid data base of

independently verified quantified bioeffects is available will meaningful safety standards be developed and reassurance of the public be achieved.

When safety of RF from sources other than cellular telephones is considered, the situation becomes more complex. The developing world of wireless networks will ensure that the entire body is radiated from multiple sources. An individual operating a terminal will be exposed to high GHz microwave radiation in addition to the electric and magnetic fields associated with the VDT. From the perspective of public concern, there is an emphasis on the need for credible data on risk to pregnancy. Much of the research on teratogenic effects involves high power exposures and resulting abnormalities and fetal resorptions that are known to be due to whole body hyperthermia in rodents.

An appropriately sensitive endpoint for low level chronic exposures would be the study of fetal brain development. There are specialised procedures available including embryo culture techniques that have been used to study non-thermal effects of non-ionizing radiation. Changes in brain tissue of developing or adult mammalian systems are not easily recognised but may occur with RF exposure. Intriguing effects on memory function in rats exposed acutely to 0.6 W/kg SAR have been reported. Current information is that this exposure also produces DNA breaks at SAR 0.6 to 1 W/kg.

The potentiation of effects on the CNS or sensory organs by pollutants or medication needs to be addressed. The recent reports of substantial lowering of the threshold for microwave-induced corneal lesions (2.6 to 0.26 W/kg) by administration of a glaucoma drug emphasises the difficulties in this area. All other ocular effects are obviously and predictably, due to temperature increases in the lens. Research is urgently needed to substantiate these reports and identify the mechanisms involved.

Studies involving chronic exposures are most relevant to RF radiation environment. These should continue to study the effects on tumour promotion and sensory and cognitive function.

Tests of learning performance are an essential part of a research program. The potential synergistic effects of drug therapies needs to be evaluated. At the cellular level studies should include verification of the response of ionic flow and activation of ion channels in the bilipid membrane.

Work at a subcellular level should include study on biochemical process, particularly on enzyme systems such as ornithine decarboxylase, that control growth function and have a connection with tumour development. Studies on the potential RF-induced expression of oncogenes are an important basis for cancer-related effects. The effects of microwave radiation on cell proliferation, reproduction and transformation are fundamental to the study of tumour development and require sustained and thorough investigation.

For Australia to have an effective role in the human health consideration of EMR requires the establishment of:

1. an expert committee to critically evaluate dosimetry and bioeffects of published studies that will emanate over the next few years of increased funded research,
2. strategic liaisons that allow direct lines of communication with the research, regulatory, and political community,
3. research protocol for critical areas of research,
4. international collaboration to verify important studies.

To avoid the risk of introducing preconceived prejudices the best line of action would be to have a small committee direct appropriate research in an organised manner. It should be capable of identifying relevant expertise and applying the resources to specific topics and problems. If care is taken in this approach it should be possible to get relevant research carried out in a meaningful way to ensure unbiased results. By selecting individual expertise it is possible that a systematic approach can be used to develop a research protocol that holds no political bias and has a strong chance of producing definitive results. A study that ultimately provides benefit to Australia by producing information that is directly relevant to human health should be favoured. With the current status of international research in EMR there is clearly an opportunity to make a valuable contribution.

The Recent recommendation (September 1993) by the International Union of Radio Science (URSI), Commission K, is as follows;

2.3 OVERVIEW AND GENERAL DISCUSSION

There have been sporadic reports of biological effects of exposure to EMR at frequencies relevant to telecommunications, however there has been no deliberate direction of this research towards an evaluation of health effects, to date. The nature of competition for research grants has limited fundamental research of new ideas. This is obvious from the lack of follow-through of some early studies that indicated potential effects. Industry is the largest provider of funds for research and this has its inevitable consequences in terms of acceptance of the results as being truly without bias.

By far the largest funding continues to be directed towards research on ELF. The emphasis on EMR research in the USA is still on safety of power lines. The Department of Energy and Power Companies continue to invest heavily in research on ELF. Recently this has been stimulated by epidemiological reports from Scandinavia associating ELF with leukemia. There have been very few studies aimed at establishing physical mechanisms of interaction for biological effects of EMR, particularly for low-level exposures. Reports of effects at very low levels of exposures in both ELF and RF have emanated from eastern Europe. This continues to be the case. It is uncertain why these studies should contain such high sensitivity but the general opinion is that they are treated with some degree of scepticism.

Effects on cellular processes that have been reported may seem somewhat esoteric at first sight. Some are implicated in tumour development by alteration in enzyme activity and biochemical processes that control DNA replication, transcription, and the rate of cell division. The movement of calcium ions across cell membranes alters its concentration within cells where it provides an essential regulatory role in cell growth and behaviour, thus ionic flow across membranes is important. The cell

membrane itself is an efficient and sensitive receptor organ that reacts to minute changes in its chemical and physical environment. The chemistry of cell growth and behaviour is clearly affected by the electrical and magnetic environment. While the biochemical processes in cell kinetics are reasonably well understood, the mechanism of interaction by EMR is mostly speculative. Cell membrane ion-channels, gap junction intracellular communications all play an important role that may be mediated through the action of free radicals or melatonin.

In the search for sensitive biological responses to EMR it is understandable that a great deal of emphasis is placed on reactions at the cellular level.

There is some evidence of responses to low level amplitude-modulated microwave and radiofrequency radiation. Reported effects include changes in brain activity, increased enzyme activity and resulting altered rates of cell growth and proliferation, and reduced lymphocyte cytotoxicity. Taken as a whole, these biological effects are suggestive of developing neoplastic pathology. There have been reports from in vitro studies describing enhanced rates of cell transformations following exposure to amplitude-modulated microwaves at SARs up to 4 W/kg when combined with the chemical cancer promoter tetradecanol-phorbol-acetate (TPA). The cell line used in these experiments was chromosomally abnormal and the validity of extrapolating from such a specialised experimental procedure to human health, may be questioned.

The problem with the approach taken by organisations such as ANSI and IRPA or ICNIRP is that the data on which their standards are based come from relatively severe physiological reactions. Interference with normal behaviour is taken as a robust indicator of a response that is repeatable and which occurs throughout a range of species at exposure levels of around 4 W/kg. A so-called safety margin factor of ten is included to set the occupational level at 0.4 W/kg (ANSI 1990). Clearly, the fact that the response is so repeatable suggests that its stimulus is strong enough to always evoke a response. The alteration in normal behaviour is based on an increase in the mean body temperature by at least 1°C, measured in the rectum. Temperature increases in the CNS were not estimated but it would not be surprising if localised hyperthermia occurred. A change that overcomes the homeothermal control mechanism and elevates the temperature of the whole body to an extent that it interferes with normal behaviour, including feeding, certainly represents a substantial effect.

It appears that the standards organisations prefer to base their standards on gross physiological responses initiated by significant temperature increases. It is, perhaps, more difficult to correlate a direct human health effect with the more sensitive cellular responses that cannot be easily explained by thermal mechanisms. The problem is that the Standards imply safety thresholds but it is not possible to identify these on the basis of current equivocal or disparate research.

The main concern about the ANSI and IRPA standards is that their selection criteria restricts the data base to reports of thermally-mediated effects from a single, i.e. acute, exposure to a single source. The Australian Standard is similar and also includes an exemption for devices emitting frequencies below 1 GHz and powers of less than 7 W. It is odd that cellular telephones should be exempted when they

represent a unique device that operates with its transmitter placed against the user's head.

Cancer

There is no evidence that low levels of electromagnetic radiation at frequencies up to 300 GHz can directly alter the DNA genetic material of cells and initiate cancer. However, there is some evidence that EMR alters enzyme synthesis in ways similar to known chemical cancer promoters. There is some evidence that microwave radiation influences the transport of calcium through cell membranes, stimulates the synthesis of ornithine decarboxylase within cells and may alter the expression of DNA synthesis by cells, thereby, promoting more rapid development of malignant cells in vitro and of tumours in animals. There is evidence from in vitro studies that these effects can be produced under conditions where heating is unlikely to be involved. Some of the reported bioeffects of EMR are not proportional to dosage, and the reported "windows" of intensity and frequency present a challenge to scientific understanding and explanation. Although EMR is not considered to be capable of initiating neoplastic pathology there is a limited data base suggesting that EMR may promote the growth of malignancies, particularly when initiated by a chemical or physical agent.

Past chronic exposure animal studies have produced conflicting results, with one study (Chou et al 1992) giving either a positive or a negative result depending on whether one interprets a real effect as; (1) an increased incidence in all cancers in the population, or (2) an increased incidence of a specific cancer.

Exposure protocols need to be strictly controlled. If there is the smallest risk of enhancing cancer promotion then experiments should be designed to optimise their statistical power. Apart from the obvious need to control all environmental variables this involves testing for a modest increase in the incidence of a known cancer from chronic exposure (daily, throughout life) to a known RF field that can be quantified as an in situ SAR. It is well accepted that in situ dosimetry is significantly altered by orientation with respect to the field. The worst-case situation occurs when the animal's body is parallel to the electric field, particularly in the MHz frequency range. The exposure conditions must involve a worst-case situation which is constantly repeatable to have any real value in determining thresholds. There is little value in radiating rodents that are free to move about when the in situ SAR is strongly dependent on their orientation in the RF field. Comparison of results of biological effects must take account of differences in species and microwave frequency, in addition to SAR, as resonant conditions relate directly to the size of the animal relative to the wavelength.

True scientific protocol requires the establishment of an hypothesis which must be repeatedly tested before any inference can be drawn from the results. The in vitro cell studies have provided some clues about setting such hypotheses. Perhaps the most important were the experiments of Cleary et al (1990 a) which demonstrated an altered rate of DNA synthesis and proliferation of human glioma cells after a single exposure to microwave radiation. This abnormal behaviour is consistent with early changes seen in cells that lead to tumour formation. Effects were observed at both 27 and 2450 MHz frequency and with cw or pulsed waveforms. Furthermore, Cleary

(1990 b) also reported the effect in cultured human glioma cells. The exposures were applied over a range of SAR, with the lowest level at which the effect was observed being 5 W/kg. Although the exposure conditions have been reported as non-thermal it is difficult to see how the exposure could avoid large thermal gradients from the cells to the cooling fluid surrounding the cell culture vessel.

What makes these studies interesting is that the effect occurs after a single 2 h exposure and lasts for up to five days. Thus, a daily exposure regimen would reinforce the effect. This is what is required in the promotion phase of cancer development. The connection between accelerated growth of human brain tumour cells in culture to that occurring in vivo during repeated exposure to EMR is one that deserves close examination. Hence the need for data from chronic animal studies. The extrapolation of results from laboratory rodents to humans is always fraught with difficulties and divergent opinions. Epidemiology studies may be an option, although the cost/benefit ratio may not be acceptable, and scientists are frequently sceptical of the results.

The transformation of normal cells into malignant neoplasms involves alterations of the nuclear DNA and its genetic code This can be induced by physical agents such as ionizing radiations or chemical promoting agents such as the phorbolester tetradecanol-phorbol-acetate (TPA). This chemical promoter apparently acts on receptor molecules in the cell membrane thereby triggering a specific calcium-dependent and lipid-dependent protein kinase enzyme system, protein kinase C. Another effect of TPA is the synthesis in cells of ornithine decarboxylase, an effect that has also been reported after exposure to microwaves.

Most serious researchers concede that the bulk of the scientific literature is of a poor standard. This has lead to some concerned scientists establishing working groups. A non-ionizing radiation sub-committee of the IEEE (Chair Prof. M. Meltz) is currently working towards establishing an expert scientific committee that will critically review publications. It is intended that the critiques will be available, although the means by which this will be achieved is not determined. Because of concerns of litigation it is probable that it will be through personal communication. It is recognised that many publications (including those frequently cited) have significant inadequacies in the descriptions of dosimetry and biological protocol.

Comment

It is evident that, at least in the world of EMR, science has become a business, as evidenced by the growing number of environmental and epidemiological consultants. This is prevalent in the USA but also exists in the UK. The danger with this approach is that there is a tendency to adjust the research to fit the needs of the industry providing the funding. The scientific value of many of the science entrepreneurs may be questioned, as first principles of "where can I do my best science" are replaced by "where can I get funded". Meanwhile, epidemiology may be considered to be more of an art-form with the added bonus that it deals with "environmental" issues that are currently politically attractive.

The annual BEMS conference attracts a large number of posters and presentations that are not reviewed. This results in a wide range in quality and the format does not

allow an opportunity to identify valid data. The danger here is that it is easy to assume that the general standard is poor (and indeed many presentations were quite inadequate) and, therefore, disregard most of the positive effects as being probably due to experimental artefact. This subject is in desperate need of a true workshop to identify areas of scientific consensus. It will require a dedicated effort by strong-willed individuals to break the mould of mediocrity that currently prevails.

2.4 TOPIC SUMMARY AND CONCLUSIONS:

BIOLOGICAL EFFECTS OF EMR TELECOMMUNICATIONS FREQUENCY

2.4.1 Human Studies

Heating

Healthy people can tolerate an elevated body temperature of 1°C for periods of less than 1 h, during which an increase in sweating, skin blood flow and cardiac output occurs. A SAR of 1 W/kg would be expected to result in a rise in body temperature of approximately 1°C in healthy subjects at rest in light clothing and in moderate environmental conditions. Adverse environmental conditions and moderate physical exercise will reduce the tolerable level of SAR, as would some medication or compromised thermoregulation.

Whole-body SARs provide no information about responses to high, localised SARs induced by specific exposure conditions or by high peak amplitude pulses. Furthermore, the relationship between local SAR and temperature increase is not clearly established.

Perception

RF and microwave radiation can be perceived audibly and by temperature receptive sensors in the skin. There are no specific thresholds of skin perception because of their dependence on frequency, exposure duration, the sensitivity of the part of the body exposed, and on the area exposed. Because of the greater penetration at lower frequencies, perception of skin warming by microwave and RF frequencies in the range of 0.5 - 100 GHz is not a reliable mechanism of protection against potentially harmful exposure.

People with normal hearing are capable of perceiving pulse-modulated RF radiation between 200 MHz and 6.5 GHz as audible buzzing, clicking, hissing or popping noise, depending on modulation characteristics. It is generally accepted that the sound results from the thermoelastic expansion of brain tissue following a small but rapid increase in temperature on absorption of the incident energy. The perception threshold for pulses shorter than 30 μs depends on the energy density per pulse, rather than an averaged value, and has been estimated as about 400 mJ/m^2 (_ 15mJ/kg). Reports of altered EEG in humans exposed to RF radiation are equivocal,

probably due to the difficulty of avoiding field perturbations and measurement artefacts.

2.4.2 Animal studies

Ocular effects

The lens of the eye is considered to be sensitive to RF radiation because of its lack of a blood supply (and consequent limited cooling ability), limited damage repair capability, and its tendency to accumulate damage and cellular debris. Local temperature increase, induced by RF exposure is responsible for the production of cataracts (opacities) in the lens of anaesthetised rabbits. The most effective frequencies are in the range of 1-10 GHz. The threshold temperature is 41-43°C with a corresponding local SAR 100-140 W/kg. Primate eyes were shown to be less susceptible to heating by microwaves than rabbit eyes, possibly due to the greater shielding by the primate skull and the thinner lens. Cataracts have not been produced in conscious primates after chronic exposure to power density up to 1.5 kW/m^2.

Recent, well-conducted, studies by one research group show the retina, iris and corneal endothelium of primates to be susceptible to low level pulsed microwave radiation. The latest report identified pulse shape as an important parameter where pulses with a sharp rise-time were most effective in producing damage to the retina and in depressing electro-retinograms at SAR 2.6 W/kg within the eye. Degenerative changes in the iris and cornea were observed at localised thresholds of 0.26 W/kg after the application of timolol maleate, a glaucoma drug. The energy level per pulse was 2.6 mJ/kg. This important finding requires verification by an independent research group.

Haematology and immunology

Reported effects are usually transient, resulting from acute, thermally-significant exposures. Small, transient changes may be of little consequence in the long-term. A common response was a decrease in peripheral lymphocyte count and an increase in the neutrophil count in mice and rats exposed at 5 - 13 W/kg and 1.5 - 3.0 W/kg, respectively; sufficient to raise the rectal temperatures by 1°C. However, several other authors reported no effect on circulating blood cell count in rats exposed at up to 2.5 W/kg. These inconsistencies, may be due to differences in dosimetry estimates and environmental conditions which would alter the induced temperature effects.

Changes in natural killer cell and macrophage activity were reported after acute exposure of hamsters at SARs _ 13 W/kg or mice at SARs _ 21 W/kg with an associated increase in rectal temperature of several degrees. An increase in the primary antibody response of B- lymphocytes was reported in rodents exposed to levels above 5 W/kg. An increase in immune response has been reported (BEMS 1994 meeting, not yet published) in male mice after 7 daily exposures to 2.45 GHz, cw or pulsed at SAR of 0.14 W/kg. A transient change was also reported in the responsiveness of B- and T- lymphocytes to specific mitogens after 13 months of

exposure in a life-time (27 months) radiation study on rats at SAR up to 0.4 W/kg (all other haematological indicators were normal; plasma corticosteroid levels were unchanged). The acute exposure of primates and rats to RF radiation at SARs of 3-4 W/kg, sufficient to raise rectal temperature by 1-2°C, resulted in elevated plasma corticosterone levels.

Teratogenic effects

Elevated body temperature is teratogenic to a number of mammalian species including primates. Thus, RF- or microwave-radiation-induced maternal hyperthermia is teratogenic in animals. In these studies, species differences and the use of different environmental conditions have led to some inconsistencies. Exposure at 11 W/kg raised the maternal temperature to 43°C in rats and induced embryonic and fetal death and developmental abnormalities. At 6-7 W/kg fetal growth retardation and postnatal behavioural changes occurred. Exposures below 4 W/kg generally had no adverse effect. Similar effects were described in mice, but at higher SARs. In addition, one study reported that while exposure at 4-5 W/kg produced no direct effect, it increased the effectiveness of a known chemical teratogen.

Irrespective of the SAR, substantial birth defects occur when the core temperature of the pregnant mother is increased by more than 2.5°C. Exposures that increase the maternal temperature by 1 - 2.5°C generally do not result in structural malformations but may significantly increase the incidence of abortions and resorptions, result in lower fetal body weight, or alter the behaviour of the exposed offspring. Non-specific stress during pregnancy is associated with reduced fetal and birth weight.

Recent studies reporting retarded embryonic development following acute or chronic exposure of avian embryos to low SAR (0.05 W/kg) at 428 MHz implicate a non-thermal mechanism that is, as yet, unexplained.

Heating

The most readily understood and accepted bioeffects data apparently result from an increase in tissue or body temperature of 1°C or greater. Most of these responses have been reported at SARs above 1-2 W/kg. However, differences in size and thermoregulatory ability preclude direct extrapolation of threshold SAR values from laboratory animals to humans. For a given temperature increase the required SAR value is substantially higher for small animals. Therefore, data from mice may underestimate the heating effect in humans.

Cancer-related studies

In Vivo

There is a lack of clear evidence for a mutagenic or carcinogenic effect of RF radiation. In a study of chronic exposure of rats from 2 months to up to 27 months of age at SARs of up to 0.4 W/kg the total incidence of neoplasia (benign and malignant) or of specific cancers was not increased. However, the total number of primary malignancies in the exposed group was significantly larger than in the

controls. An earlier study looked for both spontaneous production and promotion of cancers. Chronic microwave exposure of mice at 2-8 W/kg was reported to result in an SAR-dependent increase in the progression or development of spontaneous mammary tumours or chemically-induced skin tumours. Another study showed that repeated exposures at 4-5 W/kg followed by the application of a non-carcinogenic dose of a known carcinogen to the skin, resulted in a three-fold increase in the number of skin tumours. These observations need replicating and extending. However, a great deal of care is required in developing the experimental design in such a way that provides for a realistic assessment of in situ dosimetry and which minimises the effects of stress.

Studies are currently in progress to evaluate; (a) the potential promotion of cancer (primarily brain tumours) in rats exposed chronically to cellular telephone frequency and absorbed dose, (b) the possible increase in incidence of tumours in a strain of mice genetically predisposed to lymphomas.

In Vitro

Some in vitro studies have implied a role for microwave exposure in cancer induction. Enhanced transformation rates were observed in cells exposed to combined amplitude-modulated microwaves (4.4 W/kg) and X-rays followed by treatment with the chemical promoter TPA, compared to cells exposed only to X-rays and TPA.

Similar effects were reported in a further study when exposure to microwaves and/or X-rays (1.5 Gy) was followed by treatment with the chemical cancer promoter TPA resulting in a dose-dependent induction of neoplastic transformation. Microwave exposure also slightly enhanced the effects of X-irradiation and TPA on transformation rate. Transformation studies can be susceptible to experimental confounding factors, and the human health implications of data from chromosomally abnormal C3H10T1/2 cells for carcinogenesis in vivo is uncertain. Future studies should examine the responses of normal cells and animal models. Evidence that low level amplitude-modulated microwave radiation changes the intra-cellular levels of ornithine decarboxylase, an enzyme involved in tumour promotion, suggests that further research is necessary.

Genetic studies

There is no evidence from acute or chronic exposures to microwave radiation that shows an increase in mutation or chromosome aberration frequency in male germ cells at normal physiological temperatures. There is no verified report from studies using chronic, low level exposures (1-5 W/kg) of dominant lethal mutations in mice or rats. There is no confirmed evidence that RF or microwave radiation has clastogenic effects on somatic cells.

Reproductive cells

The testis is a heat-sensitive organ and is normally maintained at several degrees Celcius below body temperature. Male germ cells (particularly during meiosis) are

known to be adversely affected by elevated temperatures. Chronic RF exposure at about 6 W/kg has produced transient infertility in male rats where the irradiation caused the rectal or testiclular temperature to rise by 1.5-3.5 °C. Transient reduction in fertility is relatively minor compared to either accelerated, abnormal growth of germ cells (and possible genetic consequences), or retarded development after fertilisation.

Nervous system responses

Exposure to very low levels of amplitude modulated RF or microwave radiation has been reported by several groups to alter brain activity, measured by electroencephalography (EEG), and to affect calcium mobility in chick brain tissue in vitro. Effective SARs in vitro were less than 0.01 W/kg. The use of sophisticated techniques has recently allowed investigation of ion fluxes through cell membrane channels. However, the reported RF-induced changes in calcium ion mobility have not been readily replicated. Models of nonlinear processes have been proposed including, power density and modulation frequency “windows”. It has been suggested that the effects result from weak, co-operative interactions at the cell membrane. The physiological significance is not established although it is accepted that Ca2+ concentration plays a major role in the regulation of cell processes.

RF radiation exposure can modify the action of drugs. The effects of low level RF radiation on the influence of neuroactive drugs, such as tranquillisers or stimulants, on EEG activity are variable. RF-induced altered permeability of the blood-brain barrier might affect the action of psychoactive drugs. The experimental evidence suggests that the acute exposure of conscious rats to microwave radiation at 13 W/kg, sufficient to increase brain temperature above 40°C, can alter the permeability of the blood-brain barrier.

Learning impairment

The threshold for disruption of conditioned behavioural responses in acutely exposed rodents is within the range 2.5 to 8 W/kg. The lowest threshold occurred with more deeply penetrating radiation. Impaired performance was also reported from chronic exposures to 2.45 GHz radiation at 2.3 W/kg. In all cases the mechanism appears to be thermal as colonic temperature was reported to increase by at least 1°C during irradiation. The acquisition of learned tasks is more sensitive to disruption with thresholds having been reported in the range 0.14 to 0.7 W/kg for chronic exposures to cw radiation at 2.45 GHz. Impaired short term memory function in rats has been repeatedly demonstrated (within the same laboratory) following acute exposure to 2.45 GHz at SAR of 0.6 W/kg.

2.4.3 CONCLUSIONS

Many of the biological effects of acute exposure to electromagnetic radiation are consistent with responses to induced heating of about 1°C, or more. Biological effects have been most reliably reported at SARs above 1-2 W/kg. Most animal data indicate that implantation and the development of the embryo and fetus are unlikely to be affected by microwave radiation which results in an increase in maternal body

temperature by < 1°C. Such an exposure is not mutagenic and will not result in somatic mutation or hereditary effects.

Reports of non-thermal effects on cell and whole animal developing systems are inconsistent. Changes in phase transition temperatures in lipid cell membranes and consequent ionic fluxes during microwave radiation may offer clues to understanding the process of cell surface receptor and intracellular signal amplification.

The implications of reports of cell resonance effects at narrow frequency bands (or "windows") may have significance for molecular resonance in the GHz frequency range in specific telecommunication applications.

A number of research centres have planned, or have in-progress, chronic exposure studies to determine if radiation from cellular telephones can promote the development of cancers in rodents. Because of the complexities and expense of such studies none have so far been designed to study a dose-response. With the variability in species, exposure protocols, choice of primary carcinogen or co-promoter, there is a high probability that none of the studies will be exact replicates. As a whole-life study in rodents takes 2 - 3 years it will be some years before the data base shows any improvement from in vivo cancer studies.

Other in vivo studies that are capable of producing effects in the short term include; teratogenesis, interaction with the central nervous system, impaired memory function, and ocular damage from low level microwave exposures.

Research on these important issues may be more cost-effective and have a high probability of achieving useful information about human health. The cost-benefit ratio of epidemiological studies is arguably poor. An assumption is made that some form of cancer may result from RF exposure, although no accepted mechanism exists. The hypothesis is, at best, based on a weak association with ELF and cancer. Because of the long latency period for the development of human cancers a prospective study will require long-term study. The probability of achieving scientifically acceptable data is low.

2.5 PLANNED AND CURRENT RESEARCH

The investment of US $25 million by the CTIA is a clear admission of the need for a recognised research program. There are a number of other research programs in the US (at least two), Germany, France, of the order of US $2-3 million each. To be effective, the existing apparent haphazard approach to research on biological effects of microwave radiation needs to be directed. An effective central body should be able to establish an agenda that identifies the most directly relevant topics in a total research program. The CTIA has established a Scientific Advisory Group, and it is hoped that this body will go some way towards achieving such a goal, without prejudice. US researchers have been invited by CTIA to submit expression of interest (approx. 1 page description) for intended projects of bioeffects at CT frequencies. A selection process will invite full grant application by the end of 1994. It is evident that CTIA will select, and directly influence, research that it funds. Having attended the so-called "workshop on safety of cellular telephones", 13-17 June 1994

in Copenhagen, it seems that this might be unduly optimistic. In a presentation by George Carlo (Chairman of the CTIA Scientific Advisory Group), it was clear that there are considerable concerns about the way the program will be administered and conducted.

According to Carlo, peer review is important; therefore the "peer-review committee" (appointed by CTIA, or Carlo) will decide what studies to fund, it will peer-review the results of those studies and any publication will be reviewed by this selected group prior to submission to peer-review journals. This level of monitoring of the output is not surprisingly, treated with suspicion. It is difficult to perceive of truly unbiased data or interpretation arising from such studies.

The type of studies described by Carlo as important may not be the most appropriate. The use of "standard battery of toxicology tests" is appropriate when dealing with toxic chemicals but have unacceptably low statistical power for a cancer study that may involve a weak promoter where a dose response or reliable endpoint has not been established. His program has identified epidemiology studies as important, while the common opinion is that there is negligible chance of identifying a risk, certainly within the next 10 years. This issue was clearly put into perspective in a balanced presentation by Michele Coleman (BEMS 1994).

Similarly, the ideal of mechanistic studies is fine, but unlikely to achieve a result until verified bioeffects have been identified. There does not seem to be an agenda to fund studies on CNS effects and ocular damage that have been identified at low level acute exposures. However, the subject of CNS effects in animals and humans is planned in research programs in Germany (Telekom) and France (French Telecom Research Centre).

Because of the complexity of the subject there is an obvious need to develop a multi-disciplined team to undertake high quality research. One such centre is currently being established in San Antonio, Texas, where there exists a large diverse resource in facilities and personnel for in vitro and in vivo work, spread over a number of academic institutions and the US Air Force Base. A single facility that includes a wide range of expertise on a single campus exists in Loma Linda, California, although the work is primarily focused on ELF in vitro research. Much of the research in the microwave frequency range has been funded by the USAF. This includes studies within the USA and elsewhere, such as on numerical techniques for dosimetry at Kings College London. The USAF continues to contract out much of its research needs.

In the UK the LINK study, funded through the Department of Trade and Industry (DTI) involves a multicentre study with nine academic institutions and three commercial organisations. The emphasis is on computer modelling for dosimetry.

Part of the research program of the CSIRO Division of Radiophysics is the development of critical biological studies. One such program that would have benefit to the telecommunications industry, the CSIRO and Australia is the independent evaluation of thresholds (and the true dose-response) for microwave-induced ocular damage. It is also intended to study the teratogenic effects in specialised embryo culture conditions. CSIRO has local and international academic alliances that allow

collaborative research on these and other vital topics. The frequency range will extend from cellular telephones to wireless PCNs.

3.0 ANIMAL STUDIES

Animal studies allow assessment of the potentially hazardous effects of physical or chemical agents on different body systems. The potential for adverse effects on reproduction and prenatal and postnatal development can be tested. The induction of mutagenic changes is important in the assessment of possible hereditary effects. Carefully controlled animal studies are an essential step in the extrapolation of biological effects to human health and safety.

3.1 OCULAR EFFECTS

SUMMARY

The absorption of radiofrequency electromagnetic energy, particularly in the GHz frequency range, has been shown to result in damage to ocular tissues in experimental animal studies. The site of damage depends on the radiation frequency (related to depth of penetration) whereas the magnitude of effect primarily depends on the power density of the field, the quantity of absorbed energy and on the duration of exposure. The lens of the eye is susceptible to microwave and RF heating because of its lack of a blood supply and hence limited heat dissipating capability. Its constituent fibres have a limited capacity for repair and tend to accumulate the effects of minor insults.

Microwave induced temperature increase has been shown to produce cataracts in the lenses of anaesthetised rabbits. Microwave frequencies between 1 and 10 GHz are most effective in inducing lens cataracts. The threshold temperature for cataract induction from prolonged exposure (>100 mins) is 41 - 43°C, with a corresponding SAR of 100-140 W/kg resulting from exposure to power densities greater than 1.5 kW/m2. Most experimental work on microwave induction of lens opacities (cataracts) has been carried out using near-field exposures at 2.45 GHz. The intense exposures used were generally far above perception threshold and the animals were normally anaesthetised. Cataracts produced in rabbits eyes are either caused by intense exposures sufficient to damage other ocular structures and rapidly produce opaque lenses or less severe exposures that result in posterior cortical opacities several days or weeks after exposure. The mechanism for cataract formation is considered to be thermal in origin.

Lens opacities have not been produced in the eyes of rhesus monkeys after acute exposures to 5 kW/m2 (anaesthetised) or after chronic exposures of conscious monkeys to 1.5 kW/m2. The difference in acute response may be due to structural anatomical differences in the eyes and skull of rabbits and monkeys. Recent studies on monkeys have shown that other structures including the cornea and iris are susceptible to microwave radiations in combination with ophthalmologic drugs where the exposure levels are too low to involve a thermal mechanism. Well-conducted studies by a single research group (Kues et al 1992, 1994) have shown degenerative changes in the retina, iris and corneal endothelium of primates to be caused by low level microwave irradiation, particularly when pulsed. Localised threshold SARs were found to be as low as 0.26 W/kg when irradiated together with the glaucoma drug, timolol maleate. It is clearly important that these results are independently verified.

The apparent sensitisation of ocular tissues to microwave radiation by the application of a drug used in the treatment of glaucoma may provide evidence of a non-thermal effect. Timolol maleate normally offers protection to the eye against heat induced disruption of the blood aqueous barrier and the ocular temperature was said to have increased by less than 0.8°C at a SAR of 0.26 W/kg during the irradiation (Kues et al 1992).

The extrapolation of results of animal experimentation to human exposures is complicated by anatomical/structural differences in the head and eyes that result in different in vivo exposure conditions. Frequency and orientation dependent factors may have a significant impact on EM field distributions in the eyes of different species.

Experimental Evidence

3.1.1 Cataracts

Posterior cortical cataracts have been reported to form within 1 week of exposure to 2.45 GHz radiation at approximately 4.2 kW/m2 for 5 min or 1.5 kW/m2 for 60 min (Carpenter 1979). The reaction varied from narrow translucent or milky bands in the posterior cortex that disappeared within a few days to permanent lesions. The extent of cataract formation varied with the power and duration of the exposure from a few fibrous “streaks” at the posterior suture to diffuse opacities.

The threshold power density for cataract formation in the rabbit eye by a single exposure of up to 100 min was calculated to be 1.5 kW/m2 (Guy et al 1975). Based on temperature measurements in a dead animal it was estimated that the peak level of SAR occurred in the vitreous humour immediately behind the lens, with a threshold for 100 min exposure determined to be 138 W/kg. Calculation of the heat flow within the rabbit eye predicted threshold temperatures at the back of the lens of 41 - 43°C, similar to the experimental data on temperature induced cataract formation in dogs. Induction of cataracts in the lens was shown to be heat-dependent when cataractogenic RF exposures applied to hypothermic rabbits failed to produce lesions (Kramar et al 1975). The existence of a thermal mechanism was given further support in a study that produced cataracts in rabbit eyes by heating the lenses above 43°C with circulating heated water.

Different results were reported in rhesus monkeys where 2.45 GHz radiation did not produce cataracts, even after exposure to power densities up to 5 kW/m2 for 60 min (Kramar et al 1978). This is far above the threshold for cataract formation in the rabbit and sufficient to cause severe facial burns in the monkey. Peak temperatures occurred behind the lens in the monkey eye but were lower for a given exposure than those in the rabbit. Power densities of 2 and 5 kW/m2 raised the retrolental temperature to 39 and 42°C, respectively. The different anatomical structure and size demonstrate important species differences. The extrapolation of results of animal experimentation to human exposures is complicated by anatomical/structural differences in the head and eyes that result in different in vivo exposure conditions.

Frequency and orientation dependent factors may have a significant impact on EM field distributions in the eyes of different species. It is well known that absorption of EMR by a lossy dielectric scatterer such as the mammalian head alters as a function of its shape and the applied frequency (NCRP 1986). It has been shown that (at 2.45 GHz) the measured field intensity at the position of the head of a rabbit was reduced by 40% by the presence of the animal in the field, and by a further 40% when its ears were fastened against its body (Carpenter et al 1974). In a comparison of the effects of 2.45 GHz radiation (Kramar et al 1978) cataracts were induced in rabbits but not in monkeys (table 3.1.1). These differences have been interpreted as being due to differences in field concentrations and heating of the lens.

The efficacy with which microwave or radiofrequency radiation can induce cataracts depends on the depth of penetration and hence on frequency. It has been reported that below 1.5 GHz the dimensions of the orbit-eye combination are too small to result in local field concentration (NCRP 1986).

Table 3.1.1 Summary of Studies on Cataractogenic Effects of Microwave Radiation

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At frequencies above 10 GHz, penetration decreases and power absorption is increasingly restricted to the superficial tissue. At 915 MHz the estimated distribution of SAR (Guy et al 1974) in the eyes of rabbits gave the peak SAR as 25% lower than that resulting from exposure at 2.45 GHz. The maximal SAR was found to occur in the rabbit brain, being 36% higher than in the eye. It is likely that other biological endpoints will become limiting factors before exposure is sufficient to induce cataracts. At higher frequencies of 35 and 107 GHz effects of acute exposure were limited to the cornea of rabbit eyes (Rosenthal et al 1976).

Whole-body exposure to far-field radiation, which is relevant to many occupational situations, has not been reliably associated with experimental cataract induction. The lenses of anaesthetised rabbits exposed in the far-field to 3 GHz for 15-30 min at 5 kW/m2 were unchanged. Cataracts were not found in macaque monkeys trained to expose their faces to 9.3 GHz radiation at 1.5 kW/m2 for a total exposure period of up to about 10 h over 3 months (McAfee et al 1979). In a study of the cumulative effects (table 3.1.1) of repeated sub-threshold exposure of anaesthetised rabbits to 2.45 GHz radiation, the lowest power density capable of producing cataracts was 1.2 kW/m2 for 1 h, repeated 20-24 times (Carpenter 1979).

3.1.2 Corneal Lesions

In addition to lens opacity, corneal endothelial lesions were produced in the eyes of anaesthetised monkeys exposed to continuous or pulsed wave (10 μs pulses repeated at 100 pulses per second) 2.45 GHz radiation (Kues et al 1985) (Table 3.1.2). Pulsed radiation produced endothelial lesions after a single 4 h exposure to 100 W/m2 where the average SAR in the anterior chamber of the eye was estimated in vivo as 2.6 W/kg. Body temperatures dropped during exposure by about 2.5°C in both sham-exposed and exposed monkeys due to the anaesthesia. When the

exposure was increased to 4 h on three consecutive days, there was increased vascular leakage from the iris blood vessels into the aqueous humour (Kues et al 1988). When the eyes were pretreated with the ophthalmic drug timolol maleate used in the treatment of glaucoma, the leakage was increased at power densities as low as 10 W/m2 where the local SAR was estimated at 0.26 W/kg (Monahan et al 1988).

Table 3.1.2 Summary of Ocular Effects from Low Level Microwave Radiation

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Damage to the retina has since been reported (Kues et al 1990) following exposure to pulsed 2.45 GHz radiation at 50 W/m2 for 10 weeks. When exposure to 100 W/m2 followed timolol maleate treatment extensive vacuolation of the outer retinal layers was observed together with focal retinal detachment. The effects were produced when microwave radiation immediately followed the application of a single drop of the ophthalmic drug timolol maleate (0.5%) or pilocarpine (2%). When combined with either drug the power density threshold was reduced by an order of magnitude (from 10 to 1 mW/cm2) for the induction of corneal endothelial lesions and increased vascular permeability of the iris (Kues et al 1992). Sodium fluorescein iris angiography was used to diagnose vascular integrity. Positive results were also obtained using the glycoprotein horseradish peroxidise showing that microwave exposure resulted in diffusion of large molecules (40,000 molecular weight, and 100 times larger than sodium fluorescein) out of the iris blood vessels.

In the latest addition to this work on ocular lesions from low SARs, Kues et al (1994) reported cytological damage in retinal neuroepithelium under various exposure conditions, when monkeys were chair-restrained. The effect is considered to be permanent as it is still apparent at one year post-irradiation. Using frequencies of 1.25, 2.45 and 2.85 GHz, they reported effects at 4 W/kg SAR that were related to the shape of the pulse and the ratio of peak power to pulse length rather than to the SAR value. When applied using rapid rise-time square pulses, the effects were demonstrated by histology and depressed electro-retinogram. The cellular changes reported include cytoplasmic vacuolation and disrupted plasma membrane. The mechanism is uncertain. At a frequency of 2.45 GHz, and 10 µs pulses repeated at 100 Hz, the effects were observed at a SAR of 2.6 W/kg (average value in the eye, i.e., not whole-body average).

It has been proposed that the action of free radicals may be involved in the breakdown of the ocular membranes leading to extravasation. Oxygen radicals are known to increase vascular permeability (Hull 1985) in the rabbit iris. As both timolol and pilocarpine are known to bind to ocular melanin, and microwave interaction with melanin generates free radicals, a potential mechanism exists. It needs to be established if free radicals can be released by the low energy levels causing vascular leakage in these animal experiments.

3.2 HAEMATOLOGY AND IMMUNOLOGY

SUMMARY

The literature contains reports of a large number of studies on the effects of microwave and RF radiation on the haematopoietic system and on immune responses. These have been well reviewed (Roberts 1983; Smialowicz 1984; NCRP 1986; Szmigielski et al 1988; NRPB 1992; WHO 1993). The conflicting nature of many early reports makes interpretation difficult and although later studies have been improved with more rigorous experimental design and improvement in dosimetry, the overall effects of microwave and RF exposure are still not well understood. There is good evidence that receptor sites on cell membranes are sensitive to EMR and, therefore, some effects on the sensitive immunological system may be expected. Many of the effects are transient. Contradictory effects have been reported in rodents.

Various components of the immune system have been affected by microwave exposures. Interpretation may be confounded by the complex nature of immune responses, which can involve changes in the numbers of circulating lymphocytes and leucocytes, and the sensitivity of the system to minor changes in temperature. Consistent effects on the haematopoietic and immune systems are mostly associated with thermal stress, although the occasional report appears at SAR levels too low to induce significant amounts of heating. A recent report of stimulated immune response in male rats exposed to low level (0.14 W/kg) microwave radiation is contrary to expectations. Difficulties in interpretation are exacerbated by the experimental constraints of making isolated observations within a complicated sequence of changes.

This problem is common to much of the research carried out on cellular RF responses. Separate research groups generally study a small part of a chain of events. Species difference is a further variable that complicates these issues.

Introduction

The lymphocyte population consists of B-lymphocytes, the precursors of plasma cells or antibody secreting cells, and T-lymphocytes required to express cellular immune responses including delayed hypersensitivity, cell-mediated cytotoxicity and helper cell function. Experiments have been studied on the mitogen responses of B- and T- lymphocytes, the number of B- lymphocytes bearing complement receptors, natural killer cell (a T-lymphocyte sub-group) activity and the antibody response of B-lymphocytes. Lymphocytes from exposed animals have been studied by way of their in vitro response to mitogens (agents that stimulate transformation to lymphoblasts and mitotic division). Thus, the functional integrity of the cell and the relative frequencies of B- and T- cells can be evaluated by using B- and T- specific mitogens.

Experimental Evidence

3.2.1 Haematopoietic System

Early studies measured peripheral blood cell concentrations and reported an increase in erythrocyte and neutrophil counts but a reduction in total leucocyte and

lymphocyte counts in rats exposed to pulsed 24 GHz microwave radiation at 100 W/m2 for 18 h or 200 W/m2 for 7.5 h. The SARs were estimated to be 1.5 and 3 W/kg, respectively (Smialowicz 1984). These experiments are typical of many early studies that are complicated by the lack of appropriate sham-exposed controls and absence of interpretation of the biological significance of the effect.

Heating is often involved in haematological responses to microwave and RF radiation. A reported decrease in peripheral lymphocyte count and increase in neutrophil count (Liburdy 1977) was observed in mice exposed to 26 MHz at a SAR of 13 W/kg, which raised the rectal temperature by 2 - 4°C (Table 3.2.1). The response was greatest after 3 h exposure. In contrast, exposures that were not accompanied by a detectable increase in body temperature have reported absence of effects.

A lack of effect on peripheral blood count in mice exposed to 2.45 GHz was reported where the SAR was estimated at 22 W/kg (Smialowicz et al 1979 a). Peripheral blood cell count was unchanged in rats, in the absence of a measurable rise in whole body temperature, following exposure for; (a) 1 h per day for 90 days to 2.4 GHz at 50 W/m2 (SAR estimated at 1 W/kg) (Djordjevic et al 1977), (b) 22 h per day for 70 consecutive days to 970 MHz at a SAR of 2.5 W/kg (Smialowicz et al 1981a), or (c) for 8 h to 2.45 GHz at SAR 0.44 to 2.2 W/kg (Galvin et al 1982). See table 3.2.1.

Table 3.2.1 Summary of Reported Effects of Electromagnetic Radiation on the Haematopoietic System

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Substantial abnormalities in haematopoietic development in bone marrow cells have been reported in guinea pigs following a single exposure to 3 to 4°C hyperthermia for 60 min (Edwards & Penny 1985). Similar significant changes in nuclear development were observed following a temperature increase of only 2.5°C for 6 mins when produced by localised absorption of pulsed ultrasound (Barnett et al 1991) in a single acute exposure.

A review of early studies (Smialowicz 1984) reported a lack of consistent effect of microwave or RF exposure on peripheral blood cells in developing rats. Studies by the same author (Table 3.2.1) also reported no consistent changes in erythrocyte, leucocyte or differential leucocyte cell count in rats exposed prenatally and postnatally (for up to 41 days) over a range of frequencies; 100 MHz radiation at SAR 2-3 W/kg (Smialowicz et al 1981 b); 425 MHz radiation at 3-7 W/kg (Smialowicz et al 1982); and 2.45 GHz radiation at 1-5 W/kg (Smialowicz et al 1979 b).

The apparent trend of a temperature-related effect has doubtlessly contributed to the notions, commonly expressed, that if the energy deposition from EMR does not heat it cannot hurt. This rather simplistic approach is only acceptable for gross effects. The subtleties of cell membrane responses requires an understanding and development of other non-thermal mechanisms.

Studies on the effects of microwave exposure on haemopoietic tissue in bone marrow revealed abnormalities in nuclear structure and depressed mitosis (Baranski 1971) in guinea-pigs and rabbits exposed to pulsed or continuous wave 3 GHz microwave radiation at 35 W/m2 for 3 h per day over a period of 3 months. The SAR was estimated to be 0.5 W/kg and rectal temperatures were unchanged.

Studies to evaluate the effects of low level exposure on the haemopoietic stem cells using in vitro colony forming assays have been inconsistent. Huang and Mold (1980) exposed mice to 2.45 GHz radiation at 150 W/m2 (SAR 11 W/kg) for 30 min per day for 9 days and reported a reduction in the ability of bone marrow cells to form myeloid and erythroid colonies. Rectal temperature was variable, but not significantly increased. An inconsistent lack of effect on cloning efficiency of myeloid stem cells from mice exposed for up to 360 h to 2.88 GHz pulsed microwaves at SARs up to 4.5 W/kg was reported (Ragan et al 1983). In a review Smialowicz (1984) suggested that there is a marked difference in the kinetic response of the haematopoietic system to heat stress from microwave- induced heating and conventional heating. Radiation at 2.45 GHz frequency is quite penetrating (in small animals) and is likely to have set up temperature gradients within the mouse different to those set up by external heating, even though rectal temperatures were similar.

3.2.2 Immune System

A single study on rhesus monkeys reported enhanced mitogen response in lymphocytes after 30 min exposure to 10.5, 19.27 or 26.6 MHz radiation at SARs between 0.4 and 2.0 W/kg (Prince et al 1972). Rectal temperatures were reported to be increased by 2.5°C at the higher level of exposure.

Contradictory results have been reported using the appearance of a surface marker (complement-receptor) specific to a stage in the maturation of B-lymphocytes, following microwave radiation. One group of workers (Wiktor-Jedrzejczak et al 1977, 1980) reported an increase in the number of complement-receptor positive lymphocytes and an increase in B- cell mitogen response following exposure to 2.45 GHz radiation at 15 W/kg for 30 min. The effect was thought to be due to stimulation of B- cells into early maturation. Independent duplication of the study found a similar result only when the exposure level was raised to 28 W/kg resulting in a level of thermal stress that killed some mice (Smialowicz et al 1981 c) (See Table 3.2.2).

There is a suggestion that differences in results may be due to differences in mice strain specificity as Schlagel et al (1980, 1982) reported a negative effect in Balb/C mice and an increase in complement-receptor lymphocytes in CBA/J mice. It has been suggested that the difference in response between the two strains may be due to the presence of a single gene (Schlagel et al 1982; WHO 1993). An important experimental variable that has not been adequately investigated is that of the environmental conditions associated with each of the exposures. Differences in air

flow, humidity and ambient temperature may significantly alter the levels of thermal stress for a given level of microwave exposure.

Liburdy (1980, 1987) has examined the central role of thermal stress in the effect of microwaves on the immune system. Mice were exposed or sham-exposed for 15 min (single or repeated exposures) to 26 MHz radiation at 5.6 W/kg or to warm air to induce an increase in core temperature of 2-3°C. A number of effects were observed when the RF-treated mice were compared with either the sham-exposed or the heat-treated animals.

Table 3.2.2 Summary of Reported Effects of Microwave Irradiation on the Immune System

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A transient reduction in peripheral lymphocytes and an increase in numbers of neutrophils occurred, which could be sustained by multiple exposures. RF exposure also resulted in an increase in T- and B-lymphocytes in the spleen and elevated plasma corticosteroid levels. In addition, the ability of mice to develop a delayed hypersensitivity (to sheep red blood cells) was suppressed by the RF exposure.

The effect of RF exposure and elevated temperature was also determined on lymphocyte migration (Liburdy 1980). This was measured by the activity of radio-labelled splenic lymphocytes in mice exposed for 1 h to 2.6 GHz radiation at 3.8 W/kg. This was compared with exposure to 19 W/kg or to warm air, both of which were sufficient to raise rectal temperatures by 2°C. Exposure at 19 W/kg caused a significant alteration in the distribution of lymphocytes between the lung, spleen and bone marrow, whereas exposures to 3.8 W/kg or warm air did not produce these changes.

Liburdy suggested that whole-body RF or microwave exposure induces heat stress which activates the hypothalamic-hypophyseal-adrenal complex to release adrenal steroids into the blood, leading to the transient changes in blood cell counts and other haematopoietic and immunologic changes associated with RF or microwave exposure. The difference in response to exposures with warm air and microwave radiation is probably due to differences in energy deposition. Microwave-induced heating works by a different mechanism by being more rapid, and will have acted as a thermal stress for longer than warm air in a given exposure.

Exposure to thermogenic levels of microwave radiation has also been shown to cause changes in macrophage and natural killer cell (NK) activity, implicated for example in tumour cell cytolysis (Table 3.2.2). Activation of macrophages and some transient decrease in the NK activity of T- lymphocytes was reported after exposure to 2.45 GHz radiation (Table 3.2.2). Since colonic temperature (and plasma corticosteroids) was appreciably elevated at the higher level of exposure, the decreased activity is probably due to heat stress.

The latest reported effects from a group in Hungary (Elekes et al 1994) adds a further degree of uncertainty to the subject. The data was presented at the BEMS conference and, therefore, has not yet been peer-reviewed, but a paper has been submitted for publication (for this reason the data is not included in the table 3.2.2). In their study Balb/C mice were exposed to 2.45 GHz, cw or 50 Hz amplitude modulated, at SAR 0.14 W/kg. Exposures of different durations were applied for six consecutive days and mice were injected with sheep red blood cells on the second day of exposure. The number of antibody producing cells in the spleen of male mice was significantly increased with daily 3 h exposures. Exposures for longer durations had less of an effect. Female mice were unaffected. No logical explanation was given for the observed result. The authors have experience in ionizing radiation biology and have recently turned their attention to EMR.

3.3 TERATOGENIC EFFECTS

SUMMARY

It is well understood that a moderate elevation of body temperature during embryonic/fetal development is teratogenic in many animal species (Warkany 1986) and in humans (WFUMB 1992; Edwards 1986, 1993). Data from whole-body heating of pregnant animals in environmental chambers, indicates a threshold of 2.5°C above basal physiological temperature for the development of major abnormalities in the central nervous system (Germaine et al 1985). The type and magnitude of effect depends on the gestation stage and extent of the thermal insult.

Thus, exposures to microwave or RF radiation that will induce significant rises (>1.5°C) in maternal body temperature would be expected to result in teratogenic effects. Most of the literature reports effects of exposure to substantial levels of SAR and the associated adverse developmental effects are consistent with RF-induced hyperthermia. These are gross effects that are easily detected.

More sensitive, and potentially important, disturbance of CNS function has not been adequately investigated, particularly where where offspring may appear normal. Research in this area is recommended.

Most of the work has been clearly focused on the safety issues relating to microwave ovens at 2.45 GHz frequency. It is tempting to assume that teratogenesis will only be produced when the RF radiation is sufficient to significantly raise the embryonic or fetal temperature. However, recent reports from a single laboratory have claimed delayed development in chick embryos exposed to 428 MHz at 5.5 mW/cm2 which they consider to be a non-thermal effect.

Similarly, a report by an apparently respectable research group (Tofani et al 1986) of significant effects on postimplantation survival and cranial ossification in rat fetuses following chronic exposure to very low level RF radiation cannot be explained by the accepted thermal mechanism (Table 3.3.1). Data that is relevant to exposures at telecommunications frequencies, particularly for cellular telephones, is urgently needed.

Introduction

Cells are most sensitive to damage by physical agents, such as heat, during the process of cell division. If mitosis in neurons is arrested by a transient temperature increase during embryonic development the resulting neural deficit may not be restored, although the fetus may continue to develop and appear morphologically normal (Edwards et al 1974). There are critical periods during gestation when the embryo is more susceptible to teratogenic effects. At the time of formation of the neural plate and closure of the neural tube interactions can result in severe neural tube defects, retarded brain development, exencephaly, and microphthalmia. Other effects have been reported following a single brief exposure to an increase in temperature of 3.5°C (Cuff et al 1993).

These gross effects are readily detected. However, low level interference that delays development of the cerebral cortex or impairs neural migration at later stages (around 22 weeks human gestation) is far more difficult to detect. The resulting impairment of neurological function may create learning difficulties. Non-deforming retardation of brain growth with reduced learning performance is the most common abnormality found in offspring from heat-exposed guinea pigs (Edwards 1968). The literature on teratogenic effects of electromagnetic radiation does not address this more sensitive issue.

3.3.1 Experimental Evidence

Exposure to high levels of RF will induce significent rises in the temperature of the mother and embryo. The resulting hyperthermia will bring about abnormal development both by direct interaction on the embryo and fetus and indirectly through compromised maternal physiology. Such an effect has been demonstrated where absorbed ultrasonic energy produced maternal hyperthermia (Barnett & Williams 1990). The teratogenic nature of hyperthermia is now widely accepted (Edwards 1993).

Although many of the studies on RF- induced teratogenicity applied repeated exposures this would add little value to the results if the effect was due entirely to a thermal mechanism. For the type of abnormalities reported, there is no reason to assume that repeated exposures at subthreshold levels would be any more effective than a single exposure to heat. In fact, the bioeffects data base on hyperthermia consists primarily of results from a single exposure to heat usually at a predetermined critical stage of neural development.

Table 3.3.1 Summary of Teratogenic Effects of RadioFrequency Radiation

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In reviews of the teratogenic effects of RF exposure (O'Connor 1980, 1990) the effects commonly described for rodents (CNS abnormalities including exencephaly, reduced fetal weight, and increased fetal resorptions) are typical of those induced by a single exposure to whole body hyperthermia.

The reported abnormalities and deaths (Lary et al 1982) in rats exposed to 11 W/kg at 27.12 MHz were associated with elevated rectal temperature to 43°C in the dam (Table 3.3.1.). This represents an increase of 4.5°C above the basal temperature for rats and exceeds the threshold temperature level for such abnormalities (Walsh et al 1985; Germaine et al 1985; NCRP 1992; WFUMB 1992). However, later experiments by the same author found the threshold temperature for a 40 min. exposure to be 41.5°C (DðT 3°C).

Teratogenic effects of RF radiation have been demonstrated in both rats and mice, although usually at higher SARs in the latter animal species. There is no evidence from hyperthermic studies to suggest different teratological effects in species although some animals such as rats may be more likely to abort. Different effects are most likely to be a function of body dimension relative to the RF field and relative efficiencies in dissipating body heat.

In fact, the results of studies on the thermal effects of RF radiation in species of different body mass (Gordon & Ferguson 1984; Gordon 1988) show that substantially greater dose rate is required to raise the body temperature in smaller animals. The SAR required to increase body temperature by 1°C in a 0.3 kg mouse is approximately 40 times greater than that required for a 3 kg rabbit. This being the case, one might question the value of using small animals such as mice to extrapolate biological effects to humans where the relative body mass could result in differences in absorbed dose by factors of 3 orders of magnitude. The data derived from mice would, thus, substantially underestimate an anticipated thermal effect in humans.

There have been a number of reviews of the literature on hyperthermia and RF teratology literature that agree on a reliable association between the magnitude and duration of heating and the consequent bioeffect. Berman (1984) and Berman et al (1984) concluded that malformations and prenatal death occur when the core temperature of RF-exposed dams exceeds 40°C. At lower temperatures the primary effect is decreased fetal or neonatal weight. The results of a dose-response study by Lary et al (1986) support this view (Table 3.1.1).

Table 3.3.1 Summary of Teratogenic Effects of RadioFrequency Radiation

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The temperature threshold for gross anatomical malformations and prenatal death in rats was 41.5°C (being 3°C above their normal body temperature).

Nawrot et al (1981) exposed pregnant mice at stages pre-and-post-organogenesis to a range of microwave power and reported fetal abnormalities including cleft palate that are commonly associated with hyperthermia. They stated that exposures to power densities of 21 or 30 mW/cm2 (SARs 28 and 40 W/kg, respectively) elevated maternal colonic temperature by 1 or 2.3°C. The exposure regimen of 8h per day repeated daily for seven days is far beyond that required to induce the reported effects by heat alone. A single exposure to ambient temperature increase above 2°C for 1 hour is sufficient to produce such effects in a range of animal species (Edwards 1993). The authors also reported that the normal rate of maternal weight gain during pregnancy was depressed when the maternal temperature increased by 1°C. This is clear evidence that maternal physiology was compromised by the severe exposure conditions. Similar effects from maternal physiological compromise were reported in a study into the mechanism responsible for ultrasound-induced fetal weight reduction in mice (Barnett & Williams 1990). These effects were produced under conditions in a single exposure that avoided temperature increase at the fetus.

A review by Lary and Conover (1987) describes studies by two groups where the body temperature of rats was lowered prior to exposure to 27 and 2450 MHz radiation. Intensity levels that normally induced abnormalities produced no effect in hypothermic rats indicating that the mechanism for effects was thermal and not due to field-specific effects.

There have, however, also been some reports of teratogenic effects of RF radiation that are inconsistent with a thermal mechanism. Tofani et al (1986) reported significant development perurbation in rat fetuses following exposure throughout gestation (20 days) to extraordinarily low SAR of 0.1 mW/kg. Saito et al (1991) reported retarded development and embryonic death in chick embryos exposed to 428 MHz, SAR 5.5 mW/kg throughout most (20 days) of the incubation period. Saito et al (1986, 1987) also reported retarded development and reduction in thymus weight in newborn mice following exposure to 433 and 906 MHz at similarly low levels. As the papers are written in Japanese it is impossible to give any further details or comment on the content. Results of another author (Jensh 1984 a, b) that do not fit the accepted scheme of temperature-based teratogenic effects are from chronic exposures. Rats were exposed for 8 h per day throughout pregnancy to 6 GHz at SAR of approximately 7 W/kg. While rectal temperature was reported to be unchanged, the fetuses showed growth retardation. There was no evidence of structural abnormalities but female offspring exhibited impaired learning ability and males showed increased activity levels (Table 3.3.1). The validity of dam's rectal temperature as a measure of RF teratogenesis is questioned.

Several investigators have reported significant physiological and behavioural changes in animals prenatally exposed to RF fields which produced little or no increase in body temperature, while others have reported no effects at these levels. Of the positive-effect reports, decreased fetal or postnatal body weight was most commonly reported. This effect may be due to: (1) highly non-uniform absorption of RF energy producing localised appreciable levels of heating in the uterus or fetal or maternal organs, or (2) due to a non-specific stress response.

A commonly reported effect associated with low level interactions with various physical or chemical agents is that of apparent growth retardation, usually detected as low birth weight. Such effects have been reported in the teratogenesis literature, and described as a fetal stress response. The effect has been reported following exposure to low intensity ultrasound where insignificant bulk heating was involved (Barnett et al 1990; Tarantal and Hendrickx 1989).

Saito et al (1991) reported lethal and teratogenic effects in chick embryos following exposure to 428 MHz RF radiation at a power density of 5.5 mW/cm2. The low level radiation was applied throughout most of the incubation period over 20 days. The authors justify their use of chick embryos in preference to mammals on the basis that temperature was controlled and SAR was accurately estimated. Whereas, in rodents the body temperature fluctuates considerably with metabolic activity and the maternal animals move about in the RF field causing substantial variations in their SAR. Delayed embryonic development was demonstrated by the incubation period being prolonged by approximately 1 day in the exposed group. Lethal effects were found in 60% of the exposed group where SAR ranged from 3.1 to 47.1 mW/kg depending on the position of the egg in the field. By comparison, deaths in the control group amounted to 16%. The authors report these effects as evidence of non-thermal effects of RF radiation. They speculated that RF radiation interferes with cell-cell interaction during embryonic cell development and migration. These authors have also reported adverse biological effects in mice from low intensity RF radiation at 433 and 906 MHz (Japanese language paper). Effects included reduced weight of the thymus in offspring of irradiated mothers and prolonged gestation.

In a follow-up study, Saito and Suzuki (1993 Japanese Teratology Society Conference) reported retarded development measured as a reduction in somite number in chick embryos following exposure to the same SAR levels of RF radiation at 428 MHz. In this study embryos were exposed for 48 hours and examined immediately afterwards. Somite counting is a standardised method of quantifying development in vertebrate embryogenesis It was concluded that gene expression in early embryogenesis had been disturbed by a non-thermal mechanism. The evidence for this claim will, presumably, be stated in the published paper.

Most modern studies, particularly at ELF frequencies, are carefully designed to avoid unwanted exposure (and potential cellular responses) from ambient power line electromagnetic fields. Specially shielded incubators are custom built for cell culture exposure systems. It is not certain that this fastidious approach is applied to the teratogenic RF studies. The initiation of subtle cell responses (e.g. involving alteration of intracellular calcium ion concentration) appears to depend on an ELF component in the exposure. It is, therefore, possible that the effects of RF and microwave radiation may be potentiated by the presence of an ELF field generated

by heaters, transformers and electric fans in commercial incubators. Indeed, the authors may be correct in their assessment that the observed adverse effects on development are due to interference of the cell-cell interaction and migrations. Nevertheless, the reported effect is important. The potential for a synergistic effect between ELF and RF exposures in embryonic and fetal development needs to be further investigated.

Reference has been made in the media to a report from Germany (Telecom Europa 1993, refer to chapter on media headlines) of lethal effects in chick embryos from exposure to radiation from cellular telephones. It has been impossible to obtain any publications or information on this matter from the original source. It is assumed that the media article was originally prepared from a verbal presentation. In the absence of a published paper no further comment can be made at this time.

Results from Marcickiewicz et al (1986) suggest a synergistic association of teratogenic drugs and high intensity RF exposures.

3.3.1 Summary of Teratogenic Effects of RadioFrequency Radiationiation

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Other non-thermal effects

In a study on the potential teratogenic effects to clinical levels of magnetic resonance imaging (MRI) a statistically significant increase in the incidence of eye malformations was observed in offspring of mice (Tyndall & Sulik 1991) exposed for 36 min on day 7 of gestation.

MRI includes a strong magnetic field and an RF component of 64 MHz. Although no dosage information was provided, it was stated that MRI devices are limited in the USA to power density levels that do not produce a temperature rise greater than 0.2°C. Eye malformations, primarily microphthalmia, were produced in a C57BL/6J strain of mice that is genetically predisposed to this abnormality (10% spontaneous incidence). The authors claim this to be the first report of a teratogenic effect of MRI. Their measurements of maternal core temperature show bulk heating is not the cause, however, they cannot exclude the possibility of localised heating. While this finding is of interest for medical safety, its usefulness to the scope of the current report is limited due to the absence of dosimetic information. Interpretation is complicated by the high magnetic field strengths and possibility of localised RF absorption.

3.3.2 Implications

Hyperthermia is a known teratogen. Radiofrequency heating is potentially more hazardous than whole body environmental heating. Conventional sources of heating warm the surface of the body allowing the thermoregulatory system to control core temperature via heat receptors in the skin. The slow heating can trigger the synthesis of specific heat-shock proteins that can afford thermo-tolerance to dividing

cells (Walsh et al 1985). However, rapid heating of deeper tissues resulting from absorption of RF energy can cause significant heating and short-circuit the thermoregulatory and thermoprotective mechanisms. The thermoregulatory response to RF heating may be delayed until the temperature of the blood entering the hypothalamus increases. As fetal thermoregulation relies on the maternal homeostatic mechanism the delay would be extended until the maternal blood temperature increases significantly. The human fetus is situated approximately 2 cm below the abdominal skin throughout pregnancy. It is conceivable that localised hot-spots could occur in the fetal brain without initiating a measurable physiological response in the mother.

A study by Lary et al (1982) drew attention to the potential adverse effects from exposure to high intensity RF fields from diathermy medical equipment. A review of teratogenic effects of RF radiation (Lary & Conover 1987) described a number of adverse effects in humans following inadvertent exposure to 27.12 MHz diathermy medical equipment.

3.3.3 Recommendations

The suggestion of risks of harm to the unborn child from any environmental component in modern life is taken seriously by the general population. The potential risk of interference with embryonic and fetal development therefore urgently requires directed research. Sporadic negative reports under different experimental conditions do not quell the concern raised by a single report of an adverse effect. Worst-case models can be established which allow temperature measurement and evaluation of biochemical and developmental effects using in vitro embryo culture procedures.

If laboratory animals are used then appropriate adjustments on scale and allowance for resonant frequencies must be determined to allow extrapolation to human exposures. Studies need to be undertaken that test for the possibility of impaired CNS function in offspring that appear normal. It is not sufficient to merely consider gross endpoints such as physical abnormalities. Through links with other common agents such as caffeine, cigarettes, alcohol and drugs, the public appreciates the risk to mental performance. It is most urgent that a substantial data base is established, particularly at intended frequencies and exposure conditions for wireless PCNs.

Sensitive assays such as alteration of neural protein production, synthesis of heat shock proteins and transcription of messenger RNA need to be employed to characterise embryonic stress. These studies should be designed to support research on RF interaction with the developing central nervous system. The potential synergistic effects of environment pollutants and pharmacological agents need to be explored.

3.4 THERMAL/PHYSIOLOGICAL EFFECTS OF EMR

SUMMARY

Heating is the most widely accepted physical mechanism responsible for initiating biological responses and/or changes (whether biochemical, functional or behavioural). A number of repeatable effects including alteration of the plasma concentration of corticosteroids following stimulation of the hypothalamus, teratological effects and death have been produced at SAR levels sufficient to cause significant heating.

Threshold exposure levels for thermal effects in various animal species have been used as the basis for standards for safe human exposure limits (IEEE 1992; ANSI 1992; INIRC 1991; NCRP 1986). However, the relevance of basing exposure standards entirely on thermal effects in laboratory animals exposed acutely to RF radiation is questionable, particularly when chronic exposures to low levels of RF radiation are more appropriate studies for implications to human health. The current data base for non-thermal bioeffects is inconsistent and may not be considered sufficiently robust for such an assessment of dosage.

The issue of cumulative dose from both repeated exposures and radiation from multiple sources has not been specifically addressed.

INTRODUCTION

The best understood mechanism of interaction with electromagnetic RF radiation is that of tissue heating. RF energy interacts primarily with water molecules. Water molecules are dipolar because each one is electrically unbalanced with more negative charge at one end and more positive charge at the opposite end. Thus the molecules align themselves with an externally applied electric field. As RF fields are not static, the water molecules experience an oscillating electric field that changes at the rate of the applied RF frequency. The consequent vigorous agitation of water molecules generates heat. Similar vibrational forces can occur with ions in electromagnetic fields. A detailed explanation of the interaction between RF radiation and molecular components of biological systems is given in a report by the NCRP (1981).

One would expect that alterations in cellular function would, at least, approach a linear relationship of; power: absorbed dose: temperature increase: biological response. In complex biological systems in the animal body the presence of energy deposition hot spots and regional anatomical differences in heat dissipating capability (vascular perfusion, conduction) will distort the curve. Nevertheless, the expectation would be of an evident dose-response. When the biological response is triggered by some other factor (e.g. cell receptor response to ligand or agonist, or depolarisation of cell membrane potential) one might expect an all-or-none response.

3.4.1 Experimental Evidence

No single expression of dosage is perfect for all occasions. There can be difficulties in using an estimate of absorbed dose (SAR) to quantify thresholds of biological effects amongst different animal species with different body mass. This is particularly so for thermally-induced effects, as Gordon (1988; Gordon & Ferguson 1984) has shown a wide variation in temperature elevation for a given SAR for laboratory animals. The resulting biological effect is dependent on both the extent of

temperature elevation above the physiological, basal, temperature and the duration for which the hyperthermic insult is maintained. If there is such wide variation for robust effects of whole-body heating it is hardly surprising that apparent discrepancies exist where more subtle non-thermal effects are involved.

It is appropriate, therefore, that physiological responses are used as indicators of interaction with low level EMR. It is known that in response to non-specific stress, the hypothalamus stimulates the adrenal complex to secrete the glucocorticoids, corticosterone and cortisol. This response has been used by some researchers to attempt to quantify microwave-induced heat stress in laboratory animals.

There is remarkable consistency in the correlation of SAR and rectal temperature in data reported by the same author (Lotz & Michaelson 1978; Lotz & Podgorski 1982; Lotz 1983) from rats (2.45 GHz) to monkeys (1.29 GHz) where SAR around 3 W/kg induced approximately 1°C temperature increase (Table 3.4.1). This is not consistent with reports on correlating thermal physiology with body mass (Gordon 1987; Gordon & Ferguson 1984). Meanwhile, exposure at 918 MHz to SAR of 4 W/kg for 10 h produced no change in rectal temperature in rats (Moe et al 1976). Repeating the exposure over 21 days did not alter the levels of plasma

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Table 3.4.1 Some Thermal and Physiological Responses in animals exposed to microwave radiation

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3.4.2 Behavioural Effects

There have been a number of publications on the alteration in behavioural patterns in mammalian species exposed to microwave radiation. Traditionally, rats are used as subjects that can be trained to perform functions or to learn a route to food through a maze. Conditioned response behaviour typically involves a food morsel as a reward for pressing a lever. Short-term exposures to microwave radiation can alter trained performance, motor behaviour and thermoregulation. Interruption of this behaviour pattern requires a significant stimulus. The thermally-induced reaction to whole-body microwave exposure is recognised and forms the basis of the development of the ANSI safety standard. Comment on its suitability is made in a separate chapter on standards and regulations. The subject has been extensively reviewed and the current text will only deal with recent significant additions to the literature on the effect of pulsed microwaves.

Auditory perception by humans of pulsed microwaves requires small amounts of total absorbed energy (approx. 2 to 40 μ J/cm2 energy density at 2450 MHz, according to Chou et al 1982). Yet this pressure-wave-induced sensory response has not been reported to affect behaviour patterns in non-human primates. This factor indicates the relative severity (and insensitivity as an experimental endpoint) of microwave-induced-hyperthermia-mediated behavioural responses.

A recent study (D'Andrea et al 1994) used only four male rhesus monkeys exposed to pulsed microwaves (5.62 GHz, 100 pps, 2.8 μ s pulse duration) for 20 mins at high peak powers where the SARs ranged from 2 to 6 W/kg. Significant alterations in lever responding and reaction time were observed during exposures at 4 W/kg, but not at 2 W/kg. This result has remarkable similarity to that reported earlier by de Lorge (1984). The energy densities within the pulses ranged from 156 to 776 μ J/cm2. In a review article by D'Andrea and de Lorge (1990) it was stated that "at 918 MHz it is reasonable to assume that the threshold for behavioural effects lies within the range 0.9 - 2.0 W/kg." Some of these studies were carried out at 918 MHz frequency and found a threshold SAR value around 2 W/kg for disruption of behavioural activies in male rats (Moe et al 1976; D'Andrea et al 1980; Lovely et al 1977, 1983). Effects observed included reduced food intake, decreased blood sugar level and some level of increased activity. The exposures were repeated daily for many weeks. Altered behaviour was reported in studies carried out at 2450 MHz frequency (cw) at SAR values from 0.14 W/kg (D'Andrea et al 1986; De Witt et al 1987) to 3.2 W/kg (Lovely et al 1983). In a review of the topic D'Andrea and de Lorge (1990) specify that the SAR threshold for significant behavioural effects from long-term exposure at 2450 MHz is between 0.4 - 0.7 W/kg, and at 915 MHz is between 0.9 - 2.0 W/kg. By comparison, short-term acute exposure behavioural changes were associated with a minimum whole-body temperature increase of at least 1°C from SARs approximately 4 W/kg.

A rather more interesting finding that seems to have escaped much publicity is the depressing effect of microwave exposure on memory function in laboratory rats (Lai et al 1989, 1994). The radial-arm maze test was used to demonstrate impaired short-term memory function following an acute exposure of 45 min to 2.45 GHz RF at power density of 1 mW/cm2 and estimated whole body SAR 0.6 W/kg. The mechanism of effect has been proposed as one of activation of endogenous opiods in the brain resulting in decreased cholinergic activity in the hippocampus (learning centre). In addition, DNA in brain cells was reported to be damaged, assayed by electrophoretic techniques (Lai, private communication). The effects were observed with both pulsed (2μs, 500 pps) and c.w. waveforms. Breakage of DNA in the CNS and testes has also been reported recently (Sarka et al 1994) using the same sensitive electrophoretic technique, following exposure to microwaves at 1.18 W/kg SAR.

An interesting finding in irradiated laboratory rats that is difficult to explain, in terms of a mechanism reported circulatory collapse and pools of blood in the gut (similar to that occurring in heat stroke) followed by death. The effects have been observed at microwave frequencies of 1, 10 and 35 GHz (Frei 1994) at SAR 12 - 14 W/kg. Death occurred within 15 to 35 min. For exposures at 10 and 35 GHz no significant change in rectal temperature occurred, as penetration at this frequency was limited to the skin.

4.0 THE CELL MEMBRANE, ION EXCHANGE AND CELLULAR EFFECTS OF EMR

SUMMARY

The cell membrane is considered as the primary site for EMR interaction with cellular systems. Interference with membrane-mediated signal detection, transduction, or amplification processes may underlie many of the biological non-thermal effects reported in the literature. The mobilization of cellular calcium ion (Ca2+) by electromagnetic radiation, or other stimuli, is an important biological response in the regulation of cellular activities.

A common finding is that calcium ion concentrations and Ca-dependent cellular processes are affected by EM fields. While the data on calcium efflux is equivocal, it cannot be ignored that independent research groups have reported an increase in 45Ca2+ efflux from brain tissue exposed to low levels of microwave or RF radiation, usually modulated around 16 Hz. The positive effects were supported by a further report of altered calcium ion efflux in human neuroblastoma cells exposed to 915 MHz modulated at 16 Hz. As the effective SAR in all of these studies was below 0.05 W/kg this suggests that a non-thermal mechanism of interaction exists that depends on the extremely low frequency modulation component. The efflux assay system requires further research which may yield useful information in determining the means by which EMR exposure conditions can sensitise and affect cell membrane responses. The significance for human health of such transient ionic changes is uncertain.

Apart from gross effects on metabolism and membrane structure that may result from substantial bulk heating, there is good supporting evidence of discrete changes in cell membrane permeability where heating does not occur. There is gathering evidence of non-thermal effects of EMR. Molecular lipid composition of bilaminar membranes is altered at specific structural phase-transitional temperatures. Evidence is given of enhanced permeability of lymphocytes to sodium at a specific temperature rather than due to a temperature increase (Liburdy 1992). Membrane stability is reduced by a downward shift in the lipid phase-transition temperature. Microwave radiation (unmodulated) has been shown to reduce the phase-transition temperature. Calcium ions are implicated in providing structural integrity by cationic bridges in the cell membrane.

It is unlikely that any single interactive mechanism is responsible for the range of effects observed at the cellular level. Research is needed at the level of ionic channels to demonstrate the mechanism of ion transport into and out of cells during exposure to EMR.

4.1 Introduction

RF radiation at frequencies up to several hundred GHz are known to be nonionizing forms of energy, because their quantum energy is too low to cause physicochemical or biological effects by ionization of molecules. Ionizing radiation readily produces

chromosomal damage in cells. This is the major reason why biologists and physicists have long held the view that non-ionizing electromagnetic energy can produce detectable effects only via mechanisms involving significant heating in cells, such as the non-excitable cells of the immune system. During the past 10 years, however, bioelectromagnetics research has shown that nonionizing electromagnetic energy can induce a variety of biological effects not only by thermal interactions but also through interaction mechanisms that do not involve any macroscopic heating. Low-intensity field effects, which apparently are not induced by thermal interactions, are referred to in the literature as athermal, or alternatively, non-thermal field effects.

4.1.1 Cell Membrane

Cell membranes have a high content of fat molecules (phospholipids) that partition each cell from its neighbour. This plasma membrane is comprised of a double layer of phospholipid molecules, approximately 40 Å thick. A steady state potential of approximately 0.1V (equivalent to an electrical gradient 100kV/cm) exists across the membrane of most cells. Glycoprotein molecules protrude through the cell membrane and form a strongly negatively charged glycocalyx on its outer surface which provides a receptor site for hormones, antibodies, neurotransmitter molecules and cancer promoters. Tissues comprise of aggregate of cells separated by narrow fluid channels, approximately 150 Å wide, through which these substances travel to reach binding sites on cell membrane receptors (Adey 1992). This intracellular space provides preferred strongly conducting pathways for electromagnetic fields, having considerably lower electrical impedance than cell membranes. Cell to cell communication occurs via this route.

Within cells, molecular systems mediate essential processes of metabolism, reproduction and responses to environmental stimuli. Cells interact primarily with their physical and chemical environment and communicate through the cell membrane. The enveloping cell membrane acts as both sensor and effector. As a sensor, it detects altered chemistry in the surrounding fluid. It offers a path for inward signals generated on its surface by a range of stimulating ions and molecules, including hormones, antibodies and neurotransmitters. As effectors, cell membranes may secrete substances synthesized internally, including hormones, antibodies and structural proteins such as collagen. Both the sensor and effector functions are susceptible to manipulation by natural or imposed electromagnetic fields. The interaction triggers a cascade of events at the biomolecular level that may profoundly alter cell growth activity and proliferation. It is suggested that receptor-mediated influx of calcium in epidermal cells or mast cells is due to molecular vibration at the receptor sites and is not voltage-activated. Such an influx is observed, for example, following binding of the epidermal growth factor (EGF) to its specific receptor resulting in a 4-fold increase in intracellular calcium while the membrane potential was unchanged (Moolenaar et al 1986).

4.1.2 Ion Channels

Present in the cell membrane are specialised channels for ion transport that regulate ion fluxes required to regulate proper cell function. Important examples of such signal transduction events at the cell membrane are the binding of extra-cellular ligands (e.g. hormones, proteins) to cell surface receptor sites, and ion-channel

transport across the lipid bilayer. Both events result in structural changes in the bilayer organisation that initiate the activation of diverse biochemical pathways transducing signals to internal cellular sites (Gardner 1989). Calcium plays a key role in this signalling process.

Such an effect is among the earliest detectable events triggered by binding of a ligand (e.g. antigen, receptor antibody or mitogenic lectin) to an appropriate receptor on the outer cell surface. The subsequent cascade of cellular reactions in lymphoid cells is best understood for T- cells (Weiss & Imboden 1987). Ligand induced Ca2+ mobilization is reflected by an initial rise in the cell's internal concentration of calcium ions {Ca2+}i which is caused by inositol 1,4,5-triphosphate-induced release of Ca2+ from intracellular stores and followed by a sustained receptor-mediated Ca2+ influx from the extracellular medium. Perturbation of these events with chemical agents (such as Ca2+ channel blockers, Ca2+ - specific ionophores) or lowering the extracellular Ca2+ concentration by using chelators can alter Ca2+ membrane fluxes and subsequently modify cellular activity. Effects produced include altered cell proliferation, secretion, motility, or cytotoxicity (Harris et al 1988; Lichtman et al 1983). Ca2+ regulation in lymphoid cells of the immune system could be similarly affected by appropriate EMR interaction.

The interaction of EMR fields depends on the efficiency of energy transfer to components in the cell membranes. Dipolar components, such as polar amino-acid side chains and cell surface bound water molecules will undergo rotational field orientation at microwave frequencies. At sufficiently high levels of specific absorption rates (SAR > 1-10 mW/gm) this motion will result in heating (ANSI 1982). Localised heating at the cell membrane can alter the phase of phospholipid molecules. The phase transition temperature may be altered under such conditions.

4.2 Experimental Evidence

According to Cleary (1990) there is definite evidence, from in vitro studies, of direct, frequency-dependent and field-strength dependent alterations of various types of mammalian cells by RF radiation. The variety of effects suggests multiple macromolecular mechanisms. There is some evidence to suggest that EMF-altered Ca2+ regulation is an early trigger of field effects in cells of the immune system. Given the established role of Ca2+ in the regulation of lymphocyte proliferation it has been proposed that EMR-altered Ca2+ regulation can modify lymphocyte DNA synthesis (Walleczek 1992). Most of this research has been carried out at ELF where, for mitogen-activated cells, EMF signals were effective modulators of both Ca2+ uptake and DNA synthesis. These results suggest that activation of transmembrane Ca2+ signaling is required in order to obtain field effects on both Ca2+ uptake and DNA synthesis. Similarly, increase in calcium uptake and DNA synthesis has been reported following single exposures at microwave frequencies (Cleary 1990). The use of an agonist co-promoter further reduced the exposure threshold level.

Evidence is given of enhanced permeability of lymphocytes to sodium at a specific temperature rather than due to a temperature increase (Liburdy 1992). Exposure for 90 min to 2450 MHz at 6 mW/gm power density produced no effect at 40°C, but resulted in a two-fold increase in accumulation of 22Na+ in rat lymphocytes at 37°C.

This cell type is critical to the immune system and is reported to exhibit a loss of cell surface proteins and alteration of membrane permeability when exposed to microwaves at normal body temperature. Inhibition of the intracellular Na+/K+ pump (and consequent accumulation of Na+ ions) has also been reported in human erythrocytes exposed to 2450 MHz frequency at 37°C (Allis & Sinha-Robinson 1987).

The findings that microwave fields influence both passive and active sodium transport in eukaryotic lymphocytes and erythrocytes at 37°C may have important implications for the immune system. Na+/K+ transport is critically involved in intracellular enzyme function, and regulation of cellular growth and functions. The transport of sodium, potassium and calcium is vital in lymphocyte proliferation and maturation, and antibody production. It is possible that microwave-induced alterations of cation transport can perturb nuclear processes such as DNA synthesis. It is noteworthy that increased DNA synthesis has been reported in human lymphocytes following a single exposure for 2 h to 2450 MHz, at SAR of 5 to 50 W/kg at 37°C (Cleary et al 1990 a). This laboratory has also reported increased proliferation and transcription of glioma (human brain tumour) cells using similar exposure conditions (Cleary et al 1990 b). The altered rate of growth was maintained for up to five days after the irradiation. <

4.2.1 Ion Fluxes

In many types of cells (neuronal, cardiac, secretory) fluctuations occur in membrane potential and are accompanied by oscillations in the concentration of intercellular ions. The most commonly studied effect is that of altered concentration of intracellular free ionized calcium [Ca2+]i resulting from Ca2+ influx via voltage-sensitive calcium channels in the cell membrane. So called oscillatory Ca2+ responses also occur in non-excitable cells (Fewtrell 1993) in response to a stimulus at the cell membrane receptors. Early experiments reported alteration of Ca2+ efflux from avian brain tissue irradiated with RF modulated at 16 Hz (Bawin et al 1975; Adey 1981; Blackman et al 1982).

The use of sensitive endpoints for bioeffects research seems to be inevitably accompanied by publication of contradictory findings. The very nature of highly sensitive systems involving fluxes in ionic composition suggests that a response may be elicited by some aspect of experimental conditions that might differ between separate laboratories testing the same biological endpoint. The issue of calcium efflux response to RF fields is no exception. Early studies exposed isolated chick brain tissue to power densities 10-20 W/m2 at 147 MHz and reported statistically significant increases in labelled calcium ion (45Ca2+) efflux when the field was modulated at frequencies from 6-20 Hz. The SAR was estimated as 0.002 W/kg and the effect considered to be non-thermal with the maximum effect at 16 Hz modulation. No effect was observed from unmodulated fields (Bawin et al, 1975). This work was replicated in other laboratories at 450 MHz carrier wave frequencies where the effect was observed at specific modulation frequencies and at specific power density windows (Sheppard et al 1979). Enhanced efflux of calcium ion from chick brain tissue was also reported for power density windows at a frequency of 147 MHz modulated at 16 Hz, but was subsequently found to be related to the temperature of the preparation (WHO 1993; Blackman et al 1991).

Calcium ion efflux was increased in rat synaptosomal preparation by exposure to 450 MHz, amplitude modulated at 16 Hz with a power density of 10 W/m2 (Lin-Liu & Adey 1982). Meanwhile, a number of negative results were reported in rat brain tissue preparations exposed in vitro to 1-2 GHz, pulse modulated at 16 Hz and other ELF frequencies with power densities of 10 to 150 W/m2 (Shelton & Merritt 1981; Merritt et al 1982). However, the negative studies were not exact replications of the exposure conditions and experimental protocol used by Bawin or Blackman.

Positive effects have been reported at carrier frequency relevant to cellular telephones when human neuroblastoma cells in culture were exposed to 915 MHz at SAR of 0.005 and 0.05 W/kg modulated around 16 and 60 Hz (Dutta et al 1984, 1989).

Detection of changes in calcium concentration can be confounded by complicated dynamics of calcium cytoplasmic concentration and intracellular stores of free Ca2+ . The location of these stores varies with different types of cells. Muscle cells are known to store calcium in a specialised organelle, the sarcoplasmic reticulum, however, it is not understood how Ca2+ ions are transported across its membrane into the cytoplasm. The structure and intracellular location of Ca2+ stores in other cells is still a subject of debate (Rossier et al 1991; Krause 1991). It is known that intracellular Ca2+ concentration changes as calcium is released from stores or as Ca2+ traverse the cell plasma membrane in response to stimuli. Excitable cells are thought to respond when depolarisation of the cell membrane potential activates voltage-sensitive Ca2+ channels and allows influx of Ca2+. Non-excitable cells are thought to lack voltage-sensitive Ca2+ channels, nevertheless variations in extra cellular Ca2+ concentration modulates the frequency Ca2+ oscillations in many cells (Kawanishi et al 1989).

Despite the difficulties in interpretation of reported results, the fact exists that the literature contains a number of reports of imbalance of ionic concentration resulting from exposure to EMR. A recent attempt to verify a report of enhanced calcium efflux (Schwartz et al 1990) in amphibian cardiac muscle was unsuccessful (Wood et al 1993) and demonstrated the wide variability in intracellular calcium levels. The excised hearts were irradiated with RF 240 MHz amplitude modulated by 16 Hz at SARs up to 0.36 W/kg. The studies are important as calcium plays a critical role in the physiology and contractile operation of cardiac muscle. It is important that these studies are repeated with more sensitive ionic detection procedures. A study is currently being developed to use computer acquired data from the confocal microscope and fluorescent molecules to obtain information in real time on Ca2+ movements.

4.3 Possible Mechanism

It is thought that Ca ions form cationic bridges with protein/phospholipid moieties on the cell surface. When the Ca ions bind to the polar, anionic head groups of phospholipids in the membrane they provide stability to the membrane by raising its structural phase transition temperature (to 40°C). Exposure to microwave fields reduces the phase transition temperature to around 37°C resulting in destabilisation of the bridges and release of protein from the cell surface (Liburdy 1992). At the same time membrane permeability is altered. This effect of protein shedding in

lymphocytes and erythrocytes has been recently reported after brief exposure of _ 30 min at 2450 MHz (cw) and 60 mW/kg (Liburdy 1992, 1994).

It is thought that loosely bound proteins play an important role in the transduction of signals to integral proteins that span the bilipid membrane. Exposure of liposomes to 2450 MHz at only 0.6 mW/kg for 5 min resulted in a reduction in the main structural phase transition temperature from 39.5 to 38°C (Liburdy 1994). Radiofrequency radiation fields have also caused the release of immuno-globulin (Ig) from antibody receptor sites on the surface of B-lymphocytes (Liburdy & Wyant 1984) at non-thermal exposure conditions (2450 MHz, SAR = 0.117 mW/gm).

Free Radicals

Due to its extreme reactivity towards macromolecules, hydroxl radical (OH*) is a highly toxic moiety that is probably implicated in many molecular biological effects. It is known to cause strand breakage and base modification in DNA, crosslinking of nucleic acids and proteins, enzyme inactivation and lipid peroxidation. Thus, it has the capability to significantly intefere with and alter the growth and development processes of cells. Exposure to many chamical compounds and non-ionizing radiation are capable of inducing free radical production at the cellular level.

There is increasing support for the theory that free radicals play an important role in discrete, important sub-cellular events during exposure to microwaves. The field of magneto-chemistry is beginning to have an impact on the understanding of subtle effects in molecular biology of cell systems. Chemical bonds consist of paired electrons with opposite spins. Free radicals are highly charged and can only form bonds between radicals of opposite spins. Electron spins may be altered by EM fields and radicals prevented from uniting. Recent information on the small unstable molecule, nitric oxide (NO), as a physiological mediator has shown the importance of oxygen free radicals in biological systems. NO is understood to modulate neurotransmission and regulate cerebral arterial blood flow and has been implicated in the pathogenesic of Alzheimer's disease.

The microwave-induced lowering of phase transition temperature and increasing membrane permeability is inhibited by the presence of antioxidants, thereby implicating free radical involvement (Liburdy 1993). A number of laboratories have reported enhanced permeability to sodium cation in erythrocytes during exposure to microwave fields (Liburdy & Penn 1984; Clearly et al 1982; Allis & Sinha-Robinson 1987; Lotz & Saxton 1989; Liburdy 1992).

4.4 Implications

Studies on alterations in calcium flow generally measure the end result of an interaction, and mostly speculate on the actual mechanism of flow and its initiation process. Studies with RF and microwave exposures tend to present phenomenological data. The process of trying to correlate between studies that often use different exposure protocols, different cell types and subsequent variation in dosimetry is complicated further by the absence of an accepted mechanism by which the effect occurs.

Much of the literature on cellular effects of EMR lacks a dose-response and reported effects are considered to be due to some non-thermal mechanism. Biochemical pathways in signal transduction are becoming better understood, but much of these so-called non-thermal mechanisms are speculative. There are serious gaps in the knowledge which need to be studied rather than dismissed as fanciful ideas. Studies that are directed towards understanding the underlying principles in cellular non-thermal reactions need urgent support, particularly where there are genuine health implications, such as in the control and development of neural proteins, or alteration in the cell cycle kinetics in brain glioma cells. Some interesting data has been published on the effects of microwave radiation (27 and 2450 MHz, single exposure for 2 h), on glioma cell proliferation, assayed by 3H-thymidine incorporation in DNA (Cleary 1990). Similar accelerated growth effects were demonstrated for human lymphocytes exposed to SAR of 5 W/kg. The altered growth rates lasted for up to 5 days after the irradiation.

There is a flaw in the notion that applies “safety” standards that only refer to measurable gross physical quantities. When considering biological consequences it is essential to understand that the extreme lethal levels can be less harmful to the organism/individual than a seemingly negligible change that modifies the behaviour and development of cells. For example, it is now well understood that during early pregnancy, at the time of closure of the mammalian neural tube, hyperthermia can have devastating effects for the developing embryo and fetus. Large temperature increase results in embryonic death and abortion. However, modest temperature increase can interfere with the critical developmental processes and result in a range of severe abnormalities of the central nervous system including exencephaly, micrencephaly, microphthalmia (Edwards 1993).

While some opinions might consider that apparently esoteric studies on a specific cell reaction in a petri dish has little relevance to the "real world" of human health hazards from irradiation with EMR, the advantages of these studies cannot be overlooked. Analysis of molecular and ionic behaviour in EM fields is fundamental to understanding whether EMR can perturb enzymatic and biochemical control pathways and interfere with cell growth and development. Of course, reactions in a simplified controlled in vitro environment cannot be directly extrapolated to the in vivo situation where homeostatic humoral and thermal feedback control systems dominate. In vitro studies are far more sensitive than animal studies and allow more precise quantification of dosage and control of environmental variables. Any safety recommendation or guideline needs to take account of the possibility of risk from all mechanisms. The current ANSI standard apparently only considers data based on animal behavioural changes resulting from a gross thermal effect that elevates the whole body temperature by at least 1°C. Meanwhile, there are many reports of biological effects that cannot be attributed to heating and are, consequently, ignored by the Safety Standard. The reported biological effects are clearly responses in some, as yet, undefined way to the EM field.

At the other end of the spectrum human epidemiology studies are extremely crude, by comparison. There are enormous difficulties in gaining high statistical power due to the wide range of environmental factors and complicated behavioural patterns of mobile populations. It would need to be an extremely robust effect that could be detected above the background “noise” level. Many environmental factors, chemical,

UV, power lines, stress, airborne pollutants, are said to be associated with human cancers and will mask the effects of another potential agent such as EMR. Without knowledge gained from laboratory research such surveys would not have a realistic hypothesis to test and, therefore, would have little chance of uncovering useful information. It is rather optimistic to propose that a population survey will provide scientifically acceptable information when no known mechanism exists and a probable outcome cannot be predicted.

5.0 CANCER STUDIES

SUMMARY

There is increasing concern about the possibility that RF exposure, particularly from cellular telephones, may play a role in the causation or promotion of cancer, particularly in blood forming areas of the CNS. Experimental evidence from in vitro and in vivo studies indicates that EMR exposure does not produce adverse genetic effects and is, therefore, unlikely to have a direct effect on tumour initiation. There is, however, some evidence of subtle changes in cell behaviour and proliferation rate that could be consistent with an effect at the level of tumour promotion. In vivo studies have shown accelerated rates of growth of certain tumours when microwave exposure is applied after the initiation of known carcinogens. Stress is an important potential confounder. Dosimetry and the effects of resonant frequency, body orientation are important factors that must be carefully controlled. Cellular studies give evidence of microwave-induced neoplastic transformation. There is no convincing evidence that athermal microwave irradiation produces clastogenic effects.

The potential for direct effects on DNA through enhanced absorption of microwave frequencies has not been supported by subsequent studies. Results of studies related to cancer induction by microwave or RF radiation are equivocal. Many early studies are severely limited by inadequate dosimetry and poor histopathology.

Further research in this area is needed to resolve many of the controversial issues. A number of long-term exposure studies are about to begin (three are in-progress). It will be interesting to see if there is any similarity in the design that will allow effective cross-comparisons of data.

5.1 Molecular Mechanisms in Radiation Induced Cancer

The relative binding energies of EMR and the organic molecular bonds in mammalian cells provide the limitation on the likelihood of cancer production by direct action on DNA. The binding energy of typical chemical organic molecules is approximately 300 kJ per molecule, i.e. 3 eV or 10-19 J per single bond (Burkart 1993). Whereas ionizing radiation particles release large energies (approx. 5 MeV, or 10-13 J) and easily damage DNA or cellular components, the relatively low energy levels in EMR fields are generally considered to be incapable of damaging DNA directly. The photon energy is about 10-3 eV at 300 GHz and decreases linearly with decreasing frequency (NRPB 1993).

However, biological response to absorbed radiation energy is complex and depends on many parameters. A common by-product of radiation interaction with water molecules is the formation of chemically-reactive free radicals. With low level ionizing radiation, the activity of free radicals is thought to constitute the major cause of cancer production while direct action on the nuclear target molecules occurs with

high level exposures. Radicals can react with DNA of the cell nucleus and damage the genetic code.

The hormone melatonin, has been suggested as an inhibitor of cancer by way of its ability to act as a potent free radical scavenger. Suppression of melatonin production is associated with increased breast cancers in women. Evidence is accumulating to show that such free radicals are formed in cellular responses to EMR (Liburdy). There are differences in biological sensitivity due to the type of cell and its position in the cell cycle. Cellular kinetics of tissues are important in their response to radiation. Generally, cells in S-phase or M-phase would be expected to be most sensitive to physical insult. The environmental conditions, temperature, degree of hypoxia or presence of antioxidants are important in the intracellular interactions.

While it is generally accepted that incorrectly repaired or unrepaired modifications of the DNA molecule are the main cause of radiation induced cancer, other “epigenetic” mechanisms have also been recently proposed. The epigenetic effects include; initiation of membrane lipid peroxidation, or loss of intercellular signalling such as gap junction mediated transfer of messenger molecules (Lowenstein 1979). Subtle changes in the genome that do not adversely affect the proliferative capabilities but may impair regulation of cell growth can lead to the late somatic effects of cancer. Loss or alteration of crucial genetic information in gonadal cells may create a risk of congenital disease.

Malignant cells are defined by certain characteristic features such as unrestrained proliferation, angiogenesis (the ability to attract blood supply), infiltration into neighbouring and distant tissues, and the evasion of attacks by the immune system. Such characteristics could be the result of genetic modifications, i.e. a somatic mutation, or result from epigenetic changes. Epigenetic factors, which do not lead to irreversible changes in the primary structure of the genetic code, could produce de-differentiation, activation and expression of normally suppressed genes involved in the production, binding or signalling of growth factors, inactivation of regulatory genes, or the loss of growth controlling cell-cell-interactions (gap junctions) between a transformed cell and its environment. It may well be that both genetic and epigenetic factors have to act in parallel to let a cell escape the division-restraining signals of its environment (UNSCEAR, 1986).

The origin of cancer is not well understood. However, some quantitative models of cancer induction based on simplified hypotheses have been proposed (Whittemore 1978), based on the concept of multi-stage carcinogenesis, initially developed as a model for skin cancer in mice (Farber 1980). The currently accepted model of carcinogenesis involves a multistage process (NRPB 1993; Cridland 1993) of at least three stages: initiation, involving genetic mutation of one or more cells; promotion, involving the multiplication and accumulation of damaged cells; progression during which further genetic abnormalities accumulate resulting in increased malignancy. In addition, increased proliferation may be associated with carcinogenesis by fixing and amplifying naturally occurring genetic damage, and thus may serve a role as a co-promoter.

It is believed that initiation can occur in response to a single brief exposure to an agent, and that it becomes a permanent change occurring within a single mitotic

cycle. It probably involves the production of a stable genetic mutation. Initiation, is generally considered to occur in the genome. Further steps towards an overt malignancy are generally assumed to be epigenetic in origin, promotion and progression. An alternative hypothesis can be based on two initiation events, the activation of an oncogene and inactivation of a tumour suppressor gene. Promotion is typically a more protracted process requiring repeated exposure to the promoting agent. It is usually reversible if the promoting agent is removed and is therefore unlikely to result from genetic mutation. Promoting agents induce cellular proliferation which allows initiated cells to multiply, expressing an altered phenotype. The best characterised pathway by which promoters can affect cell proliferation involves interference with normal cellular control system through cell surface receptors. Cell growth factors bind to specific receptors which transfer the signal across the plasma membrane and activate signal transduction, biochemical pathways for cell growth and DNA synthesis.

Many cellular phenomena may also be relevant in the development of a transformed cell. At the level of DNA, any change affecting the primary structure, and hence its function, may also affect growth control. Secondary influences, such as endogenous or exogenous growth factors, e.g. female steroid hormone in breast tissue, or levels of melatonin, may increase the probability of initiated cells passing through the stages of promotion and progression to cancer. The administration of exogenous drugs can also affect promotion. Oncogene activation involves the induction or enhanced expression of gene products in growth and differentiation.

5.2 Cellular studies

Cancers result from the multiplication of cells which exhibit abnormal, malignant behaviour and tend to invade and destroy adjacent tissue, or by metastasising they invade other body tissues. Usually, these cells grow at an accelerated rate and often appear to be less differentiated than normal cells.

There have been suggestions that exposure to EM fields may result in an increased risk of cancer. The equivocal nature of such epidemiological reports at ELF has sustained the debate, and recent claims of brain tumours caused by use of cellular telephones have fuelled speculation.

It is important that biological aspects of EMF exposure are fully investigated to determine whether any mechanism exists by which such fields could affect carcinogenesis. Biological tests for identifying potential carcinogens involve either whole animal or cell culture systems which, ideally, should be used in a complementary manner. Each test type has advantages and limitations, with neither being ideal systems. Cellular studies have the advantage that they provide a rapid screening method for potential effects, have greater sensitivity to weak carcinogens, and are more amenable to detailed molecular analysis, thereby allowing study of underlying mechanisms of interaction. Cell transformation assays represent a method for assaying changes consistent with tumorigenesis without knowing the genetic nature of the damage giving rise to the change. After plating at low density, transformed cells, which have an altered phenotype, may be identified using morphological criteria. The problem with existing cell transformation assays is that they are generally based on established cell lines which are known to be atypical.

The C3H/10T1/2 transformation assay has been used to investigate the effects of electric and magnetic fields.

Signal transduction pathways are complicated systems, but some important elements include inositol phosphate metabolism, intracellular calcium ion concentrations, and activation of specific protein kinase enzymes. As these represent important aspects of normal cell growth, detection methods have been developed in assays for study of the cellular effects of EM field exposures as a potential promoting agent, apart from the endpoint of increased proliferation. Tests for elevated enzyme activity such as ornithine decarboxylase, 51 - nucleotidase, and ATP-ase are commonly used. DNA synthesis is an essential prerequisite for cell division and is, therefore, one of the most commonly used endpoints of enhanced proliferation.

In the process leading to tumour progression, an initiated cell is acted on by a tumour promoting agent and produces a clone of cells with altered genotype, or genetic complement. During progression these cells change from pre-malignant to increasingly malignant phenotype by undergoing loss of growth control and acquisition of invasive behaviour. This may require chromosomal aberrations that inactivate tumour suppressor genes (Cerutti 1988).

Experimental evidence

Initial studies claiming preferential absorption of microwaves by DNA molecules, and therefore giving evidence of direct interaction, have not been confirmed in subsequent studies in different laboratories. It was reported that microwave absorption in purified DNA was greater than for water at 8-12 GHz (Swicord & Davis 1982). Later studies using plasmid DNA (ranging in size from 5 to 30 kb) in aqueous solution found no evidence of enhanced absorption of microwaves over a range of frequencies from 0.1 to 12 GHz (Gabriel et al 1989; Foster et al 1984).

Studies on the potential mutagenic effect of RF radiation have used fungi and yeast and detected no effect at frequencies of 2.45, 8.7175, 9.4, 17, and 70-75 GHz with SAR of 10-30 W/kg.

Determining the rate of DNA synthesis provides a measure of cell proliferation. Before cells can undergo normal mitotic division they must replicate their DNA during the well-defined S-phase stage in the cell cycle. Incorporation of 3H-thymidine is a commonly used assay. Cultures of normal human lymphocytes are widely used.

Transcriptional regulation is a key factor in the control of cellular growth. A number of oncogene products, including those encoded by c-myc, -fos and -jun have been shown to function as transcription factors.

The cell studies that are continually referred to as evidence of potential carcinogenic effects of microwave radiation are those showing enhanced proliferation (Cleary et al 1990 a, b) and cell transformations (Balcer-Kubiczek & Harrison 1985, 1989). Cleary et al reported increased proliferation in human lymphocytes and increased rate of gross transcription in LN71 human glioma cells. However, a recent study, given as an offered presentation at the BEMS conference (Stagg et al 1994) showed the

absence of a convincing effect at exposure conditions similar to that emitted by cellular telephones. It is typical of this field of research that similar studies never actually attempt to replicate the protocol used in studies reporting an effect. The work of Cleary et al used frequencies of 27 and 2450 MHz, cw, applied for 2 h and quoted estimated SAR for so-called isothermal exposures at relatively high levels of exposure. They used human glioma and T-lymphocyte cells. The study by Stagg et al used a similar assay for incorporated 3H- tdr and quoted values for power densities up to 3.7 mW/cm2 RMS values. The RF field was 837 MHz, TDMA pulse modulated and was applied for 24 h to two cell types. Different results were obtained for each cell type. Primary glial cells (rats) showed no effect on DNA synthesis. However, C6 glioma cells showed a significant increase in thymidine incorporation, although curiously there was no significant difference in cell doubling times.

Cell transformation assays test for genetic alteration that gives rise to an altered phenotype that is readily identified by the morphological appearance of the transformed cells. The main problem with this test system is that the cell lines used are generally atypical. The strongest evidence of microwave radiation producing malignant transformation abnormalities comes from the work of Balcer-Kubiczek and Harrison (1985, 1989, 1991). They exposed the mouse embryonal fibroblast line C3H/10T1/2, which are commonly used in this assay, and which contain already genetically altered chromosomes. Exposure for 24 h to 2.45 GHz, pulse modulated (120 pps) and SAR 4.4 W/kg, together with X-irradiation, promoted transformation of cells. The effect was enhanced significantly when the chemical promoter TPA was added. Irradiation with microwaves and X-rays produced additive effects, suggesting that they produce effects at different targets, possibly supporting the concept of epigenetic interaction of microwaves.

A recent study (funded by Motorola) has failed to show any effect on proliferation rate of glial cells following 24 h exposure to up to 3.7 mW/cm2 at 837 MHz for 24 h (Stagg et al 1994). Co-promotion of transformed fibroblasts was not enhanced (Cain et al 1994). However, there was some doubt about whether or not his exposure elicited specific (c-os, c-jun) oncogenes (Phillips et al 1994).

The results of a study by Prausnitz and Susskind (1962) at 9.27 GHz pulsed radiation (2 μs pulses at 500 pps) average power density 1 kW/m2, contribute very little to the debate. Swiss mice were exposed for 4.5 min per day for 5 days per week for 59 weeks. Rectal temperatures rose by an average of 3.3°C in the exposed group which initially comprised 200 mice, while the control group comprised only 100 mice. The study was abbreviated by an outbreak of pneumonitis and terramycin was administered during the last 3 months of irradiation. A total of 132 mice were sacrificed 7, 17 or 19 months after the initial exposure. 168 mice died, (68 without adequate post-mortem analysis). Monocytic or lymphatic "leucosis" (defined as a non-circulating neoplasm of white blood cells) and lymphatic or myeloid leukaemia (defined as a circulating "leucosis") occurred in 35% of the 60 exposed mice compared with 10% of the 40 control mice. Interpretation of the results is difficult and the study has been extensively criticised (NRPB 1991) on the grounds that "leucosis" and "leukaemia" were inadequately defined and identified, that the infection may have confounded the results, that a large proportion of mice (23%) died without a cause of death being identified and that statistical analysis was absent. An analysis

(chi-square contingency table) carried out on the two groups with elevated levels of leucosis found the results to be of marginal significance ($0.1 > p > 0.05$).

A study (Spalding et al 1971) that examined the effect of 800 MHz radiation on longevity in 24 RFM mice produced inconclusive results. The mice were exposed in a highly-non-uniform-field, where the average SAR was less than 1.5 W/kg, and the peak whole-body SAR in the centre of the waveguide was sufficient to result in the death of 4 exposed mice. The authors reported a non-significant increase in the life-span of the remaining 19 exposed mice (664 days) compared to the 24 controls (645 days).

In a study using 50 AKR/J male mice, which spontaneously develop a high incidence of lymphatic leukaemia between 26 and 56 weeks of age, Skidmore and Baum (1974) irradiated with very short (5 ns rise time; 550 ns decay time) pulses of 447 kV/m peak electric field strength and pulsed at 5 Hz for 5 days per week for 33 weeks. The fraction of mice which had leukaemia at the end of exposure was 9/42 (21%) in the exposed group, compared with 11/24 (46%) in the sham-exposed group. However, the absence of a complete analysis of leukaemia incidence precludes any definite conclusion. The number of animals used is also small for rigorous statistical analysis.

Szmigielski et al (1982, 1988) reported that exposure of mice to 2450 MHz microwaves at 2 - 3 or 6 - 8 W/kg, for 2 h per day for 6 days per week, for varying times up to 10 months; (1) accelerated the appearance of spontaneous mammary cancer, (2) decreased the time to occurrence of skin tumours induced by a carcinogen (3, 4-benzopyrene), and (3) increased the number of neoplastic nodules developing in the lungs of mice injected with cancer cells and examined 14 days later. These results suggest that RF radiation accelerated the development of three different types of tumours.

In a promotion study (Szmigielski et al 1988) mice were exposed to SARs of between 2 and 8 W/kg for 2 h per day for some months following the injection of 2 x 105 sarcoma cells. The development of cancerous nodules in the lung showed a dose-dependence. However, at an exposure of 2 - 3 W/kg the effect was comparable with that which can occur from chronic non-specific stress. It has been suggested by the authors that impaired immune surveillance resulted in a lowering of resistance to neoplastic growth. The skin tumour study reported an increased number of tumours when microwave radiation followed a sub-carcinogenic dose of benzopyrene.

The results of a study of 100 rats exposed for most of their lifetime at about 0.4 W/kg (Chou et al 1992) have created some disagreement in interpretation. The exposure consisted of 2.45 GHz frequency pulsed (800 pps, 10 μ pulse width) waveform modulated at 8 Hz. The whole body average SAR was estimated to range from 0.4 to 0.15 W/kg for rats weighing 200 to 800 gm, respectively. Rats were exposed for 21.5 h per day from 8 weeks of age for 25 months (i.e. lifetime). There was some evidence of effects on corticosterone level after 13 months, that was not repeatable in a smaller follow-up study. The important result was a statistically significant increase in incidence of primary malignancies in the exposed (18) compared to control (5) group. The numbers of such spontaneous cancers are too low to achieve statistical significance when classified according to each type. There is a developing

opinion that a single toxic agent may be capable of producing more than one type of tumour.

Comments on the protective role of melatonin, Prof. Reiter (University of Texas, Health Science Centre, San Antonio) has been quoted as saying that the suppression of melatonin by magnetic fields could result in a higher incidence of cancer in any tissue, and therefore a wide range of different tumour types.

5.3 COMMENTS ON CANCER-RELATED STUDIES

If EMR is suspected of being involved in cancer development there are a number of issues that need to be tested:

(a) What cellular evidence exists, such as altered DNA, RNA, transcription rate, colony forming efficiency?

(b) Is there evidence of cell membrane changes resulting in altered ionic distribution?

(c) Is there evidence of immune response impairment, that may allow tumour development to proceed?

(d) Is there in vivo evidence of an increased incidence of tumour growth in laboratory animals or in humans?

It is virtually impossible to detect effects with epidemiology surveys without prior knowledge of the most likely biological effect. Teratologists now acknowledge that unless the full spectrum of abnormalities is known there is a very small chance of detecting even a strong teratogenic compound by epidemiology. For example, a drug such as thalidomide, which can produce a wide range of limb deformities can only be identified with certainty if all reports of every expected deformity from digital amputations to absence of one or more limbs is included. The use of a specific single effect would preclude its detection. To detect, with any degree of certainty, the effects of EM radiation, information is required on mechanisms of interaction to predict the likely consequences.

The use of genetically compromised animals that are predisposed to a certain type of cancer may be inappropriate as the high base level incidence may mask small differences from the mean value thereby reducing its statistical power. Past chronic exposure animal studies have produced conflicting results, with one study (Chou et al 1992) giving either; (a) a positive or (b) a negative result depending on whether one interprets a real effect as, (i) an increased incidence in all cancers in the population, or (ii) an increased incidence of a specific cancer.

The studies currently undertaken by Adey's group represent the most thoroughly controlled chronic exposure protocol employed to date, and are being carried out at a frequency relevant to cellular telephones. Results will be available in 1995, although it will be some time later before a publication appears. Whatever the result, it will at best represent a starting point for subsequent careful study. It is most important that new studies learn from this experience.

Rigorous animal experimental studies are demanding, expensive and require dedicated attention to detail for extended periods. The appropriate combination of specialised facility and trained staff is a rare commodity. Carefully worked protocols using sufficiently large exposed, sham-exposed and control groups are essential to achieve a valid evaluation of this effect. Small scale experiments comparing groups of less than 100 have low statistical power and therefore contribute little to the debate. Similarly, studies which irradiate animals with rapidly growing brain tumours are confounded by the premature death of the animal. Thus, the consequences of long term exposure to low level radiation are not tested. A recent presentation (Salford et al 1993) is such an example, where a total of 62 rates were irradiated with 915 MHz at six different exposure regimes for 7 h per day until death. Each animal had been inoculated with a large dose of glioma cells at five days prior to irradiation and died as a result of rapid growth of a large brain tumour.

True scientific protocol requires the establishment of an hypothesis which must be repeatedly tested before any inference can be drawn from the results. The in vitro cell studies have provided some clues about setting such hypotheses. Perhaps the most important were the experiments of Cleary et al (1990 a) which demonstrated an altered rate of DNA synthesis and proliferation of human glioma cells after a single exposure to microwave radiation. This abnormal behaviour is consistent with early changes seen in cells that lead to tumour formation. Effects were observed at both 27 and 2450 MHz frequency and with cw or pulsed waveforms. Furthermore, he also reported the effect in cultured human glioma cells (Cleary et al 1990 b). The exposures were applied over a range of SAR, with the lowest level at which the effect was observed as 5 W/kg. Although the exposure conditions have been reported as non-thermal it is difficult to see how the exposure could avoid large thermal gradients from the cells to the cooling fluid surrounding the cell culture vessel.

What makes these studies so interesting is that the effect occurs after a single 2 h exposure and lasts for up to five days. Thus, a daily exposure regimen would reinforce the effect. The connection between accelerated growth of human brain tumour cells in culture to that occurring in vivo during repeated exposure to EMR is one that deserves close examination. Hence the need for data from chronic animal studies and human epidemiology surveys. The extrapolation of results from laboratory rodents to humans is always fraught with difficulties and divergent opinions.

Relevance to Cellular Telephones

The public concern about cellular telephones and cancer exists because of reports of an association between extremely low frequencies (ELF; 50 or 60 Hz) or police radar and cancer, and because of a lawsuit about cellular telephone use and a case of parietal lobe glioblastoma. The distinction between ELF and RF is rarely made. Reports exist of brain cancer and leukemias in epidemiology studies of nonionizing radiation at frequencies different from those emanating from cellular telephones. Little is known of human experience with cellular telephones because: (a) there are no epidemiology studies at this frequency; (b) the amount and distribution of absorption is not fully known; and (c) brain cancer is a rare event (less than 1% incidence) with a long latency period. Experimental animal studies have not been

described at 915 MHz. However, a study of rats exposed to 2450 MHz radiation reported a 3-fold increase in primary malignant neoplastic lesions. Studies of different cell lines at 27 or 2450 MHz frequencies demonstrated a dose-dependent increase in growth rate that persisted for about five days, after a single 2 h exposure.

Review of the literature on radiofrequency radiation and cancer yields results from eight animal studies over a 30 year period. Several of the studies reported increases of tumour incidence in the irradiated groups, especially mammary tumours and leukemias. None of these studies, used cellular telephone frequencies. National Toxicology Program (NTP) studies of chemical carcinogenesis in rodents exhibit a correlation between mammary tumours or leukemias and decreased life span. Because radiofrequency radiation doses that did not increase body temperature had no effect on life span the hypothesis has been proposed of no positive correlation between radiofrequency radiation and cancer induction.

For any biological effect to become significant the body's homeostatic mechanism has to be overcome. Homeostasis uses cellular communications via molecules and ions to control the three basic functions of cells: proliferation, differentiation, and activation. Cancer promotion involves the disruption of cell-to-cell communication. One way that this can occur is through the closure of gap junctions between the cells. This disruption is both reversible and dose-responsive. If the promoter is removed, intercellular communication returns to normal. With chemical carcinogenesis, the promoting agent must be applied at a high dose, constantly, over a long period of time. During carcinogenesis a normal cell is transformed into a neoplastic cell (initiation), and the neoplastic cell grows into a neoplasm (promotion). Cell proliferation is important for both steps, and stimulation of cell proliferation would sensitise cells to the effects of endogenous DNA damage that occurs spontaneously. This is one pathway for epigenetic carcinogenesis. Thus, a carcinogenic agent does not have to alter DNA directly. An initiating agent may need only a single exposure to alter the genome and induce cancer, while promotion requires high doses, is reversible, and must continue for a long duration. Therefore, the risks from promotion are less than the risks of initiation.

In general, the energy level of a cellular telephone is not sufficient to break chemical bonds. Thus, nonionizing radiation is not likely to initiate, because it cannot directly induce alterations in the genome. Except for pulsed field, cell membranes absorb much of the radiation and are a target for nonionizing radiation, and for chemical agents that act as cancer promoters. Effects at the cell membrane are consistent with promotion. Because nonionizing radiation can induce ornithine decarboxylase, the mechanism of carcinogenesis would be more likely to be epigenetic.

Conclusion

Currently there are neither data that cellular telephone use induces cancer in humans, nor any data that link nonionizing radiation from cellular telephones to tumour induction in animals. The significance of some studies showing tumour promotion is uncertain.

Recommendations

If we consider the possible promoting effects of EMR on the development of cancer then the most relevant studies would be those carried out in animals exposed to low level radiation for extended durations. To be reliable, these studies need to use a sufficiently large population to be statistically powerful and must be designed in such a way that all known confounding variables are controlled. A major difficulty in conducting long-term exposure experiments is the problem of ensuring properly controlled exposures to large numbers of animals. It is essential to provide both an acceptable, low stress, living environment for the animals and a uniform microwave exposure for the entire population. RF coupling to the animals body will differ as a function of number of animals in the group, distance between them, and orientation of each animal in the RF field (D'Andrea & de Lorge 1990). At the same time, there is good reason to have concurrent exposure to normal environmental pollutants that might potentiate the effects. Finally, the protocol needs to be robust and repeatable to allow exact duplication of the study in an independent laboratory.

It is well known that the distribution of RFR in an exposed object depends on many factors including frequency, orientation of exposure, dielectric constant of the constituent tissue. The design of experimental protocols is critical if the results are to provide meaningful extrapolation to a particular RF source. Cellular telephones are used in a specific manner. Most people would hold a phone to the same ear in the same orientation and proximity to the skull. Usually one would expect the antenna to be close to the parietal bone (although many airport officials have a peculiar habit of holding the large portable phones in front of their mouth so that they look across the top of the antenna). However, assuming normal usage patterns it would make sense to design experiments so that the RF source was located towards the lateral aspect of the skull. Chou et al (1985a) found significant differences in local SARs in eight different regions of the brain of rats and these all changed in each of seven different exposure arrangements. Lai et al (1984a) reported a difference in microwave response with pentobarbital depending on whether the rat was facing toward or away from the source of irradiation in a waveguide when the average whole body SAR remained constant; patterns of energy absorption in the brain differed substantially.

6.0 GENETIC EFFECTS

SUMMARY

The majority of studies show that exposure to RF radiation does not result in an increase in chromosome aberration frequency when temperatures are maintained within physiological limits. It is well known that hyperthermia induces profound alteration in gene expression as demonstrated by the heat-shock response in early post-implantation rodent embryos (Walsh et al 1985). The so-called heat-shock response is elicited by a wide range of irritants and stresses apart from heat. There is evidence of a synergistic effect when embryos are exposed to pulsed ultrasonic energy combined with a modest increase in bulk heating (Angles et al 1990). Potentiating effects of non-ionizing radiation by environmental factors require investigation.

Reported increased frequency of cytogenetic effects after in vivo exposure to 2.45 GHz at SAR up to 20 W/kg was not successfully replicated in a study using a different strain of mouse. Reported increases in the frequency of sister chromatid exchanges following in vitro exposure have not been verified.

The literature contains disagreement on the effect of microwave radiation on chromosome aberration frequency in male germ cells.

An indicator of altered chromosome aberrations, increased dominant lethality (assessed as impaired survival of implanted embryos), was reported after acute exposure to high power levels where hyperthermic effects were dominant. There is no evidence of induced dominant lethals in rodents exposed to SAR up to 5 W/kg in chronic exposures over periods up to 8 weeks. While this is interesting, its use in establishing health risk is somewhat limited. To be meaningful for human health implications, it is essential that these studies are conducted in a manner that is relevant to environmental exposures of EMR. Humans are exposed to low level EMR from prenatal existence throughout life and it is appropriate that animal models should at least be exposed to similar conditions if the scientific data base is to be improved.

Introduction

The potential interference by EMR on the structure of DNA or chromosomes is an important consideration in somatic cells where a non-lethal change could be associated with the development of cancers. If such effects occur in the male or female germ cells, surviving mutations might be passed on to subsequent generations. These effects are conveniently studied in cell culture and small animal exposures where relatively sensitive tests can assess the rate of change in single and multiple generations.

The possibility of adverse effects of RF radiation on male germ cells has received media attention recently in the USA where claims that RF emissions from public radar guns may be responsible for an increase in the incidence of testicular tumours. It is not certain whether effects on sperm cell integrity were also considered.

6.1 Experimental Evidence

Studies on the possible hereditary interference by RF exposure are summarised in table 6.1. No confirmed adverse effects assessed by structural aberrations and sister chromatid exchanges were reported following in vivo exposures (Huang et al 1977; McRee et al 1981).

The literature contains disagreement on the effect of microwave radiation on chromosome aberration frequency in male germ cells. Original experiments exposing germ cells in male mice to microwave radiation (Manikowska et al 1979, 1985) reported an SAR dependant increase in the frequency of chromosome aberrations that has not been confirmed in subsequent studies when the rectal temperature increased by up to 3°C above the normal basal value (Beechey et al 1986). A further study exposed the spermatogonial stem cells (greatest risk of accumulating genetic damage) and found no evidence of altered frequency of chromosome translocations or fragments after in vivo exposures to 5 W/kg for a total of 120 h over a period of 8 weeks (Saunders et al 1988). There was no change in rectal temperature in exposed and sham-exposed mice. Temperature in the germ cells was not reported.

A number of studies has assessed the ability of microwave radiation to induce dominant lethal mutations which result in pre-implantation death or subsequent embryonic or fetal mortality. Contradictory results have been reported (table 6.1). Whilst one study (Varma & Traboulay 1977) reported an increase in induction of dominant lethal mutations after exposure to 1.7 GHz at 500 W/m2 (SAR estimated as 25-45 W/kg), this was not replicated in two subsequent studies. The first of which exposed mice to 2.4 GHz at either 600 W/m2 for 12 min or 8,000 W/m2 for 21 s (Ramaiaya et al 1980) without observing an effect, although up to 10% of the mice died from the severity of the exposure.

Table 6.1 Summary of studies on Genetic Bioeffects of EMR

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The second study found no evidence of increased dominant lethality in mice exposed to SAR 43 W/kg (Saunders et al 1983). However, significant reductions in pregnancy rate were observed which was subsequently attributed to impaired male fertility resulting from decreased sperm counts and an increase in the proportion of abnormally shaped sperm (Kowalezuk et al 1983). This is hardly surprising when one considers the likelihood of substantial heating of the testes from the absorbed dose.

It is interesting that previous studies apparently did not consider the possibility of impaired sperm cell function which is known to be sensitive to elevated temperature.

Beechey et al (1986) reported an increase in rectal temperature of 3°C in mice exposed to 20 W/kg, while Saunders et al (1988) reported no change in temperature at 5 W/kg in mice exposed at the same 2.45 GHz frequency.

Chronic, low level exposures are more relevant to public health risk of electromagnetic radiations. There is no evidence to date of the induction of dominant lethal mutations in mice (Saunders et al 1988) or rats (Berman et al 1980). However, the longest term of these experimental exposures was 8 weeks which is rather short, even in relation to the life span of rodents.

Studies have been carried out using standardised techniques for clastogenic and cytogenic effects following in vitro radiation with microwaves. Effects on cell cycle kinetics and cell proliferation rates are endpoints that would be expected to show a response to cellular perturbation. Elevated temperature is a common cause of altered rates of mitotic division.

Although the generally-held opinion is that the energy levels available in non-ionizing radiation are insufficient to cause chromosome breaks a recent study reported a statistically significant increase in the frequency of chromosome aberrations and micronuclei (Maes et al 1993) in human peripheral blood lymphocytes. A temperature controlled “normothermal" exposure system exposed lymphocytes in vitro in a tube containing a thermistor to regulate the microwave output and maintain a constant temperature of 36.1°C. It is not certain that the thermistor did not perturb the field or create localised "hot spots" of energy deposition. The 2450 MHz microwave exposure was pulsed (50 Hz, duty cycle 1:3) with a nominal SAR of 75 W/kg. While the paper reports an increase in percentage of chromosome aberrations and of micronuclei there is no effect on the rate of sister chromatid exchanges. Cell cycle kinetics was unchanged as would be expected if temperature was unchanged.

In a recent presentation by this group (Verschaeye et al 1994) at the BEMS conference, they reported effects from mobile telephones in 32 subjects exposed to 450 or 954 MHz. Chromosome aberrations were assayed by changes in DNA electrophoresis. In addition, rats exposed to 954 MHz showed a statistically significant increase (_25%) in the SCE frequency when microwave radiation accompanied application of the mutagen, mitomycin C. Evidence of a synergistic association is presented. However, the details of this work were very sketchy, with very small populations and little useful information on dosimetry, (no SAR values given on exposure duration). The data appeared to be sparse and the authors reported it as "preliminary". The obvious question then is; how does the acceptance of such material at an international conference assist the development of scientific knowledge? Previous studies using SCE as an endpoint have failed to demonstrate an effect of microwave radiation or a synergistic effect when applied together with known mutagens (Meltz et al 1989, Meltz 1991).

Concerns about this paper relate to the dosimetry and the population size and relevance of the statistical analysis. A result is published on the basis of two blood samples from two donors. Groups of different sizes are compared. In fact the data is weighted in one experiment where a control group of 500 was compared with exposed groups of 200 and the aberrations expressed as a percentage. The fact that only 100 cells could be examined in the third group suggests a problem in the culture

protocol. The data is rather weak, and the authors state that; “This work must be considered as a preliminary pilot experiment ... ...”. As far as implications to human health are concerned, there is little that can be inferred from this study.

Although it was not the intent to criticise individual scientific publications this may be taken as representative of some of the peer-reviewed literature. There were almost 100 papers published in the Bioelectromagnetics journal in 1993. One has to wonder about the peer-review process that allows publication of preliminary work-in-progress standard of manuscript as scientific papers. Perhaps a more restrictive policy would limit the otherwise vast number of publications in the EMR field, many of which contribute little other than adding to the confusion and fuelling the desire for more independent reviews. The situation is further exacerbated by the apparently unconditional acceptance of every abstract submitted to the BEMS annual conferences. As a result the 1994 conference yields 198 abstracts and 222 posters.

Another study has addressed the issue of possible long-term effects of RF exposure on lymphocyte chromosome integrity in an occupationally exposed group (Garson et al 1991). The endpoint involved chromosome breakages and compared a high risk group of radio-linemen with a control group from office workers in the telecommunications industry. The exposed group received radiation over the range 400 kHz to 20 GHz at or below the safety standard for occupational exposure. An assay for chromatid gaps and breaks, chromosome breaks and “other” aberrations found no statistically significant difference between the exposed and control groups. A requirement of the study was that all subjects had worked for at least 5 out of the previous 6 years as radio-linesmen, and the last exposure was no more than 12 months before the study. The lymphocytes were obtained from the peripheral blood circulation. Although this is an acceptable protocol for chromosome breaks, it might have been more desirable to have used an exposed group comprised entirely of people who were exposed to RF radiation at the time of the assay rather than up to 12 months before.

The information from this paper supports the commonly accepted view that there is no evidence that chronic exposure to low level RF radiation has clastogenic effects.

Recent reports contrary to that opinion were presented at the 16th conference of the BEMS (June 1994). In one report on the health effects of radar exposures on workers an increased incidence in aberrations and micronuclei was reported (Garaj-Vrhovac & Fucic 1994). The study group comprised 40 workers employed in antenna maintenance occupations for a mean of 12.5 years (range from 0.5 to 26 years). Peripheral blood lymphocytes were reported to have significantly higher incidence of structural aberrations and micronuclei in the exposed group (8.2 - 26 GHz, SAR mostly 5 mW/cm2 up to a maximum value of 26 mW/cm2).

These authors have previously published findings that microwave exposure is clastogenic and that it produces an increase in the number of micronuclei in human lymphocytes following in vivo exposure (Fucic et al 1992) in the workplace to pulsed microwave radiation in the range 1.25 to 1.35 GHz at power densities 0.01 to 20 mW/cm2. They also reported an increase in aberrations including chromosome and chromatid breaks, acentrics and dicentrics following in vitro (Garaj-Vrhovac et al 1992) exposure at 7.7 GHz. Increased rates of aberrations were reported for power

densities from 0.5 to 30 mW/cm2 for 10 to 60 min. It is uncertain why these studies should contain such a high degree of sensitivity.

7.0 HUMAN BIOEFFECTS

SUMMARY

People with normal hearing are able to perceive pulse-modulated RF and microwave radiation between about 200 MHz and 6.5 GHz. The sound perception probably results from the thermoelastic expansion of brain tissue caused by a small but rapid increase in temperature. The perception threshold for pulses shorter than 30 μs depends on the specific energy density in the head and has been estimated to be as low as 30 mJ/kg. Receptors in the skin are sensitive and absorb RF and microwave radiation at power densities of approximately 300 W/m2 at 3 GHz during exposure for 10 s. Meanwhile infrared radiation applied for 10 s is detected at power densities an order of magnitude lower due to its greater absorption (therefore greater SAR) in the skin. Thresholds of perception depend on frequency and exposure duration as well as the locality on the body and the exposed area. The perception of skin warming by microwave and RF frequencies in the rage 0.5-100 GHz does not afford a reliable means of protection against potentially harmful exposure from heating (Elder 1984a).

Healthy subjects at rest in light clothing and in comfortable ambient conditions (21 - 22°C, 50% RH and adequate ventilation) are able to dissipate RF power at SARs of 1 W/kg, and to up to 4 W/kg for short periods, although sweating and increased heart rate was observed in the upper part of this range after 20 min exposure. The total heat load of an exposed person represents the sum of the SAR from RF or microwave heating and the rate of metabolic heat production and must be compensated by heat loss. The limit of tolerable SAR is affected by adverse conditions (high temperatures or humidity), moderate physical exercise, some medication, or conditions which impair thermoregulation (including pregnancy). The relationship between local SAR and body temperature increase is not well established. Neither is the rise in local temperature in response to high, localised SARs elsewhere within the body. Further dosimetric research is required to determine whether local heating, rather than whole-body heating, could become a limiting factor in some circumstances.

7.1 Perception

Auditory perception

It is well established that humans with normal hearing are able to perceive pulse-modulated RF and microwave radiation as buzzing, clicking, hissing, or popping noise, depending on the modulation characteristics (NCRP 1986). First reports (Frey 1961, 1962, 1963) of this phenomenon described the perception of pulsed radiation frequencies between 216 MHz and 2.98 GHz. Pulse widths varied between 1 and 1000 μs and the average threshold power density was 4 W/m2. Sensitivity was increased by lowering the ambient audible noise levels. Since then the average power density threshold for RF hearing has been reported as low as 0.01 W/m2 in people with normal hearing (Cain & Rissman 1978). Perception of different pulse-modulated frequencies has been reported (Constant 1967) at 3 and 6.5 GHz but not at 9 GHz.

In a study of the threshold conditions for this effect in one human subject exposed to pulsed 2.45 GHz radiation (Guy et al 1975) it was determined that, for pulse widths less than 30 µs, the perception threshold depended on the energy density per pulse. A threshold value of 280 mJ/m2 (estimated 10 mJ/kg) was measured when the subject wore earplugs. An animal study measured brain stem auditory evoked potentials in guinea-pigs exposed to pulsed 918 MHz radiation (Chou & Guy 1979) and concluded that the threshold for microwave hearing is related to the incident energy density per pulse for pulses shorter than 30 µs and is related to the peak power for longer pulses (up to 500 µs).

It is generally agreed (NCRP 1986; Foster & Finch 1974) that the mechanism of acoustic perception of short pulses of RF and microwave radiation is due to thermoelastic expansion of brain tissue following a small but rapid temperature increase (<10-5°C). As the effect must depend on absorption of some incident energy it would be limited to frequencies which penetrate the skull and are significantly absorbed by brain tissue. The effect of the expansion is an acoustic pressure wave which is transmitted through the skull to the cochlea where vibration-sensitive hair cell receptors respond as they would to acoustically generated pressure stimuli. It has been calculated that the frequency of the induced sound is related to head size and the acoustic properties of brain tissue, regardless of the RF frequency (Lin 1977).

Cutaneous perception

The absorption of RF and microwave radiation can be detected by receptors in the skin, although variability in the sensitivity has been reported. Most studies have involved exposures in the frequency range 2.45 - 10 GHz (NCRP 1986; Elder 1984; Adair 1983). Microwave radiation was found to be ten to fifteen times less effective than infrared in heating the skin (Justesen et al 1982). The difference is attributed to the scattering of two-thirds of the microwave energy and the relatively small proportion of microwave energy, estimated to be one-fifth of the value for infrared radiation, absorbed in the skin. Subjective awareness of warmth is not a reliable indicator of microwave hazard. Perception threshold values are frequency dependent. Threshold response by different parts of the body is variable, at low levels of irradiation the face is the most sensitive region, the trunk intermediate, and the limbs least sensitive (by a factor of two or three). Threshold power density must be qualified by the duration of the stimulus and the area of the exposed skin; e.g. infrared power density thresholds decrease as the duration of the stimulus increases (up to a critical value), and as the size of the area of exposed skin increases. The response latency is also an important variable that depends on stimulus duration and area. In general, skin sensory receptors respond to transient rather than constant stimuli, although the effect of adaptation on the perception of microwave radiation is not known.

Consensus of a panel of a Symposium on Microwaves and Thermoregulation, Connecticut, 1981 was that microwaves of 30 GHz and above would probably be similar to infrared in their perception threshold values and may be sensed at the limit recommended by the American National Standards Institute (ANSI 1982) which is 50 W/m2 in this part of the spectrum (Adair 1983). However, over much of the radiofrequency spectrum, the perception thresholds are higher than the ANSI

standard, and the deeper penetration results in a larger mass of tissue heated by microwaves for a comparable rise in skin temperature. A further problem is that the threshold temperature (41-42°C) of cellular injury for sustained temperature elevations is below the threshold (_ 45°C) of pain. For the frequency range 0.5 MHz to 100 GHz, cutaneous perception of heat and thermal pain may be an unreliable sensory protection mechanism against RF radiation exposures.

7.2 Thermophysiological responses

Normal body temperature is maintained by a complex control system of heat loss or gain responses, including behaviour (Simon et al 1986), at a so-called “set-point” value of around 37°C. Body temperature is maintained within a narrow range (_0.5 °C fluctuation) by the processes of sweating or increasing metabolic heat production. Data on thermoregulatory responses to RF or microwave heating is obtained from experiments with passively heated volunteers. Ambient conditions such as high humidity can profoundly limit the thermoregulatory capabilities and exert a significant effect on the ability to tolerate different whole-body SARs. A change in ambient temperature of 1°C can produce a change in heat flux of about 0.15 W/kg in a clothed individual. It is clear then, that the thermal burden from a given SAR that can be tolerated in a cool, dry environment may pose a health hazard if the environment is either very hot or humid.

In an attempt to estimate the maximum SAR that could be tolerated by a fit healthy person, under strictly specified ambient conditions, Durney et al (1978) defined a rectal temperature of 39.2°C as an upper limit of physiologically tolerable body temperature. A SAR of approximately 3 W/kg was calculated to induce this rectal temperature within 1 h in a person in an environmental temperature of 40°C and a relatively humidity of 80%. Raising the ambient temperature to 41°C decreased the tolerable SAR to about 1 W/kg. The rectal temperature of 39.2°C is an estimate of the upper limit of tolerance and should not be considered as a safety limit as there is a wide range in physiological tolerance amongst different members of the population.

Other physical and physiological factors which reduce the ability to adapt to an extra heat load include old age, obesity, hypertension and effects of many drugs such as diuretics, antihistamines, tranquilizers B-blockers and amphetamines. The thermoregulatory ability of infants is not well developed while pregnant women have an extra circulatory load which may compromise their ability to dissipate heat. Heat loss from the embryo and fetus across the placental barrier may be less efficient than heat dissipation in other, well-vascularised tissues.

The American National Institute of Occupational Safety and Health (NIOSH 1972) and the American Conference of Governmental Industrial Hygienists (ACGIH 1983) recommend an upper threshold limit value of a rise in body temperature of 1°C. This is endorsed by the World Health Organisation (WHO 1980). It was recommended that rates of physical work and environmental factors should be such as to limit excursions of body temperature beyond 1°C.

Calculations relating whole-body SAR to increases in body temperature are generally supported by the results of studies of the thermoregulatory responses of

patients and volunteers exposed to RF fields of up to 4 W/kg in magnetic resonance systems. However, the subjects are exposed at rest and in controlled environments and the whole-body SARs quoted result from much higher, localised, SARs.

Shellock et al (1989) exposed the abdomen of six volunteers to 64 MHz RF magnetic fields for 30 min at whole-body SARs from 2.7 to 4.0 W/kg. Although body temperature was reported to rise by an average of only 0.1°C, all of the subjects reported feeling warm and had visible signs of perspiration on their forehead, chest and abdomen during the procedure. Abart et al (1989) reported increases in rectal or sublingual temperature of up to 0.7°C, with a mean increase of 0.33°C, in 12 healthy volunteers exposed at a whole-body SAR of 3 W/kg for 20 min. Heart rate was also observed to increase by up to 45%. The magnitude of body temperature increase was similar to that reported in 12 healthy volunteers exposed at a whole-body SAR of 4 W/kg for 20 min (Schaefer et al 1985).

In contrast, differing thermoregulatory responses (to magnetic resonance imaging) have been reported in 50 patients with unspecified clinically impaired temperature regulation (Shellock & Crues 1987). Exposure to 64 MHz RF magnetic fields at whole-body SARs between 0.4 and 1.2 W/kg for 15 min increased body temperature by 0.5°C at low SARs. The mean skin temperatures of localised areas of the hand and trunk when imaged, were reported to increase by up to 1.2°C. Another study (Kido et al 1985) reported mean increases in body temperature of 0.5°C in volunteers exposed to a magnetic resonance abdominal scan for 17 min where the whole-body SAR was only 0.8 W/kg. Heart rate increased by 3 beats per minute.

Calculations of SAR distribution based on a heterogeneous model of the human body indicate that localised SARs in small tissue volumes could be 10 to 70 times greater than the whole-body average SAR during exposure to magnetic resonance imaging (Orcutt & Gandhi 1988).

The relationship between local SAR and temperature increase is not well established. Localised heating may occur in various parts of the body depending on the conditions of exposure, particularly antenna proximity and the radiation wave-length, and on the shape and variation in tissue conductivity and blood circulation in the exposed part of the body. The amount by which localised heating will exceed whole-body average is not known at present.

8.0 EFFECTS OF EMR ON CENTRAL NERVOUS SYSTEM

SUMMARY

From studies on human perception it is accepted that very low levels of microwave exposure elicit a response, known as microwave hearing, that is thought to be due to a thermoelastic change producing a pressure wave in the brain and auditory sensory apparatus. It would not be too surprising to find associated transitory changes in the electrocortical activity, although the results in humans and animals are equivocal probably due to artefacts in experimental technique. There have been contradictory reports (by the same group of researchers) on the effect of microwave radiation on the permeability of the blood-brain barrier, making sensible interpretation rather difficult.

Changes in animal behaviour induced by high exposures (SAR > 4 W/kg) create a significant increase in body temperature and would, therefore, invoke a response in the hypothalamus and adrenal corticosteroids. Other sensitive endocrine organs such as the pituitary and pineal glands would also respond to such a gross physical insult.

Of more interest from a human health perspective are the reports of impaired learning and memory function in rats following a exposure to relatively low level SAR 0.6 W/kg. The effect has been shown to be due to microwave-induced activation of brain opiod activity. Such subtle neurophysiological responses are of particular interest. Alterations in DNA arrangement have also been detected by sensitive electrophoretic tests, following exposure to similarly low SAR. This work urgently needs verification and extension.

Introduction

Mammalian Blood-Brain Barrier

The blood brain barrier in the choroid plexus separates the brain and cerebal spinal fluid of the central nervous system from the blood (and potential blood-borne toxins or micro-organisms). The barrier consists of specialised capillaries, the cells of which form "tight junctions" in an essentially continuous layer. In contrast to most other capillaries in the body those in the cranial vault lack intracellular fenestrae that allow passage of small molecules from blood to the interstitial fluid. The pinocytotic vesicles that transport large molecules across capillaries in peripheral organs are also rare in the capillaries in the brain.

Functionally, the blood-brain barrier is a selectively permeable hydrophobic membrane that allows the passage of small lipid-soluble molecules. Lipid-insoluble substances encounter regulatory interfaces between the blood and the Central Nervous System that control their transport. Certain lipid-insoluble molecules, such as glucose, cross the membrane via carrier proteins.

Electrophysiological Responses

Since the central nervous system co-ordinates and controls an organism's responses to its environment through autonomic and voluntary movements and neurohumoral function, any effect of radiofrequency radiation is important. The reaction of the central nervous system to microwaves may provide evidence of early disturbance in regulatory function of many systems. For instance, the hypothalamus of the forebrain controls thermoregulation and secretion of hormones, while the hippocampus serves behavioural functions such as memory and emotion. Information is generally passed from one neuron to another via the release of neurotransmitter chemicals, such as acetylcholine, dopamine, serotonin, Þ-amino-butyric-acid (GABA) or endogenous opiods. Binding of the neurotransmitter to a receptor triggers a series of reactions that affect the post-synaptic cell. Many drugs exert their effects by binding to the receptors. Those which activate the receptor are known as agonists while those which block the action of the endogenous neurotransmitters are antagonists. Since changes in receptor properties can last for many days an animal's normal physiological functions can be altered by any interference in the neurotransmission pathway.

Experimental Evidence

8.1. Blood Brain Barrier

Initial work suggested that exposure to low level pulsed microwave radiation significantly affected blood-brain barrier permeability. Later workers attempted to confirm and extend these observations. The subject has been previously reviewed (Blackwell & Saunders 1986; NCRP 1986). However, the interpretation of the results is difficult; some of the evidence is contradictory and many of the results may well have been confounded by various factors such as the use of anaesthesia or the difficulty in either removing or estimating the amount of tracer. The effects of microwave radiation on the permeability of the blood-brain barrier have been investigated by tracing the penetration, after intravenous injection, of labelled compounds such as protein-bound dyes (fluorescein), radiolabelled saccharides, or horseradish peroxidase. Frey et al (1975) reported the penetration by fluorescein in anaesthetised rats after irradiation at low levels (SAR _ 0.04 - 0.5 W/kg) of pulsed or continuous microwave radiation. In a replication of this study (Merritt et al 1978) and another that exposed conscious rats to 2.45 GHz radiation (Williams et al 1984) at up to 13 W/kg the fluorescein content in brain tissue was found to increase with increasing microwave exposure and brain temperature. However, a decrease in renal clearance of fluorescein was also observed in animals which were hyperthermic (greater than 41°C) suggesting that this may have accounted for the elevation of brain tissue values. The same exposure produced opposite results on the transport of horseradish peroxidase across blood vessel endothelial cells in the brain tissue in conscious animals (Williams et al 1984). The histological assay is less susceptible to artefacts than measurement of fluctuating plasma levels, but is more difficult to quantify. An increase in peroxidase uptake was reported in conscious Chinese hamsters exposed for 2 or 8 h to 100 W/m2 (SAR estimated approx 2 - 3 W/kg) at 2.45 GHz. This effect was confirmed and shown to be reversible (Albert & Kerns 1981).

A number of authors have looked at the uptake into brain tissue of radiolabelled saccharides. The exposure of anaesthetised rats for 20 min to low levels (3 - 20 W/m2; SARs estimated to be 0.06 - 0.4 W/kg) of pulsed 1.3 GHz microwave radiation was reported to increase significantly the permeability of the blood-brain barrier to 14C-labelled saccharides compared to the permeability to 3H-labelled water. However, when brain tissue concentrations of 14C-labelled saccharides were compared to circulating plasma levels in exposed and sham-exposed animals no change in the uptake of sucrose or inulin in the brain tissue was found in anaesthetised rats exposed to continuous or pulsed 1.7 GHz radiation at an SAR of 0.1 W/kg (Ward & Ali 1985). Previous experiments reported a decrease in the uptake of sucrose into the brain tissue of anaesthetised and conscious rats exposed for up to 90 min, to 2.45 GHz radiation at SARs of 0.1 - 13 W/kg. Microwave exposure at SARs up to 6 W/kg increased permeability to sucrose but not inulin in anaesthetised rats, while sucrose permeability in conscious rats was unaffected by microwave exposure (NRPB 1993).

In a study on the effects of MRI exposure on the blood-brain barrier of the rat Salford et al (1992) reported leakage of Evans-blue stained proteins. In a subsequent study using unanaesthetised rats exposed to 915 MHz c.w. or pulsed (modulated at 200, 50, 16 or 8 Hz) they reported passage of albumin across the blood-brain barrier (Salford et al 1993). There was no significant difference between c.w. and pulsed exposures. Dosimetry information was sparse but it appears that the extravasation effect was observed to a varying extent at SAR from 0.33 to 3.3 W/kg.

8.2 Electrophysiological Responses

Changes in the function of nervous tissue, measured electrophysiologically, have been reported during or after whole-body or localised irradiation. These studies are prone to measurement artefact since the use of metallic recording electrodes can greatly perturb the applied field, causing enhanced energy absorption, and there is a chance of field-induced pickup in the leads and electrodes.

High levels of microwave exposure have produced decreases in the latency of evoked potentials recorded during exposure. Johnson and Guy (1972) exposed the heads of cats to 918 MHz radiation for 15 min at 10 - 400 W/m2 and recorded decreased latency in the evoked potentials in the thalamus above a SAR threshold of 2.5 - 5 W/kg. Similar responses were also achieved by conventional heating of the thalamus, and microwave-induced effects could be prevented or reversed with concurrent brain cooling (NRPB 1993).

A series of well-conducted experiments by Lai and colleagues (Lai et al 1984, 1987, 1988, 1989) has shown that exposure to low level pulsed and continuous microwave radiation can act as a non-specific stressor. The acute exposure of rats to pulsed 2.45 GHz radiation (2 μs pulses at 500 pps) at 10 W/m2 (a whole-body average SAR 0.6 W/kg, with a peak SAR of 600 W/kg) was shown to affect the activity of cholinergic neurons in the forebrain. The threshold was reported as 0.45 W/kg, corresponding to a specific energy per pulse of 0.9 mJ/kg (Lai et al 1989). The relative effectiveness of pulsed and continuous microwave radiation at a whole-body SAR of 0.6 W/kg varied in different regions of the brain (Lai et al 1988). Rats

exposed for 45 min immediately before daily training sessions in a radial arm maze showed delayed learning performance (Lai et al 1988, 1989).

The radial-arm maze test was used to demonstrate impaired short-term memory function following an acute exposure of 45 min to 2.45 GHz RF at power density of 1 mW/cm2 and estimated whole body SAR 0.6 W/kg. The mechanism of effect has been proposed as one of activation of endogenous opiods in the brain resulting in decreased cholinergic activity in the hippocampus (learning centre). In addition, DNA in brain cells was reported to be damaged, assayed by electrophoretic techniques following a single 45 min exposure (Lai, private communication). The effects were observed with both pulsed (2µs, 500 pps) and c.w. waveforms. Breakage of DNA in the CNS and testes has also been reported recently (Sarka et al 1994) using the same sensitive electrophoretic technique, following exposure to microwaves at 1.18 W/kg SAR.

It is vital that these studies are verified by independent laboratories. The induced changes to neural DNA are unexpected, particularly at the exposure levels used in these studies.

9.0 MECHANISMS OF INTERACTION

SUMMARY

Heating effects of microwave radiation are reasonably well understood and lead to significant physiological effects. Difficulties exist in determining the in situ heating in relation to applied dose due to the heterogeneous nature of body tissues. However, non-thermal subtle effects are considerably more difficult to recognise and understand.

It has been suggested that non-equilibrium processes are significant in the bioenergetics of living systems (Adey 1993), challenging the traditional approach of the chemistry of equilibrium thermodynamics. Rather than observing traditional dose-response effects, there have been a number of reports claiming both amplitude and frequency response "windows". The concept of an all-or-none effect at specific exposure conditions challenges conventional assumptions that the magnitude of a response increases with increasing "dose". If this can be reliably substantiated, it adds weight to the argument that there are significant as yet, unexplained, non-thermal mechanisms involved in biological effects of EMR. In recent years, a number of reports of effects of EMR have appeared which are incompatible with the concept of bulk heating and heat exchange. The altered flux of calcium ions across cell membranes has been commonly reported. The issue has not been resolved but the phenomenon may be due to molecular vibration of receptors rather than due to EM induced voltage activated effects (Moolenar et al 1986; Hoth & Penner 1992) on channels in cell membranes.

Evidence exists that microwave radiation interacts directly with cell membranes to induce functional alterations in membrane components, including ATP-ase and ion channels. The role of free radicals is becoming appreciated from evidence of free-radical reactions in melanin-containing membranes leading to changes in membrane state. The reported effects are unexpected from the existing knowledge on physical interactions since they do not appear to be described by classical intensity- or dose-response relationships. It seems to be unlikely that a single biophysical interaction mechanism will be adequate to explain all of the reported non-thermal effects of RF and microwave radiation.

9.1 MECHANISMS

An important consideration in estimating the effects of dosimetry is the coupling of RF and microwave radiation to biological systems. This depends on the orientation of the subject (animal, human or culture vessel containing cells) relative to the field, and on its dimensions relative to the wavelength. Coupling to a body is maximal when its long axis is oriented parallel to the electric field and when its length is similar to the wavelength. Therefore, maximum (resonant) absorption for an exposed subject is frequency dependent and occurs at approximately 40 MHz for an average (electrically grounded) man, 600-700 MHz for a rat and 2500 MHz for a mouse whole body (Durney et al 1978).

It is well known that the distribution of RFR in an exposed object depends on many factors including frequency, orientation of exposure, dielectric constant of the constituent tissue. The design of experimental protocols is critical if the results are to provide meaningful extrapolation to a particular RF source. Cellular telephones are used in a specific manner. Most people would hold a phone to the same ear in the same orientation and proximity to the skull. Usually one would expect the antenna to be close to the parietal bone (although many airport officials have a peculiar habit of holding the large portable phones in front of their mouth so that they look across the top of the antenna). However, assuming normal usage patterns it would make sense to design experiments so that the RF source was located towards the lateral aspect of the skull. Chou et al (1985a) found significant differences in local SARs in eight different regions of the brain of rats and these all changed in each of seven different exposure arrangements. Lai et al (1984a) reported a difference in microwave response with pentobarbital depending on whether the rat was facing toward or away from the source of irradiation in a waveguide when the average whole body SAR remained constant; patterns of energy absorption in the brain differed substantially.

If the wavelength is smaller than the overall dimensions of the body, reflection and refraction of radiation at the interfaces of different tissues with different electrical properties, (air/skin boundary), can result in localised “energy hot spots”. These hot spots can occur within the whole body at frequencies near body resonance, or within parts of the body such as the head at higher frequencies up to about 2-3 GHz. As frequencies increase and wavelengths decrease, power absorption per unit mass of tissue increases and penetration decreases. Above 10 GHz, absorption would be expected to be largely confined to the skin. When the wavelength is larger than the exposed body, contact with other conducting bodies (including the earth) will cause induced electric currents to flow within the body and between the ground. Hot spots will be felt in regions of the body where the current flow is constricted by small cross-sectional areas, particularly in occupational exposures. Operators of RF sealer-welder equipment (13.5 or 27 MHz) have experienced SARs in the wrists and ankles above 20 W/kg while the SAR to the whole body may be approximately 0.4 W/kg (NRPB 1991).

Many of the biological effects of RF and microwave radiation which have significant implications for human health can be related to the induced heating. Heating from microwave and RF radiation best relates to SAR rather than to incident power density to account for differences in coupling. Temperature rise and specific energy absorption are related as shown:

$$T = J/(htc \times 4180)$$

where T = temperature rise (°C), J = specific energy absorption (J/kg) and htc = relative heat capacity (= 0.85).

This simple worst case situation neglects the effects of cooling. However, as a “rule of thumb” a SAR of 5 W/kg applied for one hour would increase temperature by 5°C. Localised heat may be dissipated by the blood through thermoregulatory processes, although the rate of cooling varies considerably for different organs and tissues. Temperature is profoundly affected by many factors which may confound interpretation of results from different experiments. The degree of thermal stress

imposed on an animal (or human) by a given SAR is strongly affected by ambient temperature, relative humidity and air flow. The induced thermal load would be expected to increase with increasing body mass, at least in small animals. Some argument for a conservative extrapolation of effects from laboratory animals to humans comes from the observed differences in responses of mice and rats in haematology, immunology, reproduction and development (Gordon 1987; Gordon & Ferguson 1984). The difference in the ability of different species to regulate body temperature is a further confounding factor.

It would be unnecessarily simplistic to assume that bulk heating occurred evenly over body tissues and fluids and that it is the only mechanism that can result in a significant effect. Exposure conditions in an RF microwave field are altered considerably by the presence of an object which can profoundly perturb the field, depending on its size, orientation and electrical properties. Refractions and differential absorption within a biological system can result in very complex non-uniform field distributions, and energy deposition. Transmitted energy can be focussed to very localised sites within a body organ. Absorbed RF energy can be converted to other forms of energy and interfere with the function of biological systems. While most of the energy is converted into heat, this does not provide an adequate explanation for a number of biological effects associated with exposures to low level EM radiations.

Evidence of a detectable response to minute temperature increase comes from the observations of human perception of pulsed RF fields. The rapid rate of temperature increase has been attributed to the phenomenon of thermoelastic expansion of brain tissue. This effect creates a response through an auditory pathway. At the cellular level, there is a large body on data on cell membrane responses which has developed the concept of a signal transduction pathway modifying cell behaviour following stimulation by low level microwave fields that do not produce a measurable temperature rise.

It has been suggested that the resonant excitation of particular molecules may elicit specific biological effects that are independent of heating. At frequencies between 1 and 10 GHz, there have been reports for and against resonant absorption of microwave energy by DNA molecules producing mechanical vibration in the DNA (Edwards et al 1984; Gabriel et al 1987, 1989). Based on evidence of the effects of amplitude-modulated radiofrequency fields in different biological endpoints, it has been suggested (Adey 1983, 1989), that co-operative interactions on the surface of cell membranes may allow weak fields to influence cellular processes through signal amplification and transduction processes.

Possible Non-thermal Mechanisms

There are difficulties encountered in attempting to ascribe acceptable mechanisms for the observed non-thermal effects of RF (and ELF) radiation. The process has been impeded for the following reasons:

1. Bioeffects are reported under conditions where the apparent coupling of energy to the biological system is significantly less than that required by classical physical-or physicochemical-interaction mechanisms,

2. Some biological effects occur over a limited range ("windows") of frequencies or modulations,
3. Some biological effects have been reported to occur in multiple dose or intensity ranges, referred to as intensity windows, instead of showing classical dose-response relationships.

A theory to adequately explain EMR bioeffects must incorporate a biophysical-interaction mechanism consistent with modulation- and intensity-windowed responses, occurring under conditions of low-field-energy coupling to living systems.

It is claimed (Cleary 1990) that there is unambiguous evidence of direct effects of RF and microwave radiation from the results of in vitro studies. Effects include, altered cell proliferation, cell membrane receptor and mediated events, and alterations in membrane channels. Although detailed biophysical interaction mechanisms for these effects are not currently available, it is considered that interactions at the microscopic level are related to the dielectric properties of biomacromolecules and molecular assemblages in the form of membrane receptor units, ion channels and enzyme complexes.

Membrane Ordering

There is evidence from various studies of microwave frequencies to demonstrate a direct effect on the cell membrane that may be due to alteration of the membrane molecular composition. Evidence of direct interactions at the molecular level comes from results of studies on transmembrane ionic fluxes and Na+/K+ ATP -ase catalytic activity. The direct effect of microwave interaction is restricted to a limited temperature range, implicating the involvement of membrane lipid phase transition (Liburdy 1992, 1994).

A theorectical model was proposed (Robertson & Astumian 1992) of the effect of alternating electric fields on reaction rates of membrane-associated enzyme molecules, induced by conformational change. The process has been termed electroconformational coupling. The model describes field-induced alteration in enzyme (ATP-ase) activity due to the resonant coupling of the electric field to an oscillatory activation - energy barrier of the enzymatic reaction. The model predicts effects on Na+/K+ ATP -ase inhibition by RF radiation in frequency windows, but not amplitude windows.

Investigation of the possible role of melanin and free radicals in cell membranes (Phelan et al 1992) provided some interesting data. Radiation with 2.45 GHz pulsed wave, SAR 0.2 W/kg was applied to melanin-containing cells and liposomes. Exposure of B16 melanoma cells for 1 h changed membrane ordering, as measured by electron-paramagnetic-resonance (EPR) spectroscopy. Microwave exposure caused a shift from a fluid-like phase to a more solid or ordered membrane state. Similar results were obtained with liposomes that contained melanin, a redox polymer. Neither amelanotic B16 melanoma cells or liposomes exhibited the microwave-facilitated increase in membrane ordering. The microwave effect was inhibited by the free-radical scavenging agent superoxide dismutase (SOD), leading the authors to conclude that the microwave effect was mediated by the generation of oxygen radicals.

The results provide evidence of a direct specific microwave effect on a cell membrane that is dependent upon membrane composition. Changes in membrane order are known to alter the function of integral membrane proteins, such as ATP -ase, as well as membrane permeability. Consequently, microwave-induced membrane order could have physiological implications. The effect of microwave radiation on membrane order required the presence of melanin in this study. Other studies of microwave effects on Na+/K+ ATP -ase in the absence of melanin, as reviewed above, suggest the possibility of similar changes in membrane order that were related to temperature. The possibility that microwave radiation may exert a general effect on membrane order as mediated by temperature-dependent generation of oxygen radicals is supported by the results of Liburdy & Vanek (1985), who reported that temperature-dependent effects of microwave radiation on red-cell membrane permeability are dependent upon oxygen tension and the presence of antioxidants.

Thus the importance of free radicals in membrane-mediated effects of microwave radiation are becoming more widely accepted as a significant factor.

Other Evidence Of Direct Interaction

Additional evidence of a direct effect of microwave radiation on biomembranes was reported by Bolshakov and Alekseev (1992). Exposure of molluscan neurons to pulse-modulated (PM) 900 MHz microwave radiation caused increased rates of rapid, burst-like changes in firing rates. The threshold for the effect was 0.5 W/kg. Continuous wave (cw) radiation did not affect the firing rate at equivalent SARs. Mediator-induced activation of acetyl-choline, dopamine, serotonin, or gamma-aminobutyric acid (GABA) receptors was unaffected by either PW or CW microwave radiation, suggesting a direct effect of the microwave exposure on neuronal membranes.

Resonant Frequency Effects

An early publication that created a great deal of interest reported cell killing at specific frequencies in the GHz range (Grundler et al 1978). Strangely, although this work has frequently been used as an example of the peculiar phenomenon of frequency windows, there has been little work to either verify the effect or to investigate the mechanism. The feeling amongst the scientific community is divided, although there is some scepticism of the effect, nevertheless, the researchers are highly regarded.

A similar status applies to the report of enhanced, resonant absorption of microwaves by DNA molecules (Edwards et al 1984) in the 1 to 10 GHz frequency range. The reported effect could have implications to genetic effects from microwave exposure. Again, although this was a significant finding, it was some time before an attempt was made to duplicate the study. However, when it was tested (Gabriel et al 1987) the authors carried out duplicate tests on the dielectric properties of the same type of plasmid DNA in two separate laboratories. A reference sample was used to normalise the data against water and avoid recording artefacts from impedance mismatch within the system. The attempted verification failed to achieve the reported result. It is suggested that the effect may have been due to a measurement artefact.

However, a recent report of possible rearrangement of brain tissue DNA (measured electrophonetically) following low level microwave exposure (Sarkar et al 1994) may keep the debate alive for some time.

The enhancement of the effect involving corneal lesions when irradiation follows the application of the drug timolol maleate is an important finding. This may be particularly relevant to the upper GHz frequency range. It is possible that the presence of a film enhances energy coupling to the cornea and through differences in molecular composition an impedance mismatch occurs at the aqueous humour, resulting in concentrated deposition of energy in the _ 2mm thick cornea. The authors suggest the involvement of free radicals.

9.2 INTERPRETATION OF DATA

There are some problems in accepting some of the reports of biological effects of EMR due to:

a. absence of accepted mechanisms to explain the observed effects

b. absence of a dose response in many studies

c. absence of independently verified results because of inconsistencies in methodology and choice of experimental endpoints

d. proposed theories of nonlinear mechanisms, without threshold values, are contrary to established, conventional biological concepts

e. extrapolation of cell responses when grown in culture to a potential health effect in organised human tissue

f. so-called 'windows' effects at specified frequency or intensity

In terms of assessing human safety, it requires a quantum leap in philosophy to make a direct extrapolation of events occurring in a very simple biological system, such as yeast cell colonies, to the complex system of organised, differentiated adult tissue. Simple cell systems grown under controlled laboratory conditions provide a convenient and accepted method for studying fundamental processes in respiration, growth and behaviour, development and reproduction. The level of detail has extended to develop an understanding of molecular/biochemical pathways essential for normal cell growth. Thus, these systems are proven as useful test objects to establish interactive mechanisms, and many simple systems, including bacteria are routinely used in testing for toxicology and potential mutagenicity of environmental physical and chemical agents. The difficulty in extrapolation is primarily due to uncertainties about EMR exposure within the human body. The absence of an established mechanism for some of the non-thermal effects reported in cell systems creates difficulties in estimating its effect in organised tissue. Gradients in electric and magnetic fields, as well as in temperature, are quite different in cell culture (with single cell layer thickness or free cells in suspension) compared to large volumes of tissue in body organs.

The cell biology approaches involve standardised procedures to control variables as strictly as possible to allow detection of subtle effects. In this environment cell division is a constant and continuing process and the rate of growth is clearly defined for each species and strain. The rapid proliferation allows optimal opportunity to express developmental abnormalities through many generations on the way to produce neoplastic pathologies. It is not necessarily the case that cells in developed human organs will be in active states of division when EMR exposure occurs. Thus, it is likely that an organ such as the adult human brain would be less sensitive to insult than cells growing in culture.

The attenuation of microwave energy by the scalp and skull increases as a function of frequency and is difficult to relate to exposure of cells in a highly absorbing liquid medium. It has even been suggested that the human head might act as some sort of a lens that concentrates radiated energy at certain frequencies, related to wavelength. The resonance frequency for the rat head is on the order of 5.0 GHz, while the human head is approximately two orders of magnitude larger with an equivalent difference in its resonant frequency.

It is clearly essential that dosimetry is accurately characterised for experiments (in vitro cells in liquid, and animals head volume) and human exposures before meaningful evaluation of human health implications can be achieved. In the meantime, data from cellular and animal studies should be seriously considered whether or not currently accepted and demonstrated mechanisms of action exist.

10.0 RF SAFETY GUIDELINES AND REGULATIONS

SUMMARY

A number of international standards exist and have similarities. There is some concern about basing standards solely on results of a few studies on behavioural changes mediated through a significant increase in temperature of the whole body. The data base for more sensitive effects is equivocal and rather inadequate. The 7W exclusion clause for mobile telephones is considered to be inappropriate and measures are currently being adopted for its deletion from the ICNIRP standard. The German Radiation Protection regulations differ from others in that it requires data for the absolute worst-case exposure condition, regardless of whether or not it represents normal use of the device. They were first to drop the 7W exclusion clause for cellular phones.

10.1 EMR EXPOSURE GUIDELINES

Initiatives of the Commission of the European Communities

The Commission of the European Communities (EC) has proposed limits of exposure in the workplace for non-ionizing radiations through its Directorate General (DG) V (Health and Safety) (CEC, 1992). The proposed limits for electric and magnetic fields are intended as a European Council Directive on the minimum safety and health requirements regarding the exposure of workers to the risks arising from physical agents.

DG XIII of the European Commission (Directorate General Telecommunications Information Industry Innovation) has mandated the European Committee for Electromechanical Standardisation (CENELEC) to prepare an exposure standard for the protection of people against electromagnetic fields. The work is being carried out by CENELEC technical committee TC111 “Human exposure to electromagnetic fields” and its subcommittees. DG XI has also initiated a COST (European Cooperation in the Field of Scientific and Technical Research) project on “Biological effects of electromagnetic fields”. This provides a forum for technical and scientific cooperation between nineteen European countries and various research fields. The bioeffects project (COST 244) was established to study exposure of people to electromagnetic fields associated with communication systems at frequencies from DC to 300 GHz to foster exchange of information on biological research, epidemiology, and dosimetry within Europe. This arrangement has been criticised because of the absence of any organised peer-review system to control the dissemination of information. A number of national and international bodies have published, or are currently developing standards (i.e. guidance and/or regulation) for safety of human exposure to electromagnetic fields.

The standards/guidelines include:

The international Commission for Non-Ionizing Radiation Protection (ICNIRP) of the International Radiation Protection Association (IRPA) for static magnetic fields and time-varying electric and magnetic fields at 50/60 Hz and between 100 kHz and 300 GHz (INIRC 1991).

The American Institute of Electrical and Electronics Engineers (IEEE) and ANSI standard for safety levels with respect to human exposure to radiofrequency electromagnetic fields in the frequency range 30 kHz to 300 GHz, (IEEE 1991; ANSI 1992).

The Physical Agents Committee of the American Conference of Governmental Industrial Hygienists (ACGIH) "Threshold limit Values" (TLVs) for occupational exposure to static and time-varying electromagnetic fields of frequencies less than 300 GHz (ACGIH 1992).

The proposed European Council Directive on the minimum health and safety requirements regarding the exposure of workers to the risks arising from physical agents, for static electric and magnetic fields and time-varying fields of frequencies less than 300 GHz (CC 1992).

The guidelines are based on data from biological and dosimetric studies and studies on exposed populations. They apply equally to workers and to members of the public but not to people who are exposed to electromagnetic fields and radiation for medical or therapeutic purposes.

Electromagnetic interference with medical electronic devices, such as pacemakers, are effects which are not considered explicitly. Electrically or magnetically sensitive prosthetic medical devices may be adversely affected by levels of field strength below those advised by the guidelines for protection from exposure to humans. This rapidly developing topic is beyond the scope of the current report. The current standards apply restrictions on exposure to radiofrequency and microwave radiation to prevent adverse responses to increased heat load and elevated body temperature. There is some argument that this approach is incomplete as it does not consider the large amount of bioeffects data resulting from non-thermal interactions.

As frequency increases, the depth of penetration of radiation in the human body decreases and energy deposition becomes more superficial. In the tens of GHz frequency range absorption of microwave energy occurs primarily in superficial layers of the skin and the cornea. It is then appropriate to quantify exposure by power flux density rather than SAR averaged over a broad expanse of a thin layer of skin. Guidelines do not effectively take account of differences in effectiveness of pulsed versus continuous wave radiofrequency and microwave radiations, or of nonlinear responses.

10.2 RF SAFETY GUIDELINES/REGULATIONS

The American National Standards Institute (ANSI) IEEE Standard for Safety levels with respect to human exposure to radiofrequency electromagnetic fields was recently revised (ANSI, 1992). In an uncontrolled environment in the frequency range

300 MHz to 6 GHz the permissible power density is 10 mW/cm2, although the duration of exposure limit is 6 min for frequencies below 3 GHz and reducing to 10 s at 300 GHz. There was a relaxation of power density limits (20 mW/cm2 at 300 GHz) for partial body exposures, except for the eyes and testes, for uncontrolled environments. The partial body exposure allows power density of 4 mW/cm2 for frequencies in the range of 300 MHz to 6 GHz.

In determining these levels the ANSI committee set as their criteria for bioeffects data base as "only peer-reviewed reports of studies at SAR _ 10 W/kg, which had received favourable engineering and biological validation,...". The findings of the Risk Assessment Working Group were that the existing ANSI 1982 base criterion for 4 W/kg remained.

10.2.1 ANSI Standard: Is it Appropriate?

Although the current standard was issued in 1992, the accompanying bibliography forming the data base for the development of the standard mostly dated from the early 1970's to early 1980's. Out of a total 60 references only 19 are on biological effects. There are only six references that post-date the 1982 ANSI publication. Four of the bioeffects papers deal with the single subject of microwave induced hearing sensation and were written by the same individual. The list of so-called peer-reviewed publications includes a number of proceedings of workshops and conferences. Nevertheless, an important study on potential cancer production by chronic exposure to microwaves (Guy et al 1992) was not included, although the research had concluded many years earlier. Another long-term study has only been reported in a limited fashion (Toler) and has yet to be published.

Although there have been a few publications on long term studies of behavioural effects (D'Andrea & de Lorge 1990) these were not considered for the ANSI standard. Some of these studies were carried out at 918 MHz frequency and found a threshold SAR value around 2 W/kg for disruption of behavioural activities in male rats (Moe et al 1976; D'Andrea et al 1980; Lovely et al 1977, 1983). Effects observed included reduced food intake, decreased blood sugar level and some increased activity. The exposures were repeated daily for many weeks. Altered behaviour was reported in studies carried out at 2450 MHz frequency (cw) at SAR values from 0.14 W/kg (D'Andrea et al 1986; De Witt et al 1987) to 3.2 W/kg (Lovely et al 1983). In a review of the topic D'Andrea and de Lorge (1990) specify that the SAR threshold for significant behavioural effects from long-term exposure at 2450 MHz is between 0.4 - 0.7 W/kg, and at 915 MHz is between 0.9 - 2.0 W/kg. By comparison, short-term acute exposure behavioural changes were associated with a minimum whole-body temperature increase of at least 1°C from SARs approximately 4 W/kg.

It is interesting that although the bibliography extends back as far as 1950 so few publications were judged to meet the ANSI criteria. The rationale for the ANSI guideline is based on the absence of verified reports of injury or adverse effects on the health of humans who have been exposed to RF electromagnetic fields. The ANSI guideline is based on behavioural effects on laboratory animals which the committee assumes as being the most sensitive indicator of biological effects. (This view is not necessarily shared by all scientists, some of whom consider this to be a rather crude endpoint). Since the reported threshold for disruption of ongoing

behaviour in non-human primates always exceeded a whole-body SAR of 4 W/kg, this value was adopted as the working threshold for unfavourable biological effects in human beings in the frequency range from 100 kHz to 300 GHz. Some biologists are concerned about the apparent reliance on thermal mechanism of biological response when responses at the cellular level would be more sensitive. A safety factor of 10 was applied to obtain a maximum permitted whole-body SAR of 0.4 W/kg. Perhaps this may account in some way for the uncertainties involved. This is also a response to an acute exposure. It would seem to be more appropriate to base the standard on the effects of low level chronic exposures.

The US Environmental Protection Agency (EPA) has voiced its objection to the proposed incorporation by the US Federal Communications Commission (FCC) of the ANSI Standard because of its use of gross effects as a criteria for safety.

Justification of the ANSI criteria is given as: “The disruption of a highly demanding operant task is a statistically reliable endpoint that is associated with whole-body SARs in a narrow range between 3.2 and 8.4 W/kg, despite considerable differences in carrier frequency (400 MHz to 5.8 GHz), species (rodents to rhesus monkeys), and exposure parameters (near and far-field, multi-path and planewave, cw- and pulsed-modulated)”. The robust nature of this effect and the use of body temperature as an indicator illustrates that a substantial biological response is evoked. To put into perspective an increase in SAR value by a factor of three for a much smaller animal, the rat, results in circulatory collapse and is followed by death within 15 mins. The effect has been reported at frequencies of 1 and 10 GHz at SAR of 12 W/kg (Frei et al 1994) which was associated with a significant increase in body temperature, and at 35 GHz where colonic temperature was unchanged.

An important issue of the effect on SAR due to absorption as a function of increasing frequency was demonstrated by Gandhi (1990). Based on the premise that, due to the high loss tangent of water in the millimeter wave band (30 - 300 GHz) penetration into the body is restricted to 1 to 2 mm, Gandhi estimated resulting SAR for a given incident power density of 5 mW/cm2. Increasing the frequency from 30 to 60 GHz resulted in an increased SAR from 65 to 138 W/kg. In a study on absorption in pregnant women, Fleming and Joyner (1992) modelled the anatomical geometry of a pregnant woman and found that their estimates of SAR exceeded the current exposure limits prescribed by IRPA, ANSI and SAA in certain circumstances. The results indicated that the specific absorption rate in the embryo or fetus exceeded the safety standard limits for the general population (uncontrolled) in the frequency ranges 80-100 MHz in early pregnancy and for 300-1500 MHz in late pregnancy when the pregnant mother is exposed to the occupational limit of 0.4 W/kg. The standard for the general population, non-occupational (uncontrolled) exposure is an SAR of 0.08 W/kg averaged over the body of the embryo or fetus. At frequencies of 900 and 1200 MHz the estimated SAR in the fetus exceeded by a factor of three the limit set by the ANSI standard.

10.2.2 Cellular Telephones

Exclusion Clause

The Australian Standard (SAA 1990) and the IRPA Standard (IRPA 1988) contain exclusions for devices that have output powers of less than 7 Watts and transmission frequencies of less than 1000 MHz. The two types of hand held mobile telephones currently used in Australia are:- (a) (AMPS) Advanced Mobile Phone Systems operating with a maximum radiated power of 600 mW and frequencies between 825 and 845 MHz (b) (GSM) Global System Mobile with voice information digitally encoded radiates 0.8 and 2.0 W peak power in a frequency band 890 to 915 MHz. The transmission is pulsed at a repetition frequency of 217 Hz with pulse widths of approximately 0.6ms. Therefore, these hand-held mobile telephones are excluded from compliance with the Australian or international, IRPA, standard. Germany has dropped the exclusion clause and instead requires certification of compliance based on "worst case" spatial peak SAR, as exposures from "low power hand held devices has been strongly under-estimated in the past" (Kuster 1993). The ICNIRP standard is about to be amended following agreement to delete the exclusion clause.

Pulsing Effects

The GSM digital telephones have stronger peak electromagnetic fields than the analogue telephones and have been shown to cause electromagnetic interference in a range of electronic medical equipment (Clifford et al 1994, Bassen et al 1994). Increasing the power of the GSM phone did not change the symptoms.

Many of the cellular responses, including transmembrane ionic flow, are elicited by RF emission that is modulated at around 100 Hz, whereas exposure to continuous wave at the same fundamental RF frequency has no effect. There may be some reason to consider that the relatively high instantaneous power that causes EM interference may be the parameter that elicits responses in sensitive biological cell membrane receptors. This issue of critical exposure parameters is fundamental to an evaluation of potential health issues and requires urgent investigation. The process of investigating underlying mechanism of interaction has had little direct attention to date.

Dosimetry

A recent study in Australia (Fleming & Joyner 1992) assessed the RF radiation dose in a physical phantom of a human head when exposed to an AMPS Telecom cellular telephone. The telephone emitted 600 mW continuous wave radiated power which produced an average SAR of 0.7 W/kg in tissue-equivalent gel within the eye. At the same distance of 5 cm from the antenna the measured power density was 0.27 mW/cm2. No increase in temperature was detected. Using numerical estimates the same group (Fleming 1994) reported peak SAR of 1.77 W/kg /W in the skin muscle and bone adjacent to the ear.

Information received from the CTIA shows similar estimates in situ from cellular telephones used in the USA. Balzano was reported to have tested cellular phones with a physical model designed to give a worst-case estimate. In the model, signal attenuates rapidly, and the peak areas of energy absorption occurred in the cheek and mastoid area with peak exposures of 0.5 W/kg and brain exposures of 0.3 - 0.4 W/kg. When the antenna was collapsed the peak exposure was 1.1 W/kg and the

brain exposure was 0.5 W/kg. Energy can be absorbed from near field, as well as far field, and the absorbed energy is a function of the medium, as well as geometry.

Gandhi originally described the anatomy of SAR from cellular telephone exposures using a magnetic resonance imaging model of a male volunteer. The average SAR of the whole body was less than 0.08 W/kg with a peak of 0.7 W/kg at the level of the handset. Approximately 10-12% of the power is absorbed in the head and neck region. The peak SAR (behind the ear) for any 1 gram of tissue was approximately 0.2 W/kg, and the average for brain tissue was 0.014 W/kg. However, other groups including NRPB and Kings College in the UK and Swiss Federal Institute of Technology have used numerical models and direct measurement to show substantially greater values for SAR in the brain when a cellular phone is located next to the head. The UK groups have greatly refined the procedure of MRI based phantom and numerical techniques to obtain resolution for dielectric constants for specific tissues (Gabriel et al 1989; Dimbylow 1993). It seems that an error in Gandhi's model was partly due to incorrect estimate of the dielectric constants for bone and brain tissue. Using FDTD calculations on 5 x 105 cells in 2 mm3 voxels in an MRI acquired image of a human head, Dimbylow (1994 BEMS presentation) showed SAR values 3.1 W/kg averaged over 10 gm tissue inside the head. The SAR averaged over 1 gm of tissue was 4.7 W/kg for a quarter wave monopole operating at 900 MHz. When operating at 1.8 GHz the maximum SAR values along the side of the head were 4.6 and 7.7 W/kg for 10 and 1 gm of tissue, respectively. Based on these estimated SARs the maximum power that would be required to be emitted to meet the ANSI Safety Standard for the uncontrolled population (1.6 W/kg) would be 0.34 W at 900 MHz. For 1.8 GHz the maximum power value required to reach the ANSI safety limit is 0.21 W.

Lovisolo et al (1994) reported estimated SAR values of 1.9 W/kg averaged over 10 gm of liquid brain-equivalent material in a cylindrical phantom head exposed to 0.6 W cellular phone operating at 900 MHz. Using data supplied by Gabriel an anatomically correct (in terms of dielectric properties and dimensions) phantom head was used for the direct measurement of the worst-case exposure (Meire & Kuster 1994) as it was claimed that many cellular phones exceed the ANSI Standard for SAR per 1 gm of tissue. Their measurement show peak SAR levels of 3.5 and 2.5 W/kg at depths in the head of 5 and 10 mm, respectively. Bone of 5 mm thickness reduced SAR by less than 15%.

10.3 REGULATION

While cellular telephones on the market do meet an existing ANSI standard, FDA questions the adequacy of the standard.

FDA administers the Radiation Control for Health and Safety Act. Its purpose is to protect the public from unnecessary radiation from electric devices, and it covers many consumer products. Unlike the situation for medical devices, there is no premarket screening. FDA acts after marketing by recalling products, issuing civil penalties, and setting performance standards. Currently, there are insufficient data to establish cellular telephones as hazardous or to even set a safe standard. If FDA did have to go through notice and comment to set a new standard, it likely would be below today's ANSI standard (personal communication).

FDA needs research data that characterises the potential hazards, if any, of cellular telephone use as soon as possible, including emissions, biological effects and risks.

11.0 DOSIMETRY

Basic Concepts

Time-varying electric and magnetic fields induce electric fields and electric currents in conducting materials, including biological tissues. In general, biological effects depend on the strength of induced current and fields, although effects have been observed that appear to depend on other parameters. These effects are still not well understood and if they are confirmed, appropriate dosimetry may need to be developed.

Given the complex shape and non-homogeneous character of biological systems, it is exceedingly difficult to characterize completely the propagation of electromagnetic fields in the human body. The strength of the field reaching subcutaneous tissue is partly determined by absorption in the outer layers and by the reflection at the interface between different media. The amplitude of the electric and magnetic fields decreases exponentially with distance. The penetration depth of the field (ò) is defined as the distance at which the field is attenuated by a factor of e-1 = 0.368. It decreases with increasing frequency according to the equation:

$$ò = 1/(\text{sq root}(pi\ fs\mu o)$$

where f is the frequency, µo is the permeability of the free space (1.26×10^{-6} H/m) and sis the conductivity of the medium. The last quantity, in turn, depends on the frequency.

The penetration depths of high-water-content biological medium at various frequencies are given below:

f (MHz)	s (S/m)	ò(mm)
10	0.625	200
100	0.889	53
300	1.37	25
915	1.6	13
2450	2.21	6.8
3000	2.26	6.1
5000	3.92	3.6
10000	10.3	1.6

In the radiofrequency band, two quantities are commonly used to quantify the interaction between the field and the biologic medium, ie the current density (used predominantly at frequencies below 100 kHz) and the specific absorption rate (SAR). The latter describes the rate at which radiant energy is deposited into a unit mass of tissue and is usually expressed in units of W/kg. The current density can be usefully compared to those known to produce physiological responses (eg muscle stimulation) or to endogenous body currents.

The interaction between radiant energy and an absorbing medium is particularly efficient when the dimension of the medium is equal, or approximately equal, to a multiple of 1/2 the wavelength (resonance condition). Therefore, the peak absorption for an adult man exposed to a wave with the electric field parallel to the length of the body, occurs at about 75 MHz. The head resonates at much higher frequencies (approx 1GHz).

At higher frequencies, the basic interaction mechanism is the rotation of molecules in which positive and negative charges are separated in space (polar molecules). The most common such molecule in biological matter is water. Polar molecules tend to align themselves with the electric field and, as this oscillates, they tend to follow these oscillations. In this process energy is dissipated in the form of heat. The resulting increase in temperature (delta T) measured in °K can be expressed as delta T = (SAR -HLR)xt/C, where HLR is the rate of heat loss per unit mass, due to thermal conduction and convection, and t is the time in seconds.

The SAR is not readily measurable in practice, therefore in order to prevent overexposure, it is necessary to resort to published data that relate the SAR to the electric and magnetic field strengths or the power density of the incidence radiation.

The SAR can be determined empirically or theoretically. Both of these methods have limitations and rely on each other for validation and complementation. Computational methods indicate that the SAR is a function of frequency, of the wave polarization and that it peaks at resonant frequencies.

With respect to the absorption characteristics of the human body, the RF range can be divided into four regions:

- up to 30 MHz (sub-resonance range), radiation incident on the trunk is predominantly absorbed at the surface, whereas that incident on the legs and neck may result in significant energy absorption. In this range, absorption increases rapidly with frequency.
- between 30 MHz and 300 MHz (resonance range), the SAR per unit incident power density reaches a peak, as resonance conditions are attained for the whole body and body parts.
- between about 400 MHz and 3 GHz (hot spot range), significant heating may occur in particular sites in the body. The size of these 'hot spots' decreases from several cm to about 1 cm as the frequency increases.
- for frequencies above about 3 GHz (surface absorption range), radiant energy is absorbed at, and heating is limited to, the surface of the body.

Fig. 11.1 Variation of normalised SAR with frequency and related absorption characteristics in living organisms. (from WHO, 1993)

It must be stressed that the above considerations depend on the body dimensions, therefore adequate allowance must be made when extrapolating results obtained by animal studies. For example, at 2450 MHz, the SAR resulting from exposure to 10

W/m2, with the E vector parallel to the long axis of the body is about 70 times higher for a mouse (whose length is comparable to the radiation's wavelengths) than for a man (Durney et al 1980).

SARs have also been empirically measured on human volunteers or on human models. For frequencies below and close to the resonant frequencies, experimental values exceeded the calculated values by factors of 3-4 (Hill 1984 a,b,c; Guy 1987).

A good agreement between calculated values and measurements in models were found for frequencies at and above the resonant frequency for irradiation in free space and with the electric field parallel to the long axis of the body.

The SAR is also affected by several practical exposure conditions (position of the body and of the limbs, distance from the ground, footwear etc). Using the results of these computations and measurements and including appropriate safety margins, limits to the maximum acceptable SAR or, as appropriate, maximum induced current density, are translated into maximum permissible exposure levels.

Within the context of the current concerns about brain tumors allegedly caused by exposure to RF radiation from cellular phones, it is interesting to examine the absorption properties of the brain itself and of the DNA molecule.

The brain is a tissue rich in water, but with a substantial proportion of fatty tissue. It has a conductivity at about 1 GHz of approximately 1.1 S/m and a penetration depth of approximately 1.5 cm. While the brain has a metabolic rate about 16 times higher than that of muscle tissue (and therefore generates much more heat that muscle tissue), this is more than compensated by 20-fold higher rate of blood flow and a somewhat higher thermal conductivity (Guy 1974). Therefore, brain tissue is no more prone to RF heating that muscle tissue.

There have been conflicting results on the question of resonant absorption of microwave radiation in DNA. Resonance absorption peaks were reported by Swicord et al (1983) and Edwards et al (1984, 1985). Zhang (1989) calculated that resonance absorption of microwave energy in DNA is possible in the GHz and sub-THz frequency ranges. The most recent reports, however (Foster et al 1987, Gabriel et al 1987 Maleev et 1987, Rhee et al 1988, Garner et al (1990) , tend to argue against the presence of resonant absorption.

Current Issues

A new challenge has arisen recently, due to the relatively new situation of radiating antennae being routinely placed very close to the human body. Data calculated or measured in this condition are extremely dependent on the geometry of the model used.

Gandhi and co-workers used both computational and experimental techniques to obtain SARs in the human head for ten cellular phone from four different manufacturers. For their computations, they used a high resolution model consisting of very small cells (2x2x3 mm) each having appropriately defined properties reflecting their anatomical equivalent. The computation results were verified using an

head-shaped model made of tissue equivalent materials. By contrast, Balzano (1994) and Kuster (1993) used a much cruder approach, relying on a head-shaped mannequin filled with a solution that simulates brain tissue and, approximately, bone and fatty tissue.

Gandhi's results were summarized as follows:

- peak SAR over any 1 g of tissue 0.09 - 0.29 W/kg
- peak SAR over any 1 g of brain tissue 0.04 - 0.17 W/kg
- whole body SAR 0.5 - 1.1 mW/kg

The highest SAR were found to occur in tissue in the upper ear.

These figures contrast sharply with those obtained by Balzano et al (1994) and Meier and Kuster (1993), although the phones output power was the same in all cases (0.6 W).

Balzano et al (1994) measured the SAR induced in human-equivalent phantoms by two types of Motorola cellular phones. They found SARs as high as 1.4 W/kg for "Flip" phones (ie phones with a very thin radio case and a collapsible antenna; when the antenna is extended, the radiation emitted is slightly further away from the head and this results in lower SARs).

"Classic" phones Peak SAR 0.2 - 0.4 W/kg
"Flip" phones Antenna collapsed 0.8 - 1.4 W/kg
Antenna extended 0.6 - 1.0 W/kg

SARs of up to 1.7 W/kg were measured by Kuster et al (1993) under "standard" conditions and SARs as high as 5.3 W/kg under "worst case" conditions, with the antenna actually touching the head.

Mokhtech et al (1994, BEMS Newsletter March/Apr p8), also reported that local peak SARs exceeding the ANSI safety limits may be encountered.

Meier and Kuster (1993) argue that "anatomically correct shell phantoms [such as that used by Gandhi] have been proven poorly suitable to achieve good reproducibility because the position of the radio with respect to the phantom is difficult to define". Their and Balzano's approach is of determining the SAR under 'worst case conditions'.

Which of the two approaches is more appropriate is as much a political as a scientific decision. From a technical view point, the main concern is the view expressed by Balzano (quoted in Microwave News, Jan/Feb 1994, p 13) that Gandhi's results were not obtained by pressing the phone against the ear. At the time of writing, details of Gandhi's measurements have not yet appeared in the scientific literature. If Balzano's claim is correct, it casts some doubt on the usefulness of Gandhi's results.

Kuster also suggests that "for some cellular phones, it is not unusual for the antenna to touch the skull" (Microwave News, Jan/Feb 1994, p 14). Nevertheless, even Kuster's results indicate that the majority of the phones tested complied with the ANSI/IEEE C95.1 Standard (and consequently, with the Australian/New Zealand Standard), when the phones are tested under standard conditions. When tested under worst-case conditions (ie with the antenna touching the head), they all exceeded the limit, with 2 of the 6 models tested being about 50% above the recommended limit.

In order to ensure compliance with safety limits, it is necessary that testing conditions be reproducible. The requirement that compliance be demonstrated under "worst case conditions" overcomes some of the standardization problems, such as the position of the hand holding the phone. In "worst case" tests, the telephone is supported against the head by a non-conducting prop. In practice, the presence of the hand reduces the SAR measured in the head.

The question of low-level dosimetry has been given very little consideration to date. The evidence of non-thermal effects is very complex to interpret and generalize. WHO (1993) suggest that the SAR may also provide a valid measure of all intensity dependent interaction mechanisms, although some additional information may be required, such as modulation characteristics and amplitude "windows" that are biologically active. However, at this stage, it is difficult to see how these additional characteristics could be defined and even whether the observed non-thermal effects are intensity dependent.

For the purpose of further research on human subjects, "dose" or "exposure" need to be defined not necessarily in rigorous, biologically validated terms, but at least in terms that will allow to identify reliably 'cohorts' of subjects whose exposure conditions are clearly different from that of the general population and, preferably, to establish an exposure gradient. The most obvious, but not necessarily accurate, tentative definition of exposure is the time-weighted average of the field power density.

For each of these tentative definitions, the following questions need to be addressed and answered:

- how is 'exposure' distributed among the community?
- how is 'exposure' distributed among specified occupational groups?
- what attributes can be used as 'proxy' for exposure? (eg occupational title, proximity to specific sources etc)
- how strong is the association between a proxy and the 'exposure'?
- if proxies are used, what is the likely effect of inaccurate exposure assessment on the results of the study?
- are any of these proxies associated with other possible risk factors (eg chemical carcinogens, other EMR frequencies) that may confound the results of new studies?

12.0 EPIDEMIOLOGY

Epidemiology is the study of the occurrence of disease in relation to factors affecting the individual, his environment and his lifestyle. Epidemiology may be used to infer a causal link between these factors and the disease, although the biological mechanism responsible may not be identified. This, however is a difficult and often controversial process. To help distinguish causal from non-causal associations, Hill (1965) suggested nine criteria:

1. strength of the association,
2. consistency,
3. specificity,
4. temporality,
5. biological gradient,
6. plausibility,
7. coherence,
8. experimental evidence, and
9. analogy.

However, meeting these criteria need not be seen as necessary prerequisite to accept the association as causal (Rothman 1986). In particular, criterion 3 (specificity), is regarded by Rothman as "useless and misleading" and experimental evidence is seldom available for human population. Hill himself admitted that "none of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non". Lanes (1985) argued that causal inference is not part of science, but a question for public policy. While this may be an extreme position, it highlights how this question is not easily addressed using rigorous scientific thought. However, it is incumbent upon the scientist to investigate how the quality of the study may have reflect upon Hill's criteria.

Epidemiological studies of exposure to radiofrequency radiation

A number of epidemiological studies have conducted among occupational groups believed to be exposed to above-average levels of RF radiation. Some studies have reported health effects consistent with the well understood thermal hazards. For example, RF levels in excess of the recommended limits have been measured in proximity of diathermy units used in physiotherapy (Stuchly et al 1982, Delpizzo and Joyner 1987), an occupation that has been found to have an above average risk of adverse pregnancy outcomes (Kallen et al 1982).

More intriguing are the studies suggesting the possibility of hazards resulting from low-level environmental fields. From a public perception's view point, these may be roughly divided into two categories: general health surveys and cancer studies. The first group (for reviews see WHO 1981 and WHO 1993) have not established any clear evidence of adverse health effects, with the exception of some studies (Gordon 1966, Marha et al 1971, Dumanski et al 1975, Serdjuk 1977, Deroche 1971, Moscovici 1974) that reported an excess of some autonomic and central nervous system complaints and symptoms generally consistent with those of mild depression, that came to be collectively known as "microwave sickness". Because of the subjective nature of these symptoms, the reliability of these studies is difficult to

assess. Moreover, most of these studies have not been reported in the mainstream scientific literature. The possibility of a true association between exposure to RF radiation and psycho-physiologic nervous system reaction cannot be ruled out. For epidemiology to fruitfully address this question, retrospective cohort studies need to be carefully designed to prevent recall bias.

Of much greater concern in the public eye is the claim that exposure to low levels of RF radiation may result in an increase in the incidence of at least some cancers (particularly leukemia and brain tumours). This rest on three elements:

- very few in vivo and in vitro studies
- some anecdotal evidence of brain tumors that because of their position and time of diagnosis were linked to the use of cellular telephones.
- a number of epidemiological studies that suggest an association between employment in occupation presumed to be exposed to above average electromagnetic radiation

With the exception of one study (Lester and Moore 1982), all epidemiological studies on RF exposure were conducted on occupationally exposed subjects. Lester and Moore (1982) reported an increase in cancer mortality in counties within which and Air Force base was located. Their finding was rejected by a subsequent analysis of the same data by Polson and Merritt (1985). Both of these studies have limited credibility. The ecological approach used by Lester and Moore is of intrinsically low quality and is fraught with dangers. Many other potentially relevant factors were not (and could not be) taken into proper consideration. On the other hand, the type of post-hoc re-evaluation carried out by Polson and Merritt needs to be regarded cautiously, since it is open to the possibility of observer bias.

The studies on occupational EMR exposure have been the subjects of several reviews (WHO 1981, 1993). One of the most recent and complete evaluations was done by the Advisory group on Non-ionizing Radiation for the National Radiation Protection Board (NRPB) of Great Britain. With respect to occupational exposure, NRPB speculated that "the large number of observations relating to leukemia... may well be due to bias in favor of publishing results that suggest a hazard, rather than the reverse". However it regards the evidence of a brain cancer risk as "a little more consistent" and comments that "there is some to suggest that the excess increases with duration of employment". It concluded that "the evidence suggests that occupational exposure to EM fields may cause a hazard of brain cancer, but it is far from certain that it does". This statement, together with NRPB's statement that "animal studies conducted at frequencies above about 100 kHz have provided some evidence for effects on tumor incidence" may be seen as supporting the anecdotal evidence of brain tumors arising from the use of cellular phones. The NRPB Advisory Group Chairman, Sir Richard Doll was quoted as saying, that with regard to the possibility of a cancer risk above 100 kHz, "there is room for more doubt" (MW News March/April 1992, p 9).

While doubt cannot be entirely eradicated at this stage, it is hard to see how epidemiological results could support this view. The first difficulty a reviewer faces is that of determining which studies should be considered. Although some of the occupations used as markers for exposure may entail exposure to RF radiation, this has not been verified. It most cases, EMF exposure is limited to ELF electric and

magnetic fields. Therefore it is reasonable to argue that studies on electronics and telecommunications employees are studies on ELF exposure and not RF exposure. In the following tables, summarizing cohort and case-control studies of occupational exposure, the likelihood of exposure to RF/μw radiation and to ELF fields are tentatively assessed for each occupational group. Of the groups for which RF exposure is likely, only radio amateur operators and military personnel have been associated with an increase in the cancer incidence (these groups have been marked ® in the tables). In a few studies (marked ß) the occupation description was broad enough that the possibility of some of the subjects being exposed cannot be ruled out. Nevertheless, it seems reasonable to conclude that, to the extent that these studies carry any information, when placed into the wider picture, they seem to indicate that a possible association between ELF and cancer may have confounded the RF studies, but not vice-versa. It is also interesting to note that Thomas et al (1987) found that subjects exposed to RF radiation in jobs other than those involving design, manufacture, installation or maintenance of electronic or electrical equipment, did not have an elevated brain tumor risk. This argues against exposure to μw/RF radiation being the causal factor for the observed association, although stratification of samples that are already small may easily lead to observations that appear to be inconsistent, purely because of sampling variations.

Table 12.1 Occupational groups investigated in cohort studies

Table 12.2 Occupational groups investigated in case-control studies

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In summary, the epidemiological evidence of possible adverse health effects of electromagnetic fields specifically in the RF frequency band, as distinct from EMR in general and ELF fields in particular, is almost non-existent. The few associations between employment in the so called 'electrical/electronics occupations' and cancer may raise the hypothesis that exposure to μw/RF radiation is associated with some cancers, but the evidence is so weak that it barely makes a case for additional research. Nevertheless, continuing public concern, the absence of good quality epidemiological studies that may allay this concern, the results of a few animal studies and, more importantly, the in vitro studies showing that biological processes are affected by RF fields at levels below those required for significant tissue heating, will ensure that future studies will be carried out. It is therefore important to identify the major methodological issues that need to be addressed to ensure that these studies may make a meaningful contribution to understanding this issue.

Criteria for future studies

The results of an epidemiological study may be affected by bias, misclassification of exposure or of endpoint and limited sample size.

Sample size considerations

Epidemiological studies, particularly observational studies are essentially exercises in statistics. Their results, whether suggesting the presence or the absence of an association, must be qualified by the possibility that they may simply represent a chance finding. Reporting an association when one does not truly exists is called a type I error, while reporting no association when one truly exists is termed a type II error. For a given sample size, reducing the possibility of one type of error increases the probability of the other type. Which course of action is more appropriate is a matter for debate. Scientists traditionally presume the null hypothesis (no effect) and are required to prove that a health effect exists; however, public health professionals err on the side of safety, and tend to take protective action. If studies are intended to reassure the public must have a low probability of type II errors.

Unfortunately, the choice of significance tests is usually dictated by convention, rather than a case-by-case critical analysis. Usually, the level of significance is set at 0.05, two-sided and a confidence interval is calculated accordingly. This means that an association (usually expressed as a relative risk) is accepted as significant only if it is estimated that there is no more than a 5% chance that the confidence interval does not include the true relative risk. This practice leads to study results falling into two distinct groups: significant and non-significant. This is appropriate in situations where decisions (for example, to use an experimental treatment) are to be made on the basis of the study result. However, this approach is not always suitable in epidemiological research. Only if the confidence interval contains values that lies near unity, can a study result argue against an effect (Ahlbom 1993). If the interval is large, encompassing elevated relative risks as well as unity, the result is merely uninformative.

In practice, many (probably most) studies fall well short of having both a high power and high significance level. As an example, consider a study of 250 cases and as many controls in which a subject is classified as 'exposed' if he is in the top 5% of the exposure range. Assume that we are interested in detecting whether being exposed entails a relative risk of at least 2 (ie, we regard a smaller relative risk as clinically non-important). If we require the study to be significant with a confidence level of 95% (two-sided), such a study has only a 50% chance of satisfy this requirement if the risk truly exists. Conversely, if one wanted to limit the probability of a false-negative result to no more than 10%, there would be only a 50% probability that the confidence interval included the true relative risk. The wisest approach would be to acknowledge the limit of such a study and settle for a confidence level of about 77% which gives the study a similar statistical power. Confidence level decisions need to be taken a priori and convincingly explained, if the study is to be credible.

Exposure measurement errors

Direct measurement of thousand of subjects for the whole exposure period is usually impossible. Exposure is usually inferred from a point-in-time measurement or even less direct methods as job descriptions and activity diaries. Consequently, exposure is inevitably affected by non-negligible measurement errors. When exposure is measured on a categorical scale, measurement errors may lead to misclassification of exposure. Measurement errors and misclassification may be differential (if they affect cases and controls differently) or non-differential. Provided that measurement

errors are non-differential, they will not result in an artefactual association and in general will produce conservative risk estimates. Exposure measurement errors also reduce the statistical power of the study (Quade et al 1980, Freedman et al 1990, Delpizzo & Borghesi 1993) and the dose response relationship (Dosemici et al 1990, Armstrong 1990, Delpizzo 1992).

It is difficult to determine a priori what are acceptable exposure measurement errors and it may be very costly and not very effective to attempt to reduce them. At this stage, when the most important aim is to establish reliably whether an association between exposure and cancer does exists, it would be advisable to use available resources to increase the sample size to counteract the loss of statistical power.

Confounding and Bias

The term "bias" may have different meanings in epidemiology. In this case, we use the term to indicate inaccurate inferences resulting from flaws in study design, data collection, analysis and interpretation, review and publication of results. A typical bias encountered in occupational studies is the so-called "healthy worker effect". Full time workers are less likely to suffer from a number of conditions that would prevent their participation in the workforce and of a number of conditions (eg, depression, alcoholism, poverty, homelessness) sometimes associated with unemployment; as a consequence, cancer mortality may be proportionally more common than in the rest of the population. "Confounding" can also have several meanings. In the present context, it indicates a situation in which a measure of the effect of an exposure on risk is distorted because of the association of another factor(s) that influence the outcome under study. It follows that a confounder is a factor that is associated with both the exposure and the outcome of interest. Both confounding and bias can result in the overestimate or underestimate of a true risk or even create an artefactual association.

Bias may be prevented by a careful study design. Confounding may not always be prevented, but may be controlled by stratified analysis, a technique requiring the subdivision of the sample. This underscores again the importance of a large sample size.

Study design

Normally, a case-control study is preferable for cancer studies, because, given the relative rarity of the endpoint, it is more efficient to select diseased subjects before exposure is assessed. The cohort design, in which subjects are initially selected on the basis of their exposure status, is the preferable option when exposure is uncommon.

No study design is ideally suited to this situation, since both the endpoint of interest and the exposure are rare. However, given the obvious difficulties of exposure assessment, a cohort design appears to be the lesser of the two evils.

Since exposure to above-average RF fields is often accompanied by above-average exposure to ELF fields, identifying cohorts for which this is not the case is of paramount importance. Thus, feasibility studies with this aim should receive the first

priority. Suggested possibilities are military personnel, RF plastic welders and diathermy operators. Electronics and telecommunication workers, for whom elevated ELF exposure have been observed (Bowman et al 1988) are not suitable subjects.

In summary, if epidemiology is to provide any insight into the question of RF exposure and cancer, very large studies will need to be carried out. Given Australia's small population and limited resources, this may be difficult to accomplish. The possibility of international coordinated research should be given consideration.

GLOSSARY

Absorption
: In radio wave propagation, attenuation of a radio wave due to its energy being dissipated, i.e., converted into another form, such as heat.

Ambient
: Encompassing or surrounding area.

Antenna regions
: The distinction between electromagnetic fields far from, and those near to, the antenna. The regions are usually classified into three zones; near (static) zone, intermediate (induction) zone and far zone, located by drawing spheres of different radii around the antenna. The radii are approximately r < l for the near zone, r _ l for the intermediate zone, and r > l for the far zone. Note that l is the wavelength of the electromagnetic field produced by the antenna. In the far zone, field components (E and H) lie transverse to the direction of the propagation, and the shape of the field pattern is independent of the radius at which it is taken. In the near and intermediate zones, the field patterns are quite complicated, and the shape is, in general, a function of the radius and angular position (azimuth and elevation) in front of the antenna.

Antenna
: The part of a radio system that is designed to radiate electromagnetic waves into free space (or to receive them). This does not include the transmission lines or waveguide to the radiator.

Antigen
: Something the immune system recognises as foreign. An antigenic determinant is the small part, of a larger foreign target, which is actually recognised.

Athermal effect (nonthermal effect)
: Any effect of electromagnetic energy on a body that is not a heat-related effect.

ATP (adenosine triphosphate)
: A molecule used as a temporary energy store by cells. Energy is harnessed by the hydrolysis of a phosphate group, producing ADP (adenosine diphosphate) as a product.

Attenuation
: The progressive diminution in space of certain quantities characteristic of a propagation phenomenon.

Behaviour
: In animals, learning is a long-lasting change that results from experience with environmental events and includes actions such as solving a maze for food.

Spontaneous behaviours are actions that do not result from a response to direct stimulation and include behaviours like locomotor activity.

Biophysical mechanisms

Physical and/or chemical interactions of electric and magnetic fields with biological systems.

Blood-brain barrier

A functional concept to explain the observation that many substances transported by blood readily enter other tissues, but do not enter the brain. The barrier functions as if it were a continuous membrane lining the brain vasculature.

Calcium efflux

The release of calcium ions from a sample into a surrounding solution.

cAMP

A second-messenger often used in cells to transfer signals from a surface receptor to other parts of the cell.

Cancer

Any malignant, cellular tumour. The term cancer encompasses a group of neoplastic diseases in which there is a transformation of normal body cells into malignant cells. This probably involves some change in the genetic material, DNA, as a result of faulty repair of damage to the cell caused by carcinogenic agents or ionizing radiation. The altered cells pass on inappropriate genetic information to their progeny cells and begin to proliferate in an abnormal and destructive way.

Carcinogen

A chemical, biological, or physical agent capable of producing tumor growth.

Carcinogenic process

A series of stages at the cellular level culminating in the development of cancer.

Chromosome

A very long molecule of DNA, complexed with protein, containing genetic information.

Circularly polarized

If the electric field is viewed as a point in space, the locus of the end point of the vector will rotate and trace out an ellipse, once each cycle.

Clastogenic effects

Microscopically visible damage or changes to chromosomes. (Truncation, translocation, deletions, sister chromatid exchange, change in chromosome number, etc.)

Clone of cells

A group of cells all derived from (and genetically identical to) a single parent cell, by the process of clonal expansion.

Continuous wave

A wave whose successive oscillations are, under steady-state conditions, identical.

Controlled environment

Controlled environments are locations where there is exposure that may be incurred by persons who are aware of the potential for exposure as a concomitant of employment, or by other cognizant persons.

Current

The flow of electric charge.

Cycle
The complete range of states or values through which a phenomenon or periodic function passes before repeating itself identically.

Cytotoxicity
Toxic effects in cells.

Developmental effects
Effects in the developing offspring due to exposure before conception (either parent), prenatally, or postnatally to the time of sexual maturation. Developmental effects may be expressed at any time in the life span of the organism. Developmental effects are a subset of reproductive effects.

DNA
Deoxyribonucleic acid. The nucleic acid molecule in chromosomes that contains the genetic information.

Dosimetry
The measurement or the determination by calculations of the internal electric field strength or induced current density, or of the specific absorption (SA) or specific absorption rate (SAR) distributions, in humans or animals exposed to electromagnetic fields and waves.

Electric dipole
Two separated electric charges; a molecule (or other structure) having the effective centres of positive and negative charges separated.

Electromagnetic energy
The energy stored in an electromagnetic field.

Electromagnetic wave
A wave characterized by variation of the electric and magnetic fields.

Electrophoresis
A technique used to separate molecules, normally according to size.

Embryo
The early stages in the developing organism in which organs and organ systems are developing. For humans, this stage lasts between the second through eighth week after conception.

Endpoint
An observable or measurable biological, chemical, or functional event used as an index of the effect of a chemical, physical, or biological agent on a cell, tissue, organ, organism, etc.

Energy density (electromagnetic field)
The electromagnetic energy contained in an infinitesimal volume divided by that volume.

Enzyme
A protein whose function is that of a catalyst, e.g. lytic and lysosomal enzymes damage cell membrances and degrade cell debris, respectively.

Epidemiology
The study of the occurrence and distribution of a disease or physiological condition in human populations and of the factors that influence this distribution.

Epigenetic
Non-genetic

Erythrocyte
A red blood cell, or corpuscle. One for the formed elements in peripheral blood. In most mammals mature erythrocytes are biconcave discs that have

no nuclei. The cell consists mainly of haemoglobin. Erythrocyte formation takes place in the red bone marrow in the adult and in the liver spleen and bone marrow in the fetus.

Eukaryote

An organism with a defined nucleus, organelles (mitochondria, etc.) and more complex genetic mechanisms in its cells (e.g. yeast or animal cells) (of prokaryote).

Exposure

Exposure occurs whenever and wherever a person is subjected to electric, magnetic or electromagnetic fields or to contact currents other than those originating from phyiological processes in the body and other natural phenomena.

Exposure, long-term

This term indicates exposure during a major part of the lifetime of the biological system involved; it may, therefore, vary from a few weeks to many years in duration.

Exposure, partial-body

Partial-body exposure results when RF fields are substantially nonuniform over the body. Fields that are nonuniform over volumes comparable to the human body may occur due to highly directional sources, standing-waves, re-radiating sources or in the near field. See RF “Hot-spot”.

Extrapolation

An estimate of response or quantity at a point outside the range of the experimental data. Also refers to the estimation of a measured response in a different species or by a different route than that used in the experimental study of interest (i.e., species-to-species, route-to-route, acute-to-chronic, high-to-low).

Far field region

That region of the field of an antenna where the angular field distribution is essentially independent of the distance from the antenna. In this region (also called the free space region), the field has a predominately plane-wave character, i.e., locally uniform distributions of electric field strength and magnetic field strength in planes transverse to the direction of propagation.

Fibroblast

Cells of spindle or irregular shape responsible for fibre formation.

Frequency

The number of complete cycles of a periodic waveform per unit time. Frequency if expressed in Hertz (Hz), which is equivalent to one cycle per second.

Gene

The simplest complete functional unit in a DNA molecule. A linear sequence of nucleotides in DNA that is needed to synthesize a protein and/or regulate cell function.

Genotype

The genetic constitution of an individual or a cell (of phenotype) proteins with sugar (carbohydrate) groups attached, often involved in recognition or signalling mechanisms.

Gigahertz (GHz)

One billion (1,000,000,000) hertz.

Gliona

A tumour composed of neurogila in any of its states of development; sometimes extended to include all intrinsic neoplasms of the brain and spinal cord.

Growth factor

A substance which stimulates a cell to grow and divide.

Hertz (Hz)

One cycle per second.

Hormone

A chemical substance, formed in one organ or part of the body and carried in the blood to another organ or part where it alters the functional activity, and sometimes the structure, of one or more organs in a specific manner.

Hyperthermia

The condition of a temperature-regulating animal when the core temperature is more than one standard deviation above the mean core temperature of the species in resting conditions in a thermoneutral environment.

Immune system

The body's primary defense against abnormal growth of cells (i.e., tumours) and infectious agents such as bacteria, viruses, and parasites.

In utero

In the uterus; unborn.

In vitro

Literally means "in glass", isolated from the living organism and artifically maintained, as in a test tube or culture dish.

In vivo

Occurring within the whole living body.

Inositol phosphate pathway

An internal cell signalling pathway, involving the substrate inositol phosphate, with a role in controlling the cell cycle.

Ion channel (gate)

A protein which allows the passage of ions across a membrane.

Ion efflux

The movement of ions, charged atoms or molecules, from a sample into a surrounding solution.

Latency

The time between exposure to an injurious agent and the manifestation of a response.

Leukemia

A progressive, malignant disease of the blood-forming tissues, marked by an excessive number of white blood cells and their precursors.

Ligand

A specific molecule which binds to a receptor, usually with high affinity.

Liposome

A spherical structure, usually multilamelate, prepared from eukaryotic cell membranes which may be used as a carrier for glycoprotein antigens and drugs.

Lymphocyte

A cell of the immune system. The two subsets, T and B-cells, kill foreign cells and produce antibodies, respectively.

Lymphoma

Any abnormal growth (neoplasm) of the lymphoid tissues. Lymphoma usually refers to a malignant growth and thus is a cancer.

Lysis

Dissolution or destruction of cells.

Malformation

A permanent structural change in a developing organism that may adversely affect survival, development, or function.

Malignant

Harmful, virulent, life-threatening.

Maximum permissible exposure (MPE)

The rms and peak electric and magnetic field strengths, their squares, or the plane-wave equivalent power densities associated with these fields and the induced and contact currents to which a person may be exposed without harmful effect and with an acceptable safety factor.

Megahertz (MHz)

One million (1,000,000) hertz.

Metabolism

The biochemical reactions by which energy is made available for the use of an organism from the time a nutrient substance enters, until it has been utilized and the waste products eliminated.

Metastasis

A process where cells break away from a tumour and spread around the body (verb: metastasise).

Microwaves

Electromagnetic waves of sufficiently short wavelength that practical use can be made of waveguide and associated cavity techniques in their transmission and reception. Note: the term is taken to signify waves having a frequency range of 300 MHz-300 GHz.

Mitochondrion

A cellular organelle in which respiration occurs.

Mitogen

An agent which can induce cells to enter mitosis (to divide).

Mitosis

Cellular and nuclear division that involves duplication of the chromosomes of a parent cell and formation of two daughter cells.

Model

(1) Mathematical model. A mathematical representation of a natural system intended to mimic the behaviour of the real system, allowing description of emphirical data, and predictions about untested states of the system.

(2) Biological model. A condition or disease in animals similar to the condition or disease in human beings.

Modulation

The process of varying the amplitude, frequency, or phase of an RF carrier wave.

Morphology

The appearance and structure of an organism or cell. Cells may be described by their morphology or their biochemistry. (adjective: morphological).

mRNA (messenger RNA)

An RNA copy of the genetic code for a given gene, used as a template in protein synthesis. Also known as poly-A RNA in eukaryotic cells due to a "tail" of "A" nucleotides attached to the end to aid stability, transport etc.

Mutagen

An agent which can induce mutation.

Mutagenesis

The process of creating mutations.

Mutation

A stable, heritable change in the DNA sequence at a specific site in the genome of an organism. This constitutes a change in the genotype and, if expressed, may alter the phenotype.

Near-field region

A region generally in proximity to an antenna or other radiating structure, in which the electric and magnetic fields do not have a substantially plane-wave character, but vary considerably from point to point. The near-field region is further subdivided into the reactive near-field region, which is closest to the radiating structure and that contains most or nearly all of the stored energy, and the radiating near-field region where the radiation field predominates over the reactive field, but lacks substantial plane-wave character and is complicated in structure.

Neurotransmitter

A chemical substance that transmits nerve impulses across the space between nerve endings called the synapse.

Neutrophil

A white blood cell with important roles in the immune and inflammatory systems.

Nonionizing radiation (NIR)

Non-ionizing electromagnetic radiation incorporates all radiations and fields of the electromagnetic spectrum that do not normally have enough entergy to produce ionization in matter. NIRs have an energy per photon less than about 12eV, wavelengths longer than 100 nm, and frequencies lower than 300 THz.

Oncogene

A mutation of a naturally occurring gene involved in growth regulation that results in uncontrolled growth. Oncogenes are associated with the development of some forms of cancer.

Overexpression

The abnormally high production of protein from a gene (of amplification).

Phenotype (ic)

The physical constitution or description of an individual (or a cell) (of genotype).

Plasma membrane

The membrane surrounding animal and plant cells.

Plasmids

Independent circles of DNA, used by some bacteria to spread antibiotic resistance genes and by biologists to insert foreign genes into cells.

Power (surface) density

Radiant power incident on a small sphere, divided by the cross-sectional area of that sphere.

Power flux density

In radio wave propagation, the power crossing unit area normal to the direction of wave propogation. Symbol: W Unit: watts per square metre (W/m2).

Power

The time rate at which work is done. Electrical power is proportional to the product of current and voltage.

Proliferation

An increase in cell or organism numbers.

Promotion

The second hypothesized stage in a multistage process of cancer development. The conversion of initiated cells into tumorigenic cells.

Protein kinases

A group of enzymes which regulate the activity of proteins by phosphorylating them.

Proteinases

Enzymes which specifically degrade certain proteins.

Pulse amplitude

The peak value of a pulse.

Pulse duration

The interval of time between the first and last instant at which the instantaneous value of a pulse (or of its envelope if a carrier frequency pulse is concerned) reaches a specified fraction of the peak amplitude.

Pulse modulated field

An electromagnetic field produced by the amplitude modulation of a continuous wave carrier by one or more pulses.

Pulse output power

The ratio of (1) the average output power to (2) the pulse duty factor.

Pulse repetition rate

The average number of pulses in unit time during a specified period.

Radiofrequency (RF)

Any frequency at which electromagnetic radiation is useful for telecommunication. Note: in this publication the terms RF and microwave are interchangeable and refer to the frequency range 300 HZ-300 GHz.

Reproductive effects

Effects on reproduction which may include, but not be limited to, alterations in sexual behaviour, onset of puberty, fertility, gestation, parturition, lactation, pregnancy outcomes, premature reproductive senescence, or modifications in other functions that are dependent on the integrity of the reproductive system. Developmental effects are a subset of reproductive effects.

Resonance

The change in amplitude as the frequency of the wave approaches or coincides with a natural frequency of the medium. The whole-body absorption of electromagnetic waves presents its highest value, i.e., the resonance, for frequencies (in MHz) corresponding approximately to 114/L, where L is the height of the individual in metres.

RF 'hot spot'

A highly localised area of relatively more intense radio-frequency radiation that manifests itself in two principal ways:

(1) The presence of intense electric or magnetic fields immediately adjacent to conductive objects that are immersed in lower intensity ambient fields (often referred to as re-radiation), and
(2) Localised areas, not necessarily immediately close to conductive objects, in which there exists a concentration of radio-frequency fields caused by reflections and/or narrow beams produced by high-gain radiating antennas or other highly directional sources. In both cases, the fields are characterised by very rapid changes in field strength with distance. RF hot spots are normally associated with very nonuniform exposure of the body (partial body exposure). This is not to be confused with an actual thermal hot spot within the absorbing body.

RNA

Ribonucleic acid. Messenger RNA, the nucleic acid in cells that is the template for the sequential ordering of amino acids during protein synthesis, is synthesized in the nucleus of the cell during the process of transcription.

SAR

Specific absorption rate (see below)

Specific absorption (SA)

The energy absorbed per unit mass of biological tissue, expressed in joules per kilogram (J/kg). SA is defined as the quotient of the incremental energy absorbed by, or dissipated in, an incremental mass contained in a volume element of a given density. SA is the time integral of specific absorption rate (SAR).

Specific absorption rate (SAR)

The rate at which energy is absorbed in body tissues, in watts per kilogram (W/kg). SAR is defined as the time derivation of the incremental energy absorbed by, or dissipated in, an incremental mass contained in a volume element of a given density. SAR is the dosimetric measure that has been widely adopted at frequencies above about 100 kHz.

Static fields

Electric and magnetic fields that do not vary in intensity or strength with time.

Temperature regulation

The maintenance of the temperature or temperatures of a body within a restricted range, under conditions involving variable, internal and/or external heat loads. Biologically, the existence of some degree of body temperature regulation by autonomic or behavioural means.

Thermal effect

In the biological tissue or system, an effect that is related to heating of the tissue through the application of electromagnetic fields, and that can occur through other forms of heating.

Thermogenic levels

Power densities of RF that produce a measurable temperature increase in the exposed object.

3H-thymidine

A radiolabelled nucleoside used to quantitatively follow the synthesis/replication of DNA.

Time-varying fields

Electric and magnetic fields that change in intensity or strength with time. Examples include 60 Hz, modulated, and transient fields.

Transcription

The cellular process in which messenger RNA is synthesized, i.e., the process in which the genetic information in DNA is copied.

Transformation

The genetic alteration of a cell so that it will form a tumour if injected into a suitable host animal. Transformed cells also exhibit characteristic growth changes in culture (cf immortalisation).

Translation

The assembly of amino acids into a protein, using the information in RNA.

Tumour

A swelling caused by the uncontrolled growth of cells. Tumours are also called neoplasms, which means that they are composed of new and actively growing tissue. Their growth is faster than that of normal tissue, continuing after cessation of the stimuli that evoked the growth.

Tumour suppressor gene

A normal cellular gene involved in regulating cell behaviour. Mutations can contribute to cancer in a recessive fashion.

Uncontrolled environment

Uncontrolled environments are locations where there is the exposure of individuals who have no knowledge or control of their exposure.

Wavelength

The distance between two successive points of a periodic wave in the direction of propagation, in which the oscillation has the same phase. Symbol l Unit: metre (m).

Whole-body exposure

Pertains to the case in which the entire body is exposed to the incident electromagnetic energy or the case in which the cross section (physical area) of the body is smaller than the cross section of the incident radiation beam.

"Windowed" responses

Effects found within bands or ranges of frequency or intensity separated by bands or ranges without effect; nonlinear exposure-response relations.

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