Possible health effects related to the use of radiotelephones

Proposals for a research programme by a European Commission Expert Group

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Preface

Public and media concern about the possible effects on human health associated with exposure to electromagnetic fields has increased significantly in recent years. Initially, it was stimulated by publication of epidemiological studies that demonstrated an apparent increase in risk of cancer, particularly childhood cancer, associated with living close to electric power distribution lines. A number of national and international agencies concerned with radiation protection have examined the epidemiological and biological evidence linking exposure to electromagnetic (particularly power frequency) fields and cancer; these have generally concluded that, while some epidemiological data indicate a weak statistical association, the totality of scientific data does not provide convincing evidence of causality. The highly visible nature of high voltage electric power transmission lines and other elements of the electric power distribution system, such as transformer sub-stations, combined with active media coverage, has increased public awareness of the health issue.

The recent expansion of the telecommunications industry, and in personal (cellular) telecommunications in particular, has led to a rapid increase in the number of transmission antennas erected, particularly radiotelephone base station antennas. The latter are often sited close to homes, business premises and schools. Radiotelephone handsets are small, low power radio transmitters that are held close to the head when in use, and some of the power radiated by the antenna is absorbed by the head. It is not surprising, therefore, that public and media concern about the possible health effects of electromagnetic fields has also focused recently on the proximity of base stations and the use of handsets. A large database exists for possible effects on human health from exposure to extremely low frequency (particularly power frequency) electromagnetic fields; however, there are far fewer data for radiofrequency (including microwave) fields, and very few related to the emissions and exposures specific to radiotelephones. A comprehensive health hazard assessment requires such data.

The Expert Group responsible for this report was set up by the European Commission (EC) to make recommendations for a programme of scientific research, the results of which would contribute to a health hazard assessment of personal (cellular) telecommunications. The Expert Group was also asked to provide recommendations for the management structure of such a scientific programme; a mechanism by which industry could participate by providing both financial support for the programme and facilities and information; and an estimate of the financial resources required in order to undertake the proposed research programme.

The scientific work programme of the Expert Group, and most of the administration related to it, was coordinated by the UK National Radiological Protection Board. The membership of the Expert Group is shown in Appendix 1. The Expert Group met eight times, either in specialist subgroups or all together, during the preparation of the report between 4 January and 17 September 1996.

Possible health effects related to the use of radiotelephones

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Executive summary

Introduction

The recent expansion of telecommunications, and in particular personal telecommunications, has led to a rapid increase in the number of radiotelephone (mobile, cellular phone) base station antennas erected. These are often sited in public areas, sometimes close to homes, business premises and schools. Radiotelephone handsets are small, low power radio transmitters that are held in close proximity to the head when in use, and some of the power radiated by the antenna is absorbed by the head. It is not surprising, therefore, that public and media concern about the possible health effects of electromagnetic fields has focused on proximity to base stations and on the use of handsets. For the purpose of this report, the term 'radiotelephone' is used to denote mobile/cellular phones only.

Whereas a large database exists for possible effects on human health from exposure to extremely low frequency (particularly power frequency) electromagnetic fields, there are far fewer data for radiofrequency (including microwave) fields, and very few related to the emissions and exposures specific to personal radiotelephones. A comprehensive assessment of the risk of effects on human health requires such data.

The Expert Group responsible for this report was set up by the European Commission, to make recommendations for a programme of scientific research, the results of which could contribute to a health hazard assessment of the use of personal telecommunications.

Definitive answers about health hazards related to the use of radiotelephones are unlikely to come about in the short term. Health hazard assessment is carried out by considering critically all relevant published studies where the strength of the evidence for the existence of an effect and its magnitude is evaluated on the scientific merits of the studies, both individually and collectively. Replication studies are particularly important in this regard. No study or series of studies producing negative results can prove that an effect does not exist. However, an accumulation of well-performed studies producing negative results provides increasing confidence in the absence of a significant adverse health effect.

The research recommendations of the Expert Group are thus directed towards collaborative research which is directly relevant to possible adverse effects on human health, and lends itself to attempted replication by other researchers in relation to the biological model – the biological endpoint examined – and the exposure system and dosimetric techniques used. The recommended studies should, when taken together with other research already being undertaken, provide important data which will contribute towards the health hazard assessment.

The Expert Group recognises that risk communication is clearly as important in this area of uncertain risk and unestablished effects as it is with other aspects of electromagnetic field exposures, eg, power lines. However, it notes that this should be tackled in a broader context and, also, that it will form an important part of the World Health Organization (WHO) 5-year electromagnetic field research programme. Therefore, while noting its importance, no specific recommendations are made in this report.

The Expert Group was also asked to provide recommendations on the management structure of a scientific programme; a mechanism for the participation of industry in financing it and in providing facilities and information; and an estimate of the magnitude of the financial resources required for its conduct. These recommendations should be considered and, where appropriate, may be modified in relation to existing administrative/financial arrangements within the European Commission.

Composition of the Expert Group

The European Commission appointed ten members to the Expert Group. The professional disciplines covered medicine, epidemiology, biology, physics and telecommunication engineering.

Administration of the Expert Group

The scientific work programme of the Expert Group and most of the administration related to it was co-ordinated by the UK National Radiological Protection Board (NRPB).

Structure and content of the report

The report:

- provides information on the technology of radiotelephones specifically relevant to possible effects on human health
- provides information about the exposure of people associated with the use of radiotelephones
- identifies those areas of research most relevant to the assessment of risk of adverse effects on human health
- summarises relevant published and on-going research studies
- recommends areas of physical, biological and epidemiological research to be included in a research programme relevant to the assessment of risk of adverse effects on human health
- sets out a proposed structure for the management of a European research programme

Radiotelephones – the technology and exposure of people

Personal (cellular) telecommunications is a rapidly evolving technology that uses microwave radiation to communicate between a fixed base station and a mobile user. Presently, most systems employ analogue technology, where the low frequency speech signals are directly modulated on to a high frequency carrier in a manner similar to a frequency-modulated (FM) radio. The power level is effectively constant during the modulation, although some power control may occur. However, the recently introduced second generation systems in Europe, USA and Japan employ digital technology, where the low frequency speech is digitally coded prior to modulation. There is a strong trend towards hand-held radiotelephones, which means that the radiating antenna is close to the head of the user. In the relatively near future the use of digital systems will predominate.

The dominant digital access technique in Europe is **T**ime **D**ivision **M**ultiple **A**ccess (TDMA), which is used in **G**lobal **S**ystems for **M**obile communications (GSM), **D**igital **E**uropean **C**ordless **T**elecommunications (DECT), **D**igital personal **C**ommunication **S**ystem (DCS 1800), and **T**rans **E**uropean **T**runked **R**adio (TETRA).

The electric and magnetic fields surrounding a radiotelephone handset near a person's head are complicated functions of the design and operating characteristics of the handset and its antenna, and the electric and magnetic fields vary considerably from point to point.

Radiotelephone base stations use relatively low effective radiated powers and produce very weak power density levels at the ground. Nonetheless, public concern about the installation of new base stations has become an

important issue. The fact that the radiofrequency fields produced by the base stations at points of public access are less than any national or international radiofrequency exposure standard has apparently not reduced the concern of many members of the public.

Health concerns

Public concern about the health hazards of electromagnetic fields from radiotelephones has increased. Specifically, there is concern that, as the handsets deployed in the new generation of personal telecommunications systems are brought close to the head, there may be either a thermal insult produced by power deposition in tissue (acute effects) or other (long-term) effects.

A large body of literature exists on the biological effects of radiofrequency and microwave radiation. However, only a few studies have considered exposure specifically from radiotelephones or other radio systems.

Overall, the existing scientific literature encompassing toxicology, epidemiology and other data relevant to health risk assessment, while providing useful information, provides no convincing evidence that the use of radiotelephones, whether analogue or digital, poses a long-term public health hazard. However, in view of the concern about possible biological effects of the microwave radiation used, it is important to assess the existing body of knowledge on microwave radiation-induced biological effects.

Microwave radiation absorption occurs at the molecular, cellular, tissue and whole-body levels. The dominant factor for net energy absorption by an entire organism is related to the dielectric properties of bulk water, which ultimately causes transduction of electromagnetic energy into heat.

For laboratory experiments, exposure conditions can be classified in three categories: thermal, athermal, and non-thermal. There are no strict boundaries for these different exposure regimens because a number of factors may influence the characteristics of exposure.

Thermal effects and exposure guidelines

Radiofrequency (including microwave) radiation may be regarded for convenience as part of the thermal environment to which humans may be exposed.

There is currently a general consensus in the scientific and standards community that the most significant parameter, in terms of biologically relevant effects of human exposure to radiofrequency electromagnetic fields, is the specific energy absorption rate (SAR) in tissue, a quantity properly averaged in time and space and expressed in watts per kilogramme ($W\ kg^{-1}$). SAR values are of key importance when validating possible health hazards and in setting standards.

Exposure guidelines are intended to limit both whole-body temperature and localised temperature, and are expressed as whole-body SAR and as localised SAR averaged over a small mass of tissue.

Thermal effects are well-established and form the biological basis for restricting exposure to radiofrequency fields. In contrast, non-thermal effects are not well-established and, currently, do not form a scientifically acceptable basis for restricting human exposure to microwave radiation at those frequencies used by hand-held radiotelephones and base stations.

Non-thermal effects

A large number of biological effects have been reported in cell cultures and in animals, often in response to exposure to relatively low-level fields, which are not well established but which may have health implications and are, hence, the subject of on-going research.

A substantial body of data exists describing biological responses to amplitude-modulated radiofrequency (including microwave) fields at SARs too low to involve any response to heating. It has been suggested that non-equilibrium processes are significant in the bioenergetics of living systems, challenging the traditional approach of equilibrium thermodynamics.

The concept of an all-or-nothing effect under specific exposure conditions challenges conventional assumptions that the magnitude of a response increases with increasing exposure. If this could be reliably substantiated, it would add weight to the argument that there are non-thermal mechanisms involved in biological effects of electromagnetic fields.

Also, reports of 'electrohypersensitivity' to exposure to electromagnetic fields exist to a varying extent and form in some countries.

It is not scientifically possible to guarantee that low levels of microwave radiation which do not cause deleterious effects for relatively short exposures will not cause long-term adverse health effects. However, currently available research findings provide no evidence that such long-term hazards exist. In the context of radiotelephone use, only epidemiological studies could provide such evidence.

Electromagnetic interference

The Expert Group agreed that an in-depth treatment of electromagnetic interference effects related to radiotelephones, and a specification of exactly what should be done in relation to these, is not an aim of this report, but rather is a component of the much broader issue of electromagnetic interference which is the responsibility of the electromagnetic interference research and standards community. It is, however, recognised that action in this field is urgently required.

Dosimetry and exposure systems

The Expert Group concluded that the main purpose of the dosimetry and exposure components of a research programme should be to control exposure parameters in experimental systems with the aim of ensuring the quality and comparability of biological experiments carried out at different laboratories. In formulating their recommendations in this area, the Expert Group recognised the different requirements for *in vitro*, *in vivo* and human (volunteer) experiments, and dealt with them separately. The overriding principle is that the biological experiments should use values of parameters close to those existing in a real user situation, be it a handset held close to the head or irradiation from a more distant base station.

Recent results have been reported on experiments with people using actual functioning radiotelephones. In such cases there is no need to design an exposure system, but all parameters that are critical in dosimetric terms should be controlled. The way in which the telephones are operated is of major importance (test, or stand-by, or listening modes, normal or worst-case position, side of the head and movements, duration, intermittence, etc).

Recommendations for dosimetry and exposure systems research

In order to acquire experimental data reliably relevant to possible effects on human health, it is essential to carefully carry out laboratory investigations. Along with the choice of biological models, it is necessary to design appropriate new exposure systems or to improve existing ones. For this purpose, the Expert Group recommends that work on exposure systems should constitute a significant part of the research programme, and that physics laboratories work closely with biology laboratories in this respect. This will greatly facilitate control and intercomparison of biological data.

The Expert Group recommends that dosimetry and exposure systems studies should be supported as collaborative projects with the biological research and should be directed towards:

- the design and testing of exposure systems for *in vitro* and *in vivo* experiments including the presence of the specimen or animals
- for *in vitro* systems, the characterisation and control of relevant exposure parameters
- for *in vivo* systems, the characterisation of tissue values of SAR
- exposure conditions that correspond to those relevant to the use of a radiotelephone – for comparison, other exposures may also be appropriate
- for human studies, the assurance of well-defined exposure conditions
- in all cases, environmental factors that are monitored and controlled.

Biology

It is not the purpose of this report to provide an in-depth review of the biological effects of electromagnetic fields in relation to human health – several such reviews already exist – but rather to identify and summarise the relevant studies that have been carried out and published, to identify and provide information about on-going studies, and to recommend further areas of research relevant to an assessment of the risk to human health that might arise from the use of radiotelephones.

In order not to exclude any worthwhile research proposal, the recommendations for biological (and epidemiological) research made by the Expert Group are not specifically prescriptive but rather indicative of the areas of research that should be addressed and prioritised. These, together with recommended criteria for selection of research proposals, should both encourage the submission of proposals from suitably qualified research groups and aid the prioritisation and selection of the proposals for funding.

The Expert Group considered the existing peer-reviewed literature and on-going research in each of the subdisciplines, genetic, cancer, immune system, nervous system, and other effects, focusing mainly on non-thermal effects and particularly on those of relevance to human health and the use of radiotelephones. Only effects that occur within the normal physiological temperature range of the body were addressed.

Because several hypotheses for the demodulation of amplitude-modulated fields exist, the Expert Group noted that it is important to address basic interaction mechanisms in this research programme, albeit with a lower priority.

Biophysical interaction studies

The Expert Group recommends that the following be considered:

- mechanisms of signal detection and the role of electromagnetic 'noise' in biological structures
- molecular dynamics of proteins under electromagnetic exposure
- microdosimetry.

In vitro research

The Expert Group noted that cellular models are becoming more and more popular in toxicology studies, although *in vitro* experiments lack the most fundamental interactions between body organs and systems. However, many new models and techniques have made *in vitro* research very informative. They provide insight into cellular and subcellular mechanisms underlying the interactions of radiofrequency radiation and biological systems. Within the scope of this research programme, these new models and techniques should be used in two complementary directions: towards better designed animal models (promotion, cellular or humoural components, stress, ageing, etc) and towards mechanisms of possible effects (role of extremely low frequency (ELF) modulation, of membrane function and signal transduction, of free radicals, of gap junctions, etc).

Recommendations for in vitro biological research

The Expert Group views three categories of electromagnetic interactions as deserving particular attention and recommends further research into the following:

- effects on membrane function and signal transduction pathways
- effects on biochemical reactions including genomic responses
- effects on cell cycle and proliferation.

In vivo research

Some of the proposed research topics use sensitive methods which may be able to detect even minor abnormalities; the Expert Group strongly advises that the severity of such abnormalities should be compared with those induced by other known pathologies so that any possible health risks may be evaluated objectively. It is important to consider possible synergism between microwave exposure and other factors.

Genetic and cancer-related effects

The Expert Group notes that, as there is no convincing evidence that microwave radiation is directly genotoxic or carcinogenic (under athermal or non-thermal conditions), investigations on genetic and cancer-related effects should be directed particularly towards their possible promotional and co-promotional synergistic properties.

Effects on the immune system

Most *in vivo* reported results in the literature are either not relevant to personal telecommunications emissions or contradictory. Thus, this important biological system has a poorly-defined database. There seems to be no consistent finding of alteration to the immune system of animals acutely exposed to microwave radiation at moderate power levels (corresponding to SAR values below a few W kg^{-1}). Hence, some recommendations can be made for further research, while bearing in mind that effects on the immune system cannot be studied independently of other systems, such as the haematopoietic, nervous and endocrine systems.

Since few long-term exposure studies at low levels have been performed, there is a need for well-designed experiments, linked with cancer promotion studies.

Nervous system-related effects

For the evaluation of the effects of microwave exposure, investigations on integrated neuronal function and cochlear function, sleep pattern analyses and neurobehavioural studies would be appropriate. The effect on electrophysiological function should be carried out not only by recording conventional EEG and evoked potentials – these studies were essentially negative in the past – but also by magnetoencephalography because this method allows much finer spatial and temporal resolution than previous recording techniques. Such studies can be complemented by testing memory acquisition and storage before and after microwave exposure.

For neurohumoural and neurotransmitter interactions, the effect on pineal melatonin secretion requires further investigation. If previous ELF findings could be replicated by continuous or pulsed microwave exposure, such effects would be of considerable importance not only for tumour proliferation but also for alterations of sleep pattern.

Another important health issue is the possibility that incidental pathologies are aggravated by microwave exposure. This issue is already under investigation in regard to tumour proliferation but it should also include other pathological states, such as epilepsy, inflammation or ischaemia. Appropriate experimental models would be reperfusion injury after global ischaemia (for possible interference with free radical reactions), permanent or reversible focal ischaemia (to study complicating inflammatory responses), and kainate-induced kindling (for the investigation of hippocampal seizures).

The effect of microwave exposure on permeability changes of the blood-brain barrier should be addressed and, in particular, whether previously described permeability changes are a direct consequence of microwave exposure or side-effects of the experimental procedure, such as immobilisation stress or cryptic thermal effects.

Recommendations for in vivo biological research

The Expert Group recommends the following lines of *in vivo* biological research:

Genetic studies

- studies of genotoxicity on microwave-irradiated animals, including irradiation following or preceding administration of established chemical mutagens/carcinogens
- studies of genetic effects and morphological changes in brain cells from animals exposed to radiofrequency microwave radiation (for example, DNA damage).

Cancer studies

- studies of long-term carcinogenicity in normal or sensitised/transgenic animals
- studies of the influence of microwave radiation on growth of existing tumours.

Immune system studies

- long-term studies
- studies of the possible role of ELF-modulation.

Nervous system-related studies

- electrophysiological and neurobehavioural studies
- investigations of signal transduction pathways by study of the genomic response of the brain
- effects of microwave radiation exposure on permeability changes of the blood–brain barrier
- aggravation of incidental brain pathologies other than cancer (inflammation, ischaemia, seizures) .

Human (laboratory) studies

The design and construction of handsets leads to energy absorption in those brain and neck tissues near the antenna. Structures such as the vestibulum, cochlea and acoustic nerve, other cranial nerves including vagus, facialis, trigeminus, etc, the meninges, the carotids and salivary glands may possibly be exposed.

Most animal laboratory projects focus on carcinogenesis, tumour promotion and mutagenic effects. However, potential health effects might also be seen as non-cancer disorders of the above-mentioned structures, and physiological investigations and clinical examinations are needed to complement cancer-oriented research.

Recommendations for human (laboratory) research

The Expert Group recommends that laboratory studies on volunteers should be undertaken as follows:

- acute exposure of healthy volunteers to fields from handsets, and investigations of possible neurophysiological effects including neurotransmitter levels
- provocation studies, involving the acute exposure of people claiming neurological symptoms associated with radiotelephone use to the emissions from handsets and/or base stations
- disturbance of sleep patterns in people exposed to fields associated with personal telecommunications
- acute exposure of healthy volunteers to fields from handsets and investigations of possible effects on the immune system (lymphocytes – sub populations, etc).

All experiments using volunteers should be 'double blind' where appropriate.

Epidemiology

Epidemiological research can be used to investigate directly the question of whether or not radiotelephone use is a determinant of risk to human health.

Epidemiological studies, unlike most laboratory studies, tend to take several years and to be based on data arising from populations of many thousands or even millions of individuals. Hence, epidemiological studies are not likely to give the 'first warning' of any ill-effects of radiotelephones. They need to be initiated, however, so that, in a few years' time, they can provide the most direct information on whether hazards to people exist.

The question of adverse health effects is a suitable one for epidemiological enquiry, particularly because radiotelephones are widely used in the population. Indeed, certain features of their use make it likely that an epidemiological investigation could come to a successful conclusion. The large number of users gives the potential for studies of considerable power, based on hundreds of thousands or even millions of exposed individuals (although not in the near future for large numbers with very long-term exposure). The existence of quantified, recorded and dated data about exposures, from billing records (compared with the far more imprecise data usually available for many other epidemiological exposures, for instance, diet) gives a basis from which exposures can be estimated with some precision (although further data, beyond those from the billing records, would be needed to maximise the quality of exposure estimates). The exposure has laterality (users will hold the handset to either the left or right ear), which would be expected to result in laterality of any local effects; again, few other epidemiological exposures have this characteristic.

Having examined the published scientific literature, the Expert Group concludes that there are no published epidemiological studies on cause-specific morbidity or mortality specifically relating to radiotelephone use. There have been studies of health outcomes of radiofrequency radiation exposure in various other circumstances, which provide background information of interest in the context of radiotelephone use, but not direct information on its

possible hazards. The Expert Group was able to identify epidemiological studies currently being undertaken on health effects and radiotelephone use.

The Expert Group considers that studies should be inaugurated of risks of certain cancers originating in parts of the head that receive radiation exposures from handsets: namely, tumours of the brain and cerebral meninges; acoustic neuroma; and salivary gland tumours.

Brain cancer is the issue on which public concern has focused in relation to handsets, and although the radiation exposure is low, the brain is one of the sites receiving some irradiation.

Acoustic neuroma and salivary gland cancers, although less common tumours, occur in areas with direct exposure from handsets, with some specific epidemiological characteristics.

Leukaemia in adults is considered worth investigation because of the suspected sensitivity of the haemopoietic and animal systems to electromagnetic energy.

Recommendations for epidemiological research

The Expert Group considers that epidemiological studies are a crucial component in determining whether radiotelephones cause adverse health effects, and that they should form a significant component of a research programme.

The Expert Group recommends that:

- several studies of risk of brain cancer should be conducted, in different countries
- at least one study each of the risk of acoustic neuroma, salivary gland tumours and leukaemia in adults should be conducted
- the above studies should use personal data from the study subjects on exposures and confounding variables, and should not be based solely on billing records
- at least one cohort study of cause-specific mortality and cancer incidence should be conducted, if proposals of sufficient power and quality are put forward. Such a study should preferably be followed by a nested case-control study.

Research management

In respect of its recommendations on the management aspects of the research programme, the Expert Group recognises the need for the management structure to harmonise with existing administrative and financial procedures and customs within the European Commission. The recommendations made should therefore be regarded in part, or in whole, as one option, but the final management structure should be consistent with the following principles.

- The research should be of the highest quality and should be directly relevant to the question of possible human health effects related to the use of radiotelephones.
- The research should be carried out and managed in a manner such that the work is, and is seen to be, clearly independent of industry.
- The research programme should be co-ordinated and managed by a ***Research Management Team***.
- The assessment and selection of specific research proposals should be carried out by an independent scientific panel – ***Proposals Assessment Panel***.
- The disbursement of research funds should be carried out on the advice of the ***Proposals Assessment Panel***.
- The call for research proposals should be widely advertised.

- The progress of the funded research studies should be monitored by a ***Research Monitoring Panel*** comprising *ad hoc* independent scientific experts.
- The results of the scientific research should be submitted for publication in the peer-reviewed scientific literature.

Recommendations for research management

RESEARCH MANAGEMENT TEAM

The Expert Group recommends that a ***Research Management Team*** should be responsible for the overall day-to-day administration and technical management of the entire research programme. This ***Research Management Team*** could be, for example, formed from within existing administrative arrangements within the European Commission. Specific duties of the ***Research Management Team*** could include:

- the provision of Secretariat services to the ***Proposals Assessments Panel*** and the ***Research Monitoring Panel***
- the handling of all correspondence between research teams, the ***Proposals Assessments Panel***, the ***Research Monitoring Panel,*** the European Commission, the industrial and other funders, and the media and other interested parties
- the organisation of all meetings in relation to the research projects including, as appropriate, visits by members of the ***Proposals Assessment Panel*** and the ***Research Monitoring Panel*** to research laboratories, etc.

RESEARCH FUNDING

A fundamental requirement of the funding mechanism is that industry and other funding bodies should be provided with the opportunity to contribute funding and materials in kind to the research programme, but should neither have, nor be seen to have, any influence over the choice of research studies funded, the conduct or the outcome of such studies, or the publication of the results.

The Expert Group recommends that funding for the research programme should be sought from the personal telecommunications industry and other interested parties. Contributions should be used for the sole purpose of funding the scientific research programme and its management. Public acknowledgement of individual contributions for funding and materials in kind should be by the mutual agreement of the funding body and the European Commission. All donations or loans of materials in kind should be arranged through the programme management and not given directly to the research teams. A contribution to the funding or of materials in kind should confer no rights to the contributor other than acknowledgement(s) of the contribution made (where agreed) and information about the progress of the study.

The allocation of funds to specific research projects should be decided according to the recommendations for research funding of the ***Proposals Assessment Panel*** and without consultation with industry or other funding bodies unless required by the Commission.

Legally binding contracts covering the research should be between the European Commission and each of the research teams undertaking the research. Sub- and/or cross-contractual arrangements may be made in respect of collaborative research between two or more research teams.

The estimated total cost of the research programme is 24 MECU.

CALL FOR RESEARCH PROPOSALS

It is envisaged that the timescale of the biophysical and biological research programme will be 4 years, with individual research studies of duration between 1 and 4 years. By necessity, the epidemiological (cohort) programme may extend beyond this period and further funding may be necessary. It is important, therefore, that there is flexibility so that studies can be phased in as the programme develops. For example, it may be appropriate to identify further projects in the mid-to-latter part of the programme to clarify the results of studies completed in the early part of the programme.

The Expert Group recommends that calls for specific research proposals based on the recommendations of the Expert Group should be published. A first call for research proposals should invite applications for proformas. Interested research teams should complete these proformas providing, as appropriate, details of their proposed research, the facilities afforded by their laboratory, the qualifications and experience of the researchers, and details of the funding required for the research. Proposals should be assessed by the ***Proposals Assessment Panel***, who should recommend which research studies should be supported. The ***Proposals Assessment Panel*** should also indicate where collaborative projects appear either necessary or desirable.

PROPOSALS ASSESSMENT PANEL

The Expert Group recommends the appointment of a ***Proposals Assessment Panel*** comprising *ad hoc* appointed experts in the fields of scientific/technical expertise required for the assessment of specific studies in respect of potential funding within the scientific programme. The ***Research Management Team*** should act as the Secretariat for the ***Proposals Assessment Panel*** and should make all administrative and other arrangements necessary for it to carry out its functions. It is recommended that specific tasks of the ***Proposals Assessment Panel*** should include:

- critical review of proposals for research submitted for funding
- making initial visit(s) to and holding discussion(s) with prospective research teams, as appropriate
- advising on the acceptability of specific project proposals in respect of funding
- recommending changes to proposals for research studies and collaborations between research teams, where identified as being necessary and beneficial to the overall research programme.

RESEARCH PROPOSALS SELECTION CRITERIA

The Expert Group notes the importance of providing guidance on assessing proposals for research. It therefore recommends the following criteria.

Dosimetry and exposure systems studies

- Laboratories and researchers must have proven experience in carrying out and publishing the results of scientific work in the specific area of microwave radiation exposure and dosimetry of living systems.
- Exposure and dosimetry studies should form a collaborative part of a biological research study.
- Each laboratory should specify the nature of the quality assurance programme that it intends to follow in respect of its proposed research, and quality assurance documentation specifically related to the investigation should be made available to the ***Proposals Assessment Panel.***
- Where relevant, proven experience of dosimetric modelling using numerical codes is necessary.

Biophysical and biological studies

- Laboratories and researchers must have proven experience in carrying out and publishing the results of scientific work in the specific area of biophysical/biological research.
- The researchers must have proven experience of electromagnetic field dosimetry and exposure systems appropriate to microwave exposure or enter into a collaborative arrangement with a laboratory with a proven record of experience in the field.
- Proposals for research should:
  - ⇒ address issues relevant to human health
  - ⇒ set out to investigate exposure–response relationships
  - ⇒ allow differentiation between continuous wave (cw) and amplitude-modulated effects
  - ⇒ allow differentiation between thermal and non-thermal microwave effects
  - ⇒ characterise the experimental conditions such that comparison can be made with radiotelephones
  - ⇒ employ appropriate negative and positive controls.
- The researchers should have access to and obtain statistical advice in respect of the planning, performing and analysing the results of the experimental work.
- For biological effects studies, priority will be given to funding those studies where the biological model is exposed to a range of exposures representing different radiotelephones.
- The protocols for studies should be produced at the outset of each study and should be regularly updated where appropriate in order to assist future replication of the study.
- Each laboratory should specify the nature of the quality assurance programme that it intends to follow in respect of its proposed research, and quality assurance documentation specifically related to the investigation should be available on request to the ***Research Management Team***.
- Experimental studies involving the use of laboratory animals should be carried out in strict accordance with relevant regulations applicable to such use.

Epidemiological studies

The Expert Group considers that the following criteria are desirable and should be applied when selecting studies for funding. It is recognised that not all may be practical in any particular circumstance and judgement will be needed on whether sufficient are met to make a study worthwhile. It is suggested, however, that applicants should state the extent to which their proposals meet the criteria, viz:

- a proven track record by the applicants in successful conduct and publication of high quality case-control/cohort studies; availability of expertise on statistics and exposure assessments either among the applicants or from collaborators
- if case-control design; appropriate non-biased control group; non-biased methods for data collection, applied in same way to cases and controls
- if cohort design, methods that will give:
  - ⇒ complete follow-up for cause-specific mortality and preferably also for site-specific cancer incidence
  - ⇒ data on changes of exposure over time for the full period of follow-up to be analysed
  - ⇒ comparison of cancer incidence in the cohort with that in a non-exposed cohort or from the appropriate general population (from population based cancer registration)

- use of recorded quantified exposure data from billing records and also personal exposure data from individuals
- adequate data on confounding variables, and method(s) to control for confounding
- for brain tumour study, diagnostic confirmation of cases
  for acoustic neuroma, salivary gland and leukaemia studies; histological/haematological diagnosis of cases
  for brain tumour, acoustic neuroma and salivary gland studies; data on laterality of tumour
- for a case-control study, geographic and demographic choice of study population to obtain a high prevalence of use, especially long-term and long-ago use, in controls; calculation of power for a 5-year and for a 10-year induction period (since first use)
- experience of applicants in collaborative multicentre studies and willingness to make data collection compatible with parallel studies funded in other European countries
- willingness to enter data into meta-analysis and to agree mechanisms to prevent inappropriate preliminary publication.

RESEARCH MONITORING PANEL

The Expert Group recommends the appointment of a ***Research Monitoring Panel*** consisting of *ad hoc* appointed experts in the fields of scientific/technical expertise required for monitoring the progress of specific studies. It is recommended that the ***Research Management Team*** should act as the Secretariat for the ***Research Monitoring Panel*** and should make all administrative and other arrangements necessary for it to carry out its functions.

The Expert Group recommends that the functions of the ***Research Monitoring Panel*** should include:

- making site visits to the research laboratories to monitor progress on specific studies
- discussing progress and points of concern with the research teams
- advising the ***Research Management Team*** on the acceptability of progress made on specific projects in respect of continuity of funding
- recommending changes to research studies (including curtailment, extension, re-direction and collaboration) as appropriate
- critically reviewing progress reports from the research teams and material intended for publication.

INFORMATION CHANNELS

The Expert Group recognises the importance of good communications among all of the stakeholders in the research programme. It therefore recommends that the ***Research Management Team*** should be responsible for communications and dissemination of information between the funding agencies, the European Commission, the research teams, the broader scientific community, the media and the general public. The ***Research Management Team*** should prepare a report of overall research progress with a recommended frequency of twice per year. Annual open meetings could provide the opportunity for the Commission and the funding bodies to learn of progress and to provide feedback.

It is recommended that a scientific research newsletter and, if possible, Internet homepage should be available to the public and to all interested parties. The newsletter and Internet homepage should be prepared and updated regularly by the ***Research Management Team***. For completed research studies, statements, written for non-scientists, should be published in the newsletter (and on the Internet homepage), summarising their key findings.

PUBLICATION OF RESULTS

It is the recommendation of the Expert Group that the results of all the research should be placed in the public arena without undue impediment. It is, however, recognised that, in the interest of sustaining a consistent high standard and quality of presentations for the entire research programme, some editorial control may be necessary. It is, therefore, recommended that draft reports of all studies or intended presentations at scientific and other meetings should be subject to comment by the ***Research Monitoring Panel***. However, it is emphasised that their final content and presentation should rest with the authors of the studies' reports. Results of biological research of an interim or preliminary nature should not be presented at public or scientific meetings without the prior approval of the ***Research Monitoring Panel***. The results of the scientific research must be submitted for publication in peer-reviewed scientific journals.

1 Introduction

1.1 Radiotelephones – the technology

Personal (cellular) telecommunications is a rapidly evolving technology, which uses high frequency radio waves to communicate between a fixed base station and a mobile user. Presently, most systems employ analogue technology, where the low frequency speech signals are directly modulated on to a high frequency carrier in a manner similar to a frequency modulated (FM) radio. The power level is effectively constant during the modulation, although some power control may occur. However, the recently introduced second generation systems in Europe, USA and Japan employ digital technology, where the low frequency speech is digitally coded prior to

modulation. There is a strong trend towards hand-held radiotelephones, which means that the radiating antenna is close to the head of the user. In the relatively near future the use of digital systems will predominate.

The technology varies from system to system, but several different access techniques can be distinguished, which allow many users to communicate via the system simultaneously. In a **F**requency **D**ivision **M**ultiple **A**ccess (FDMA) system each user is assigned his/her own frequency band and, from the point of view of biophysical interaction, this is very similar to an analogue system, since the power is constant as a function of time. In a **C**ode **D**ivision **M**ultiple **A**ccess (CDMA) system, each user shares a frequency band with other users at all times, and thus it too resembles an analogue system, since the power is constant. In some CDMA systems the digital data rates may vary, depending on the need; this is done by sending the data for only part of the time, resulting in a random burst mode where the time between bursts is a multiple of a few milliseconds.

The dominant access technique in Europe is **T**ime **D**ivision **M**ultiple **A**ccess (TDMA), which is used in **G**lobal **S**ystems for **M**obile communications (GSM), **D**igital **E**uropean **C**ordless **T**elecommunications (DECT), **D**igital personal **C**ommunication **S**ystem (DCS 1800), and **T**rans **E**uropean **T**runked **R**adio (TETRA). Here, each user has full power on for a short time (one out of eight time slots) and is silent during the remaining time. Even though there are no low frequencies in the signal band around the high frequency carrier, the power density has a low frequency spectrum. The time structure is rather complicated, since there are longer periods involved in the control of the system, leading to basic frequencies as low as 2 and 8 Hz. None of these systems is purely TDMA, and GSM has components of random frequency hopping between carrier frequencies in a manner similar to FDMA and CDMA (ETSI, 1994; Andersen et al, 1995).

In order to reduce interference between users, adaptive power control has been introduced. This means that the actual exposure of an individual to an electromagnetic field during a conversation may vary from a maximum set by the system to some much lower level, depending on the quality of the link between the user and the base station.

Exposure of people caused by fixed base stations is also of interest, especially microcellular layouts, where the base station antennas are relatively small and placed on structures in the vicinity of users.

The carrier frequency bands allocated for these services are set mainly in the spectrum regions 800–900 MHz and 1.8–2.2 GHz. It is worth noting that, in the future, satellite personal communications with hand-held terminals in the same or related frequency bands can be expected, the main difference being in the use of different types of antenna. Higher frequency bands in the 5 and 17 GHz ranges may be dedicated to wireless computer communications with antennas on portable computers in **W**ireless **L**ocal **A**rea **N**etworks (WLAN) and, finally, the millimetre range (40 and 60 GHz bands) may be used in the future for mobile broad-band services. The research discussed in this document focuses primarily on the currently used frequency bands around 1 and 2 GHz.

1.2 Encountered exposure levels

Exposure of people can result from emissions from base stations, from mobile transmitters, and from portable radiotelephone handsets. The emitted fields will have some form of modulation imposed on them depending upon the nature of the source. These modulations may consist of amplitude and frequency modulation, pulse modulation, extremely low frequency (ELF) modulation and modulations due to the on/off nature of the emission. Some different types of power modulations are illustrated in Figure 1.1.

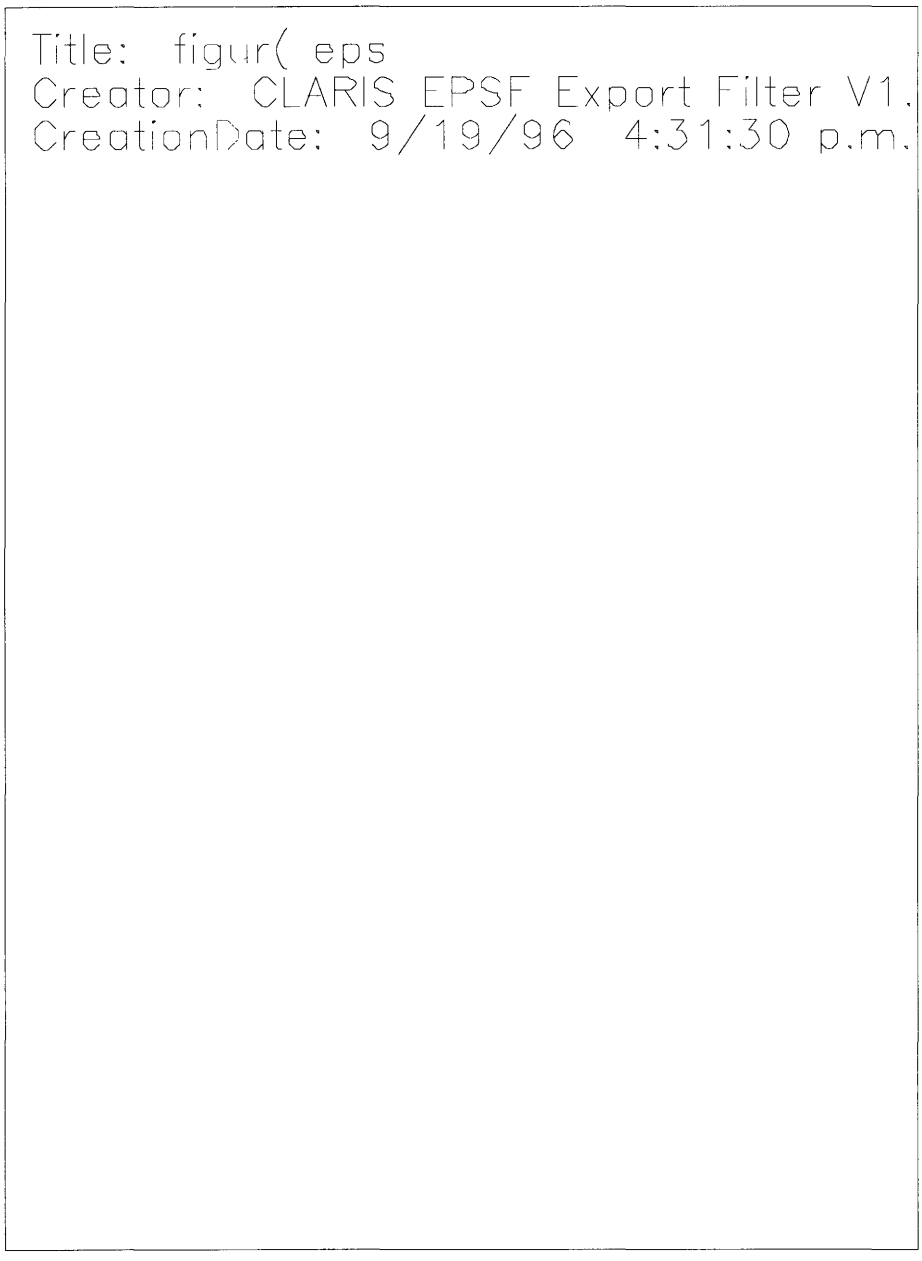

Figure 1.1. Some types of power modulation used in biological experiments. (a) Continuous wave; (b) sinusoidal modulation with a modulation index < 1; (c) sinusoidal modulation with a modulation index of 1; (d) 100% square-wave modulated wave; (e) pulse modulated wave, where duty cycle and pulse width are different. Time is expressed in arbitrary units (a.u.).

For the purposes of exposure hazard evaluation, it is always assumed that the radiated power is equal to the maximum possible, although this is unlikely to occur in practice because of the use of adaptive power control.

The electric and magnetic fields surrounding a radiotelephone handset near a person's head are complicated functions of the design and operating characteristics of the radiotelephone and its antenna, and since the distances involved are less than one wavelength, exposure is in the near-field. In this region, electric and magnetic fields do not have a plane-wave character, but vary considerably from point to point (UNEP/WHO/IRPA, 1993). This means

that the charge and current distribution on the antenna and radiotelephone handset are important. This is in contrast to the situation of base stations, where plane-wave approximations can be generally applied, characterised by a locally uniform distribution of electric and magnetic field strengths in planes transverse to the direction of propagation (far-field region).

Radiotelephone base stations use relatively low effective radiated powers compared with, for example, broadcast transmitters. Nonetheless, public concern about the installation of new base stations has become an important issue. The fact that the radiofrequency fields produced by the base stations at points of public access are less than any national or international radiofrequency exposure standard has not apparently reduced the concern of many members of the public (McKinlay, 1996).

The power classes of the various digital base stations are defined in Table 1.1. These values refer to powers measured at the input to the base station transmitter combiner and are often referred to as peak powers. The term peak power actually refers to the average power over the burst associated with a given call and the values given in the table are maximum powers with no power derating. The highest base station powers permitted are 100 W and 320 W for the so called **T**otal **A**ccess **C**ommunication **S**ystem (TACS, analogue) and GSM (digital), respectively. However, typical powers used in practice are not more than 40 W for GSM and 20 W for TACS.

Table 1.1 Power classes of various digital base stations (ETSI, 1992; 1993)*

	GSM		DCS1800	
Power class	(W)	(dBm)**	(W)	(dBm)**
1	320	55	20	43
2	160	52	10	40
3	80	49	5	37
4	40	46	2.5	34
5	20	43		
6	10	40		
7	5	37		
8	2.5	34		

* For DECT equipment there is only a single power level, which is a maximum power and it is therefore allowed to have lower output power (0.25 W).

** dBm is a unit for describing the ratio of a power to the reference power of 1 mW. A power W (watts) is said to be n dBm greater than the reference value, where $n = 10(3+\log_{10}W)$.

The transmitting antennas of base stations are formed from vertical arrays of co-linear dipoles which are phased to give a very narrow vertical beam width of about 7°, with a downward beam tilt so that the main beam is incident on the ground from about 100 m to the edge of the cell. The arrays are often mounted in corner reflectors to give sector antennas with beam widths of either 60° or 120° in the horizontal plane. Either three or six antennas are then used to provide coverage of a cell.

For 900 MHz and 1.8 GHz systems, wavelengths are approximately 33 and 16 cm and the maximum antenna dimensions are about 3 and 1.5 m, respectively. This gives far-field distances of 54 m at 900 MHz and 27 m at 1.8 GHz.

Base station antennas are normally mounted either on towers with typical heights in the range 15–50 m or on the roofs or sides of tall buildings. The antenna beams have a downward tilt of less than 10°, therefore public exposure to their main beams should not be possible at radial distances of less than 58 m. Side lobes have power levels that are at least 20 dB below that of the main beam.

The gain of a normal base station antenna is 12–14 dB, whereas that of a sector antenna is 16–20 dB. The antenna gain is a measure of the effectiveness of a directional antenna as compared with a standard nondirectional antenna. Each base station does not transmit on all carriers, but usually has a maximum of 10 channels for the digital systems and 40 for TACS. On the basis of an exposure distance of 58 m, a gain of 20 dB, and taking into account the in-phase reflection from the ground, it is possible to calculate the maximum fields to which the public can be exposed by the various systems (Table 1.2).

Table 1.2 Calculated maximum field strengths from base stations

System type	Power per carrier (W)	Number of carriers	Field strengths	
			E (V m^{-1})	H (A m^{-1})
TACS	20	40	53	0.14
GSM	40	10	38	0.10
DCS1800	20	10	27	0.07
DECT	0.25	1	0.95	0.0025

It is emphasised that the calculated values in Table 1.2 are worst case theoretical values. For worst case practical installations, a total electric field strength of 3–4 V m^{-1} is predicted; for comparison, it is worth noting that IRPA/INIRC guidelines limit the general public exposure at 900 MHz and 1.8 GHz to 41 V m^{-1} and 58 V m^{-1}, respectively (IRPA/INIRC, 1988).

When a base station antenna is mounted on a building or rooftop, it may be possible to encounter the main beam at distances of only a few metres. In such cases, it may be necessary to control access to the area immediately around the antenna and to impose distances within which people should not approach in order to ensure compliance with recommended exposure guidelines or exposure limits.

Mobile transmitters are usually vehicle-mounted and there are no physical restrictions to prevent the public approaching to even within touching distance of them. People walking past the antennas will, if exposed, be so for only a few seconds. Passengers inside vehicles with roof-mounted antennas will be partially shielded from the fields and, in the case of antennas mounted at the rear of a car, separations from rear passengers are likely to exceed 60 cm (see Table 1.3). Mobile antennas are not highly directional because their orientation with respect to a base station is variable. Accordingly, they are usually in the form of simple monopoles mounted above metal structures such as the body of a vehicle. Such structures have gains similar to those of half-wave dipoles, approximately 2 dB. Each mobile communication system has a different power class which, due to adaptive power control, represents maximum transmitting powers rather greater than typical levels. These levels are summarised in Table 1.4. However, it should be noted that the digital systems have a duty cycle of 1/8 because of their TDMA schemes and thus their peak powers may be proportionally reduced for exposure assessments. The far-field distances are between only about 2 and 4.3 cm, allowing field strengths for exposure assessments to be calculated at all but the closest distances. Assuming the maximum powers listed in Table 1.4, compensated for duty cycle where appropriate, antenna gains of 2 dB and a tolerance of up to 2.5 dB on transmit powers, the maximum field strengths at 10 and 60 cm are as summarised in Table 1.3.

Handsets are small compact radiotelephones which are held against the head while a call is made. Their electrical structure is normally that of a monopole antenna, or occasionally a sleeve dipole antenna, mounted on a metal box. The user is in the near-field of the source because the distance from the antenna to the head is only about 2 cm. Simple field calculations are not appropriate for assessment of exposure.

Table 1.3 Maximum field strengths in free space from mobile and portable transmitters

		Field strengths and distances			
		E (V m^{-1})		H (A m^{-1})	
System type	Carrier power (W)	10 cm	60 cm	10 cm	60 cm
TACS	10	291	48.5	0.770	0.129
GSM	2	130	21.6	0.343	0.057
DCS1800	1	92	15.3	0.243	0.040

Table 1.4 Power classes for mobile transmitters

	TACS		GSM		DCS 1800	
Power class	(W)	(dBm)	(W)	(dBm)	(W)	(dBm)
1	10	40	20	43	1	30
2	4	36	8	39	0.25	24
3	1.6	32	5	37	-	-
4	0.6	28	2	33	-	-
5	-	-	0.8	29	-	-

For the purpose of radiation protection, dosimetric quantities are needed to estimate the absorbed energy and its distribution inside the body. A dosimetric quantity that is widely adopted for microwaves is the Specific Absorption Rate (SAR), defined as the time derivative of the incremental energy, absorbed by or dissipated in an incremental mass contained in a volume element of a given density; SAR is expressed in the unit watt per kilogramme (W kg^{-1}).

Numerical calculations, based upon coupling from handsets to an anatomically-realistic numerical phantom of the head, have shown that, during normal operation, a radiated power of 1 W gives rise to a maximum SAR of 2.1 W kg^{-1} at 900 MHz and 3.0 W kg^{-1} at 1.8 GHz averaged over any 10 g of tissue (Dimbylow and Mann, 1994; ICNIRP, 1996).

Typical handset powers are 0.6 W for TACS, 0.25 W for GSM and 0.125 W for DCS 1800, allowing for the duty cycle of GSM and DCS 1800 systems. Tolerances on transmitter power are permitted which, for GSM and DCS 1800, are ± 2.5 dB and would result in maximum powers of 0.44 W and 0.22 W, respectively. Higher power classes are unlikely to be used for handsets because of the restrictions imposed by the battery power supplies.

To enable communication with locations not easily reachable with land networks, satellite communication systems have been recently designed and implemented. New systems will involve small portable units and hand-held sets similar to current radiotelephones. In these special cases, higher power classes can be envisaged.

Digital radiotelephones transmit information in bursts of power. The power is turned on and off, and the equipment transmits for a fraction of the time only and then is silent for the remaining part of the burst period. The basic repetition frequency is 217 Hz for GSM and DCS 1800 systems and 100 Hz for DECT; however, the spectrum also contains a number of higher harmonics due to the narrow pulse, so there are also frequencies in the kilohertz region. Owing to the complexity of these communications systems, there are also 2 and 8 Hz components in the signal, apart from multiples of 100 and 217 Hz.

One essential component in a hand-held radiotelephone is the battery. The pulsed transmitting mode causes pulsed currents in the handset and the battery package which, in turn, give rise to a concomitant low frequency magnetic field. Recently Linde and Mild (1995) measured the low frequency magnetic flux density near two models of GSM telephones. The highest root mean square (rms) value of the magnetic flux density was 1.8 μT. Values of the same order of magnitude have also been reported (Andersen et al, 1995). Analogue radiotelephones do not have this pulsed transmitting mode and, hence, do not create pulsed magnetic fields.

1.3 Health concerns

Personal (cellular) telecommunication systems are being introduced into society at a very rapid rate. Currently in Europe, more than 25,000,000 people use these systems. Public concern about the health hazards of the radiofrequency and microwave electromagnetic fields that are emitted by these devices has increased; more specifically, there is a concern that, as the handsets deployed in the new generation of radio communications systems are brought close to the head, there may be either a thermal insult produced by power deposition in tissue (acute effect) or other (long-term) effects.

In view of this current concern about possible biological effects of microwave radiation used by radiotelephones, it is important to assess the body of knowledge on microwave-induced biological effects.

Microwave energy absorption occurs at the molecular, cellular, tissue and whole-body levels. The dominant factor for net energy absorption by an entire organism is related to the dielectric properties of bulk water, which ultimately causes transduction of electromagnetic energy into heat.

The amount of heat transferred to a biological system is important for the purpose of distinguishing those cases where the biological system may be affected by a change in temperature from those where the energy is too little or too dispersed to cause any noticeable change in temperature (Veyret, 1995). For laboratory experiments, exposure conditions can be classified in three categories: thermal, athermal, and non-thermal (Sheppard, 1995). There are no strict boundaries for these different exposure regimens because factors such as animal species, environmental temperature, air flow and humidity, coolant medium, coolant flow, and exposed volume and surface may have a large influence on the characteristics of a particular exposure.

In the thermal regimen, the core temperature of the organism may rise by up to 5 °C, in spite of thermoregulation. In the athermal range, thermoregulation maintains the organism's temperature at its nominal value and, in cell culture experiments, active control of the medium temperature maintains its initial value.

Under non-thermal conditions, there is no challenge to thermoregulation or change in organism temperature.

1.3.1 Thermal effects and exposure guidelines

As described previously, when tissues are exposed to microwave fields strong enough to raise the temperature, the resulting biological effects are said to be thermal. The interaction strength is characterised by the relative dielectric permittivity of water which, at 1 GHz and a temperature of 37 °C , is about 73 times the permittivity of free space. The electric field driven movement of charge adds energy to the collisions between particles and thereby transfers energy from the field to water molecules and other molecular sites of bound charge. Successive collisions lead to rapid diffusion of the energy among neighbouring molecular constituents and to a generalised heating of the exposed tissue.

Human beings are typical endotherm organisms that regulate their body temperature through a controlled rate of metabolic heat production in the face of rather wide fluctuations in the thermal environment.

People function most efficiently when the vital internal organs are maintained at a relatively constant temperature close to 37 °C. While the temperature of individual body parts may vary from this norm, significant departures are usually associated with pathological states or potentially lethal conditions. The normal body temperature range (37 ± 2 °C) is rather large and encompasses differences in body physique, circadian variations, vigorous exercise, variations in ambient temperature, *sequelae* of food intake, age factors, menstrual cycles, and emotional factors. Individual temperature variations are much smaller, but it is only outside this range that temperature must be related to the presence of disease, pharmacological intervention, unusual activity or extraordinary environmental conditions. Radiofrequency and microwave radiation in the environment may be regarded conveniently as part of the thermal environment to which humans may be exposed.

There is currently a general consensus in the scientific and standards community that the most significant parameter, in terms of biologically relevant effects of human exposure to radiofrequency electromagnetic fields, is the SAR in tissue. SAR values are of key importance when validating possible health hazards and in setting standards (Klauenberg et al, 1995).

Possible thermal effects in the ear and the eye are also important. The latter is regarded as potentially sensitive to heating because of the limited cooling ability of the lens caused by the lack of a blood supply and the tendency to accumulate damage and cellular debris. Effects of electromagnetic radiation on the three major eye components essential for vision, the cornea, lens and retina, have been investigated, the largest number of studies being concerned with cataracts. It has been established that lens opacities can form after exposure to microwave radiation above 800 MHz; however, below about 10 GHz cataract induction requires long exposures at an incident power density exceeding 10^3 W m^{-2}. SARs in the lens large enough to produce temperatures in the lens greater than 41 °C are required. Effects on the retina have been associated with levels of microwave radiation above 500 W m^{-2}.

All these data suggest that thermal effects will probably only occur in people subjected to whole body or localised heating sufficient to increase tissue temperatures by more than 1 °C. They include the induction of opacities of the lens of the eye, possible effects on development and male fertility, various physiological and thermoregulatory responses to heat, and a decreased ability to perform mental tasks as body temperature increases. Similar effects have been reported in people subject to heat stress, for example, while working in hot environments or produced by fever.

These various effects are well-established and form the biological basis for restricting exposure to radiofrequency fields. In contrast, non-thermal effects are not well-established and, currently, do not form a scientifically acceptable basis for restricting human exposure to microwave radiation at those frequencies used by hand-held radiotelephones and base stations.

The setting of safety limits for human exposure to radiofrequency electromagnetic fields is currently performed in two steps. First, basic limits (or restrictions) for SARs inside the body are specified from biological considerations in terms of whole-body SAR and SAR averaged over a small mass of tissue. Then relationships between SAR values and unperturbed field strengths are used to set derived limits (or reference or investigation levels) for field strengths and power density to be used in assessing compliance with the adopted standard (Matthes, 1996).

Studies to relate core temperature rise with whole-body averaged SARs (UNEP/WHO/IRPA, 1993; Elder and Cahill, 1984) suggested that the 1–4 W kg^{-1} range is the threshold at which significant core temperature rise occurs. Another approach to identify thresholds of whole body thermal effects is based on the change in animal behaviour exposed to radiofrequency fields. A review of animal data indicates a threshold for behavioural responses in the same 1–4 W kg^{-1} range (UNEP/WHO/IRPA, 1993). Another review of animal data also concluded that the threshold of radiofrequency exposure in terms of the whole body SAR is 4 W kg^{-1} (IEEE, 1991).

Based on the estimated threshold and a safety factor of 10, the whole body averaged SAR of 0.4 W kg^{-1} has been widely accepted as the basic restriction for occupational exposures under controlled environmental conditions (IRPA/INIRC, 1988; IEEE, 1991; NRPB, 1993; CENELEC, 1995). For the general public under uncontrolled environmental conditions, a five times smaller value of 0.08 W kg^{-1} has often been adopted as the basic restriction.

In order to avoid excessive local exposures, maximum local SARs are limited as one of the basic restrictions in safety guidelines. Basic restrictions for partial body exposure are given in terms of maximum local SARs. Local SAR values change spatially within the body depending on the depth of penetration, shape of the body part, and tissue inhomogeneity. It is therefore important to define the mass of tissue taken to evaluate average local body SARs. The limit values of local SARs have not been unified between various standards or guidelines. Typical values for occupational exposure are 8 or 10 W kg^{-1} averaged over a mass of 10 g or 100 g in the relevant part of the body, and 20 W kg^{-1} over 100 g in the extremities (NRPB, 1993; CENELEC, 1995). For the general public, safety factors five times larger have often been adopted. However, a local SAR limit of 8 W kg^{-1} averaged over a mass of 1 g has also been adopted (IEEE, 1991).

Some national and international standards contain exclusions for devices that have output powers of less than 7 W, but some do not (NRPB, 1993). Hand-held radiotelephones are excluded therefore from compliance with those that do contain such exclusions. For this reason, the International Commission on Non-Ionizing Radiation Protection's (ICNIRP) standard is to be amended following agreement to delete the exclusion clause (ICNIRP, 1996).

1.3.2 Non-thermal effects

The thermal effects of exposure to radiofrequency and microwave radiation are well-established and fairly well-understood (Adair, 1993). In addition, a large number of biological effects have been reported in cell cultures and in animals, often in response to exposure to relatively low-level fields, that are not well established but which may have health implications and are the subject of much continuing research.

A substantial body of data exists describing biological responses to amplitude-modulated radiofrequency or microwave fields at SARs too low to involve any response to heating. In some studies, effects have been reported

following exposure at SARs of less than 0.01 W kg^{-1}, occurring within modulation frequency 'windows' (usually between 1 and 100 Hz) and sometimes within power density 'windows'; similar results have been reported at frequencies within the voice frequency (VF) range (300 Hz–3 kHz). It has been suggested that non-equilibrium processes are significant in the bioenergetics of living systems (Adey, 1993), challenging the traditional approach of equilibrium thermodynamics.

The concept of an all-or-nothing effect under specific exposure conditions challenges conventional assumptions that the magnitude of a response increases with increasing exposure. If this could be reliably substantiated, it would add weight to the argument that there are non-thermal mechanisms involved in biological effects of electromagnetic radiation.

Changes have been reported in, for example, electroencephalograms (EEG) of cats and rabbits; calcium ion mobility in brain tissue *in vitro* and *in vivo;* lymphocyte cytotoxicity *in vitro;* and activity of an enzyme involved in cell growth and division. Some of these responses have been difficult to confirm and their physiological consequences are not clear. However, any toxicological investigations should be based on tests carried out at appropriate levels of exposure.

Many important discoveries have been made regarding basic mechanisms of interaction between radiofrequency (including microwave) radiation and various biological entities, notably by exposing cells and subcellular structures *in vitro* to relatively weak fields. The effects on such entities can be characterised as non-thermal, but the gap between such effects and possibly hazardous effects on people or animals from exposure to such levels is large. Factors such as large body masses, penetration depth and internal field distributions, and changes in body orientation during exposures can vastly moderate such interactions or remove them entirely.

It has been shown that under a number of conditions, thresholds for biological effects at frequencies above several hundred MHz are decreased when the energy is delivered in short pulses.

Some people can perceive individual pulses of radiofrequency as audible clicks, chirping, or buzzing sounds, depending on the pulse characteristics and intensity of the field. This phenomenon was first investigated by Frey (1961). Since that time, there have been many studies of the auditory responses of volunteers. Several radiation parameters (for example, peak power density, energy density per pulse, and pulse width) are important in determining the threshold for humans. The phenomenon depends on the energy in a single pulse and not on the average power density. For instance, at 2.45 GHz and a threshold energy density of 0.4 J m^{-2} per pulse, an energy absorption per pulse of 16 mJ kg^{-1} was calculated (Guy et al, 1975). Most experimental results indicate that the auditory perception of radiofrequency pulses is due to the induction of thermoelastic waves in the head, rather than to direct brain stimulation by the radiofrequency radiation. For a more extensive review, see NCRP (1986).

Reports on 'electrohypersensitivity' to exposure to electromagnetic fields exist to a varying extent and form in some countries, see Section 3.2.2.5.

It is not scientifically possible to guarantee that low levels of microwave radiation that do not cause deleterious effects for relatively short exposures will not cause long-term adverse health effects. However, currently available research findings provide no evidence that such long-term hazards exist. In the context of radiotelephone use, only epidemiological studies can provide such evidence.

1.3.3 Electromagnetic interference

Radiotelephone emissions may cause electromagnetic interference (EMI) with medical electrical equipment. People with passive or active medical implants, whether they be life-sustaining or life-improving, as well as patients in intensive care units of hospitals, may be at risk owing to the malfunctioning of these medical devices if they are exposed to electromagnetic fields (Irnich et al, 1989, and references therein). Possible paths of

interaction with high frequency fields considered include: damage to electronic circuitry; induced currents; and heating of electronic implants.

1.3.3.1 Active medical implants

Active medical implants transmit energy to the body. Usually such implants are life-sustaining, such as pacemakers, defibrillators or insulin pumps. Among life-improving implants are cochlear implants and stimulators for the bladder sphincter.

Interference by high-frequency electromagnetic fields can lead to damage to the energy transmission system of the implant, to the programming unit (eg, for pacemakers) or can result in heating of the whole unit.

Among active implanted medical devices, most attention has been given to pacemakers. Interaction with an electromagnetic field can take place directly via the pulse generator or via the antenna formed by the lead system. Recent experiments have shown that the use of radiotelephones causes malfunction when the handset is active close to the pacemaker, for example, when carried in a breast pocket; however, no interference occurred when the handset was in the talking position (Barbaro et al, 1995; Carillo et al, 1995; Hayes et al, 1995; Meckelburg et al, 1996). Malfunctioning of pacemakers has also been reported as being caused by high frequency electromagnetic fields emitted from other sources, such as electric arc welding equipment, transmitters, dielectric heaters, and diathermy or hyperthermia devices. Pulsed anti-theft devices used in department stores (tested frequency range 50–150 kHz) have been shown to activate pacemakers running in demand mode (Goblirsch and Vogel, 1996) whereas higher frequency personal surveillance equipment showed less pronounced effects (Lucas et al, 1994).

Interference with cochlear implants is possible through the direct reception of radio signals, and electronic hearing aids may also be influenced by such signals, in the case of radiotelephones, from a distance of up to about 1 m. This kind of interaction is not critical for health but may cause unpleasant noises. Measurements on the possible heating of inner ear implants have been made, but no hazardous effects were shown (Chou et al, 1995).

1.3.3.2 Passive medical implants

Passive implants do not transfer energy to the body, but they may contain an energy reservoir. Among them are life-sustaining devices such as heart valves or intracardial electrocardiogram transmitters, and life-improving implants, such as all kinds of orthopaedic implants or hearing aids. In the case of an internal energy reservoir, an interaction is possible, disturbing the function. In the case of metallic implants, especially the large orthopaedic implants, an increased local energy absorption of high frequency fields might result in heating of the surrounding tissues. *In vitro* evaluations of high frequency radiation absorption and subsequent heating effects have been made for magnetic resonance imaging (MRI) applications, but only minor temperature changes were found (Shellock et al, 1993).

1.3.3.3 Other medical devices

This category comprises all active medical devices used in intensive care units of hospitals, such as heart–lung machines or different types of monitoring systems. Active life-improving systems are, for example, external fixtures.

All such devices may malfunction due to coupling with an electromagnetic field and, in the case of life-sustaining systems, lead to hazardous situations. Measurements carried out by Joyner et al (1994) showed that most

hospital equipment had an interference radius of about 1 m for 2 W digital handsets; other groups (Bassen et al, 1994; Nightingale, 1994) also found interference problems.

1.3.4 Conclusions

A large body of literature exists on the biological effects of radiofrequency including microwave radiation; however, only a few studies consider exposure from radiotelephones and other radio systems. In addition, there are presently no published epidemiological studies which directly pertain to exposures relevant to radiotelephones. Overall, the existing scientific literature encompassing toxicology, epidemiology and other data relevant to health risk assessment, while providing useful information, provides no convincing evidence that radiotelephones pose a long-term public health hazard.

The results of many studies indicate the existence of threshold levels for thermal effects, thus providing confidence that exposure to levels that are appreciably below the thresholds is most unlikely to be deleterious. However, most experimental data that indicate the existence of thresholds were obtained with single or repetitive exposures of relatively short durations. Although it is hard to conceive of mechanisms whereby exposures at well below threshold values over a long period are cumulative, very few investigations have been undertaken done that involve essentially continuous exposure of animals to low-level radiofrequency radiation (below threshold levels or those that can not cause significant heating) during most of their lifetime. The high cost of such chronic studies and the low probability that any positive effects will be found are major reasons why such studies have not yet been given high priority by funding agencies.

If non-thermal effects do exist, they must be thought of as originating from interactions of the electromagnetic field at a level that does not involve bulk water heating. Since the thermal load corresponding to the use of a mobile telephone is very low, the question of the existence of specific biological effects, which are not taken into account in the current definition of exposure limits, is thus of central importance. In order to address these issues, one approach would be to compare results obtained with extremely low frequency (ELF) and ELF-modulated radiofrequency fields, using the same biological model. Such investigations should provide insight on demodulation mechanisms, since the role of ELF modulation in the elicitation of specific biological effects is frequently claimed.

The Expert Group agrees that an in-depth treatment of electromagnetic interference effects related to radiotelephones and a specification of exactly what should be done in relation to these, is not an aim of this report, but rather the responsibility of the EMI research and standards community. It is, however, recognised that action in this field is urgent and necessary.

1.4 Current research and other relevant programmes

This section summarises the activities of a number of organisations studying possible health effects related to the use of radiotelephones. The material is limited to international or other representative (umbrella) organisations and does not include programmes of research associated with specific industrial or commercial companies. Details of these, where available, are included as individual studies under the description 'on-going research' and in more detail in Appendix 2. Some activities summarised here, like COST 244, are concerned primarily with effective communication of continuing studies and sharing of information, while others, such as the World Health Organization (WHO) electromagnetic fields programme are also concerned with health hazard assessment and still others, such as Wireless Technology Research (WTR), are themselves channelling funding for research studies to be carried out.

1.4.1 World Health Organization

In recognition of the need for an international focus for health hazard assessment and research recommendations on electromagnetic fields and human health, WHO drafted and agreed a proposal for a 5-year programme on electromagnetic fields. Many national and international bodies have become partners in the programme and, as of June 1996, over 20 countries were actively involved with six international partners and WHO collaborating institutions. Funding is currently available for about 2 years and there is, therefore, an on-going commitment to raise further funding to maintain the 5-year or more programme. The programme will have a page on the Internet which will be updated at regular intervals. Brochures will also be produced and meetings will be held.

1.4.2 International Commission on Non-Ionizing Radiation Protection

ICNIRP is an international independent commission chartered by the International Radiation Protection Association (IRPA) to advance non-ionising radiation protection for the benefit of people and the environment and, in particular, to provide guidance and recommendations on protection from non-ionising radiation exposure. ICNIRP is formally recognised by WHO and the International Labour Organization (ILO) as a non-governmental organisation in non-ionising radiation protection. The scope of ICNIRP activities is very wide covering all optical radiations as well as electromagnetic fields and radiations. It includes work on developing environmental health criteria on behalf of WHO, producing occupational advisory publications for ILO and developing recommendations for limiting exposure (exposure guidelines). A recent development within ICNIRP is the setting up of three standing Committees each dealing with a specific aspect of protection, viz, biology, epidemiology, and physical interactions and dosimetry. An important recent involvement of ICNIRP in the field of possible health effects of radiotelephones was the publication of a statement which set out the position in respect of the compliance of emissions from base stations and handsets with recommended exposure guidelines (ICNIRP, 1996).

1.4.3 Cooperation in Science and Technology (COST 244)

In 1990, a new COST (**Co**operation in **S**cience and **T**echnology) programme was proposed by the Faculty of Bioelectrical Engineering, University of Zagreb, Croatia. This proposal, COST 244, concerning the 'Biomedical effects of electromagnetic fields' was adopted in October 1992 and has since helped foster research efforts in Europe. More emphasis has been put on mobile communications since COST 244 was placed under the umbrella of the Technical Committee for Telecommunications of the European Commission. This programme currently includes 21 countries.

The programme is divided into three working groups:

- Epidemiology and human health effects
- Basic research
- System applications and engineering

Complementary to these three 'horizontal' working groups, a 'vertical' co-ordination group (mobile communications coordination committee, MCCC) has been set up to deal with all aspects of mobile communications research. The primary function of MCCC is to coordinate the organisation of workshops on mobile communications and to ensure that an executive summary is prepared after each workshop and circulated widely. MCCC also monitors the progress of all collaborative activities related to mobile communication research within COST 244. The following workshops have been held:

- Mobile communications and ELF fields – Bled, Slovenia, December 1993
- Instrumentation and measurements in bioelectromagnetics research – Plzen, Czech Republic, April 1994

- Electromagnetic hypersensitivity – Graz, Austria, September 1994
- Physical phantoms and numerical methods – Rome, Italy, November 1994
- Exposure assessment and quality control – Athens, Greece, March 1995
- Biological effects relevant to amplitude-modulated RF fields – Kuopio, Finland, September 1995

A congress was held in March 1996 in Nancy, France, to conclude the first round of the programme. This congress was common to COST 244 and the European Bioelectromagnetics Association (EBEA). A second 4-year round will commence in the Autumn of 1996. Information about workshops, publications and other activities is available from the COST 244 Secretariat or through the Internet.

1.4.4 Wireless Technology Research

WTR had its origins in the Scientific Advisory Group which arose out of the wish of the cellular telephony industry in the USA to support a research initiative to facilitate science-based decisions relating to the health and safety aspect of radiotelephones. It was commissioned to manage a comprehensive research programme to develop a scientific basis upon which health decisions could be made. It was further mandated to present advice and recommendations to the cellular telephone industry regarding health risks associated with radiotelephones and for the mitigation of any such risks. WTR derives its funds from the cellular telephony industry. Its initial strategy included collecting information on available research, reviewing this research, defining areas where more information was required and developing a research plan. This culminated in the publication in August 1994 of a research agenda for the development of data for science-based decision-making. More than 150 scientists provided input to the plan which included a 7-month peer review period. The areas of research covered by the research agenda were dosimetry, toxicology and epidemiology. The current status of WTR-sponsored studies being carried out under this research agenda are summarised in Appendix 2.

1.4.5 UK LINK–IBREHT study

The LINK–IBREHT study is a collaborative programme of physical research on the **I**nteraction of the **B**ody with the **R**adio **E**missions from **H**and-held **T**elephones. The study was initiated by the UK Government Department of Trade and Industry in collaboration with the (then) Science and Engineering Research Council, now the Engineering and Physical Sciences Research Council.

The IBREHT project is a study of the physical interaction of electromagnetic fields generated by hand-held transceivers with the human head and comprises three concurrent, related studies.

- The development of a computational model to simulate the interaction of electromagnetic fields associated with the use of a hand-held transceiver, and the application of the model to the calculation of the spatial distribution of absorbed power in the head (SAR) as a result of such exposure. This work was carried out at the University of Bradford.
- The development and construction of non-perturbing electro-optical sensors for the measurement of electric and magnetic fields in and around a physical phantom of the head when exposed to emissions from a hand-held transceiver. This work was carried out at the University of Surrey and Brunel University.
- Experimental measurements of dielectric properties, at 900 and 1800 MHz, of the principal biological tissues of the head. Also, the design and construction of a series of physical phantoms representing the head, in increasing anatomical complexity, for use in measurements of electro-magnetic fields in and around the head. This work was carried out by Microwave Consultants Ltd.

The overall project management was undertaken jointly by the National Radiological Protection Board (NRPB) and Multiple Access Communications (MAC) Limited.

1.4.6 Groupe Spécial Mobile – Memorandum of Understanding: Electromagnetic Compatibility and Bio-effects Review Committee.

The Groupe Spécial Mobile – Memorandum of Understanding (GSM – MoU) currently includes 86 countries throughout the world and has 170 members of whom 140 are operators, the remainder being national regulators.

The Electromagnetic Compatibility and Bio-effects Review Committee (EBRC) currently has seven members and its objectives are to ensure that GSM is:

- electromagnetically compatible with other electrical and electronic devices
- safe and healthy for use by the general public
- environmentally friendly.

The Committee:

- monitors papers and regulations throughout the world
- assesses impact on the industry using GSM
- provides information, advice, and directions to GMS–MoU members
- suggests methods to give a correct image of the industry to the public
- recommends research projects worthy of sponsorship by the GSM– MoU.

The above are carried out both within the context of the radiated emissions from handsets and from base stations.

The on-going task of EBRC is to collect questions and concerns from operators' experience, report processed results at each plenary meeting, make information available 'on-line', and structure information and findings according to areas of concern.

1.4.7 Forschungsgemeinschaft Funk

Forschungsgemeinschaft Funk (FGF, Research Association for Radio Applications) is German-based and represents various bodies concerned with biological effects of mobile communication systems (German Post and Telecommunications Ministry, network operators, manufacturers, universities and associations). Its main objectives are:

- to promote scientific studies on the impact of high frequency fields on people and on the environment
- to evaluate the impact of these technologies
- to draft proposals for national and European recommendations aimed to protect people and the environment
- to review thoroughly the scientific literature on these topics
- to provide substantial information about electromagnetic fields
- to promote dialogue with the general public on risk assessment.

FGF publishes regular information about the progress of its programme. Fifteen research projects have been funded by FGF since 1992, mainly in Germany, in the following areas (see also on-going projects review): nervous system, cell proliferation and calcium, cytogenetics, interference with pacemakers, etc. The scientific emphasis is on studies of non-thermal effects. So far eleven projects have been completed. In 1995 and 1996, funding levels were approximately 500 and 900 kECU, respectively. The FGF programme, which was already open to foreign institutions, is now fully open to international members and projects.

1.4.8 Other research studies

Details of other on-going research studies are listed in Appendix 2.

2 Dosimetry and exposure systems

2.1 Introduction

There is sufficient scientific knowledge about the relationship between SAR and field strengths where far-field plane-wave exposure is simulated or assumed (Chou et al, 1996). However, exposures from handsets fall within the category of near-field exposures, which are specific to the type of source and activity involved and are not, therefore, simply amenable to generalisations. For such cases, SAR can be related to transmitted power for given exposure situations, but not directly to field strengths in free space.

As a consequence of this, and in view of the widespread use of mobile phone handsets operating within the frequency range 800 MHz–2 GHz, there have been numerous experimental and theoretical studies evaluating the energy deposition (dosimetry) in the head as a function of transmitted power, frequency, exposure distance, etc.

Energy deposition from handset antennas in this frequency range occurs mainly in the superficial structure of the head. To correctly address the problem, fine resolution, anatomically-detailed models are needed. Currently these are based either on computed tomography (CT) scans or on sets of MRI slices of the human head. For SAR calculations of the head, the major tissues and organs of interest are: skin, muscle, bone, brain, cerebrospinal fluid, air (sinuses), the cartilage in the ear and nose, eye (lens, humour and sclera-humour layer), and the hypothalamus, pituitary and pineal glands. There are few published data on the electrical properties of these tissues.

The main purpose of the recommended research in the fields of dosimetry and exposure systems is to control the exposure parameters to ensure the quality and comparability of biological experiments carried out at different laboratories. Dosimetry is the quantification of the various electromagnetic and physical parameters of an experiment (to be described in some detail in the following section) and exposure systems, and the actual means of achieving the required dosimetry values in a given experiment. Dosimetry is also of significance in epidemiological studies (see chapter 4).

Biological studies can be divided into three groups; *in vitro* studies, *in vivo* studies and studies in human volunteers. The exposure systems for each of these three areas are discussed here, and recommendations for future work are made. The overriding principle is that the biological experiments should use values of parameters close to those that actually exist, whether that is a handset held close to the head, or radiation from a more distant base station.

2.2 Relevant parameters

The most significant dosimetric parameter, in terms of biologically relevant effects of human exposure to radiofrequency electromagnetic fields, is the SAR in the tissue. However, a number of other parameters are also of importance when designing and performing an experiment (for example, for ELF, see Valberg, 1995). Although the concept of dose is not yet clarified, exposure regimens should be carefully designed to provide meaningful exposure durations.

As far as base station exposure is concerned, it can be assumed that it is in the far field of the antenna, and, in those circumstances, the exposure system should provide a well-defined incident-free space field, uniform over the area of interest. The concern mainly relates to future base stations for micro-cells, which may be attached to walls inside or outside buildings where people may pass close by. Besides field strength, the polarisation should also be controlled.

For handsets, the situation is more complicated. Biological tissues are very near the antenna and complex coupling mechanisms occur. These may vary considerably from system to system, since even small changes in antenna design may lead to significant changes in dosimetric quantities. It is thus necessary to specify the geometry carefully and to measure and/or to calculate the internal and external distributions of the electric field. In some cases, the magnetic field may also be of interest, since it is closely coupled to the electric current values on the antenna. For time-modulated systems, it is imperative to use the correct repetition rates and duty cycles to emulate the real systems and, in some cases, it may even be relevant to use an actual phone system with all its features of speech-dependent timing and frame structures (see Section 1.1). When this is done, power variations should be controlled and not left to the true system to control. Since some of the biological concern is with the distinction between thermal and non-thermal effects, it will be necessary in most situations to measure and control temperature. This should be done without influencing the field distribution.

Finally, a number of environmental parameters should be controlled or at least recorded. These are the ambient electric and magnetic fields over a broad frequency range, including the geomagnetic field, at the place of exposure of the tissue or animal, the external temperature and airflow, mechanical vibrations and general noise levels.

2.3 Dosimetry

2.3.1 Knowledge of human exposure

There is a considerable quantity of scientific knowledge relating to SAR distribution in inhomogeneous models of the head exposed to a hand-held radiotelephone in various positions. The purpose of the present research programme is not to replicate those studies, but rather to ensure that the dosimetric needs of the biological studies are satisfied. However, in order to have the correct parameters, some information on human exposure is needed.

Energy deposition from close-coupled antennas in the frequency range from 800 MHz–2 GHz occurs mainly in the superficial structure of the head; it is very important, therefore, to have a detailed knowledge of the electrical properties of the outer layers, of the cartilage in the ear and nose, and of the skull. Published data for these are presently sparse. Also, little knowledge is available currently about field strengths near base station antennas, since micro-cell antennas are only just coming on the market. A future complication will come from highly-directional antennas which are being planned for producing scanning or adaptive beams, creating higher effective values of power density. In choosing values of power levels for experiments, the standard or recommended threshold levels may also be referred to as levels of interest. It should be noted, however, that this research programme is not aimed at setting standards *per se*, but rather at biological research.

2.3.2 Measurements and calculations of dosimetric parameters of exposure systems

For *in vitro* experiments, uniformity of internal electric and magnetic field values (E(t) and H(t)) and, thus, of SAR values is important. Care should be taken to characterise field distributions in the exposure system including the cell-medium. The field strength measurements require very small field probes, while SAR values can,

in principle, be characterised *via* thermal calculations or measurements using temperature sensing probes. Electromagnetic codes for calculation of field distributions in inhomogeneous media are known to give different results depending on their accuracy and resolution. New algorithms and programmes should be compared with known results in canonical situations.

The same general principles are valid for *in vivo* experiments, except that, in these cases, it will be necessary to distinguish between whole body and head-only exposures. For the latter, detailed knowledge of the internal field distribution and of the SAR distribution in the laboratory animal is required, since these may differ considerably from those for human beings.

2.4 Exposure systems

2.4.1 *In vitro* research

In vitro exposure of biological material (bacteria, cells, tissues) is preferable to animal exposure for some cases that will be outlined later (see Section 3). Exposure of these materials is usually undertaken within the culture containers themselves (flasks, Petri dishes, multi-well plates). Experiments have already been performed in a number of laboratories using various exposure systems and biological models.

At the present time, transverse electromagnetic (TEM) cells are popular. Their length is about equal to one wavelength (33 cm in air at 1 GHz), hence they fit into standard CO_2 incubators. However, coupling of the electromagnetic fields with the sample is weak, and a uniform SAR distribution in the cell culture can only be obtained when the surface of the culture medium is parallel to the septum of the TEM cell. TEM cells can be used thus in cell culture experiments within incubators but, because of the low coupling efficiency, they need to be powered by high power supplies if a high-value SAR is to be attained. Similarly, cavities and waveguides have been or could be used for the same purpose in spite of the intrinsic non-uniformity, the goal being always to obtain a well-defined uniform exposure of the sample.

Electrophysiological measurements on cells are being carried out and there is a need for the further development of exposure systems that allow electrophysiological measurements of single cells or of cell populations on the microscope staging. Such designs may incorporate loop or ring electrodes to produce *in situ* the electric or magnetic fields. Another possibility is full integration of the exposure system, like a coaxial line, with the optical system. For spectroscopic measurements (absorption or fluorescence) of cell populations placed in cuvettes, other exposure apparatus is required for real time measurements within the spectrophotometer. In some cases, the most appropriate way to expose cell cultures (especially in large containers) may be to use far-field plane-wave exposures in anechoic chambers. The control of temperature will then be achieved by placing the cell culture into a thermostatic container which should not distort the field distribution.

In all *in vitro* experiments, temperature control is of major importance since most cellular processes are strongly temperature-dependent. This is not always easy to achieve because of possible interference between the electromagnetic fields and conducting temperature probes. Temperature monitoring of the sample during exposure is essential, assuming that all efforts have been made to ensure a uniform field distribution.

2.4.2 *In vivo* research

In vivo exposure of animals has different requirements to those of cell cultures: the aim *in vivo*, is to imitate the SAR distribution inside the organism which is relevant for human exposure practical situations. For most animal investigations, rodents are used (mainly rats and mice). Biologists have extensive experience in handling these animals (especially mice) and their size allows a large number of animals to be exposed simultaneously at relatively

low cost. Two main types of exposure can thus be undertaken, either whole body or just the head. In recent years, most experiments relating to the biological effects of personal communications electromagnetic fields have been whole-body exposures of animals. These were performed in TEM cells, with the disadvantages of the limited size (one or two rats per TEM cell) and of field distortion. Waveguides have been used (either rectangular or circular), and cavities may also be designed for animal exposures. One of the 'simplest' ways is to use far-field plane-wave irradiation where animals and antennas have to be placed in an anechoic environment. Animals can be either confined, so that their position relative to the polarisation of the field is determined, or they are allowed move freely to avoid the stress caused by confinement. The microwave radiation can be linearly polarised or not. Head-only (or head-mainly) exposure of animals has now become more important. One problem with rodents is their small size relative to the wavelength: it is difficult to ensure that a predetermined SAR distribution is obtained in the head of the animal. Since most experiments are done with rats and mice, exposure systems have been designed for use with these species. Some groups use a 'carousel' arrangement in which all animals are facing a single whip antenna. Recent dosimetric studies have confirmed that most of the energy is absorbed in the head. However, the SAR distribution pattern may not be very similar to that for human beings and the electromagnetic coupling between the animals should be taken into account. An open waveguide could be used for the same purpose but this would mean that one waveguide is used for each animal. A promising method is being tried in which one or two loop antennas are used to irradiate the heads of rodents. The magnetic field produced by this type of antenna induces currents within the head similar to those induced by a handset in a human head.

2.4.3 Human (laboratory) research

Recently, results of experiments with people using actual functioning handsets have been reported. In these cases there is no need to design an exposure system but all parameters that are critical in dosimetric terms have to be controlled. Where handsets are used, the way in which they are operated is of major importance (test, or stand-by, or listening modes, normal or worst-case position, side of the head and movements, duration, intermittence, etc). In addition, great care should be taken to eliminate interference between the fields of the handset and measurement of physiological parameters, like EEG. Standardisation of exposure conditions is a possible way of improving comparisons between different experiments.

2.5 Conclusions and recommendations for dosimetry and exposure systems research

In order to acquire reliable experimental data on possible adverse effects in human, it is essential to perform careful laboratory investigations. Along with the choice of biological models, it is necessary to design appropriate new exposure systems or to improve existing ones. For that purpose, it is recommended that work on exposure systems should constitute a significant part of the research programme, and that physics laboratories should, if possible, work together to design and build apparatus that will be used jointly by several biology laboratories. This will greatly facilitate control and intercomparison of biological data. The following recommendations are made:

- design and testing of exposure systems for *in vitro* and *in vivo* experiments, including position and orientation of the specimen or animals
- for *in vitro* systems, characterisation and control of relevant exposure parameters
- for *in vivo* systems, characterisation of tissue values of SARs

- exposure conditions should correspond to those relevant to the use of a radiotelephone – for comparison, other exposures may also be appropriate
- for human studies, assurance of well-defined exposure conditions
- in all cases, environmental factors should be monitored and controlled.

3 Biology

3.1 Introduction

It is not the purpose of this report to provide an in-depth review of the biological effects of electromagnetic fields in relation to human health – several such reviews already exist (NRPB, 1993; UNEP/WHO/IRPA, 1993) – but rather to identify and summarise relevant studies that have been carried out and published, to identify and provide information about on-going studies, and to recommend areas of further research relevant to an assessment of the risk to human health that might arise from the use of radiotelephones.

Thermal effects from exposure to radiofrequency fields and microwave radiation are relatively well understood and have been the basis for standards setting for a long time. There is a lively debate on non-thermal effects for which no convincing adverse effect has, as yet, been demonstrated. However, it has been suggested that there are specific biological effects that correspond to a negligible increase in macroscopic temperature.

In this chapter, existing peer reviewed studies are summarised, focusing mainly on non-thermal effects and those applicable to the use of radiotelephones and human health. Only effects that occur within the normal physiological temperature range of the body are addressed. An overview is given of on-going research in each of the following subdisciplines: genetic, cancer, immune system, nervous system, and other effects.

The Expert Group also considered developmental studies related to radiofrequency exposure and noted that where such effects have occurred they have been due to heating. Because of this, and the nature of exposure to radiotelephones, developmental studies have not been included in this report.

Recommendations for future research are given; these are based on the identification of existing gaps in knowledge.

3.2 Review of published and on-going work

3.2.1 Biophysical interactions

3.2.1.1 Electromagnetic field interactions at the microscopic level

Classical approach A classical approach is usually adequate to describe the interaction due to forces that the local electromagnetic field exerts on the free and bound electrical charges of a biological system. While forces acting on charges depend only on the electromagnetic field (the sum of endogenous and exogenous fields) and on the electrical characteristics of the charges, the dynamics (vibrations, displacements, rotations) also depend on other properties, such as chemical bonds and collisions, and on the endogenous fields created by neighbouring charges.

Electromagnetic forces and torques may induce different effects, such as the displacements of free charges (mainly ions) from their unperturbed position, vibrations in bound charges (electrons in atoms, atoms in molecules) and rotation and reorientation of dipolar molecules (mainly molecules of water and neutral proteins) (Schwan, 1988). In the frequency range of radiotelephones, the displacement and rotation of cells, the formation of pearl chains of cells, and the deformation or fusion of cells are of no significance, and the main process is relaxation of water.

Electromagnetic fields interact with charged particles via the Lorentz force which, for cells, varies inversely with the cube of the cell radius. Some models have been developed to describe the effects of external fields on charged particles moving in and out of enzymes (Chiabrera, 1995).

There are very few biological materials with magnetic properties. Examples are ferrimagnetic crystals found in certain bacteria or in the heads of pigeons. In such cases an interaction with magnetic fields has to be considered (Rosen, 1994). Magnetic fields can influence the orientation of dia- and paramagnetic molecules and the translation of ferro- and paramagnetic materials. Because of the large time constants of such interactions, it is assumed that this effect has no relevance for high frequency electromagnetic fields. Beside passive conduction and dielectric responses, frequency-dependent ionic gating currents through membrane channels are also present, but are not yet thoroughly understood. In this area research needs exist, especially for modulated radio frequency fields.

Quantum mechanical approach All atoms have electric and magnetic properties. The core and the shell of atoms are charged and show electric and magnetic multipole moments. Therefore, different coupling mechanisms with applied electromagnetic fields are possible, such as, for example, spin resonance with high frequency fields or the Zeeman effect with static magnetic fields. In principle, such quantum mechanical effects can occur in biological materials (Chiabrera and Bianco, 1996). However, for small to moderate field strengths it is not clear how these interactions at the atomic-level influence living systems. It is generally assumed that reactions due to such effects and molecules are negligible because of the short lifetimes of intermediate states in comparison with macroscopic effects such as heating.

3.2.1.2 Dielectric properties of biological materials

In biological materials the dielectric interaction with fields leads to a polarisation of bound charges and orientation of charged dipoles within characteristic times, as described above. Addressing the response of single cells, but in the context of ensembles of cells, it is useful to describe this mesoscopic response in terms of the dielectric properties of the material. For a spatially and temporally homogeneous medium, the material permittivity and conductivity tensors are both functions of the wave number and frequency. Their frequency dependence reflects the characteristic timescales of the material, their wave number dependence reflects the length-scales.

For small wave vectors, ie, much smaller than a characteristic length of the material (eg, the intercellular spacing in tissue), the permittivity and the conductivity do not depend on the wave vector and it is sufficient to examine frequency dependence only. This case of small wave vector limit is the one most commonly used and is considered below. The tensor character is omitted for isotropic materials.

Schwan (1957) was the first to experimentally identify the three different frequency response regimes in biological materials which may be attributed to different mechanisms. For the frequency range considered in this report, the γ-dispersion is the most important mechanism; the others (α- and β-dispersion) are mentioned only because it is not yet clear if they might play a role with respect to demodulated components of amplitude-modulated fields. The α-dispersion mainly results from the displacement of the counterion layer bound to the membrane surface, the permittivity decreases by nearly two orders of magnitude from dc to 1 kHz, whereas the conductivity increases by a factor of only 2 or 3. The huge dielectric membrane barrier shields the cell cytoplasm from fields outside the membrane. In principle, α-dispersion has a time constant which is too large for pure radiofrequency fields to be effective. However, modulated radiofrequency fields may contain slow components which could lead to an interaction with the counterion layer and even result in resonance effects of the ion cloud.

The frequency range of β-dispersion is approximately 0.1–10 MHz. For frequencies greater than a few MHz, the membrane no longer shields the cytoplasm properly and, consequently, a large part of the current may

reach the interior of the cell. There it affects cellular organelles like mitochondria or the nucleus which, due to their small size, shift the relaxation curves towards higher frequencies. Below the β-dispersion range, the maximum voltage across the membrane (of a spherical cell) is proportional to the field strength in the extracellular fluid and to the radius (Schwan, 1988). It superimposes the existing resting potential of the membrane and shows the same time-dependence as the external field.

At frequencies greater than approximately 100 MHz, γ-dispersion occurs. The conductivity shows a large and sharp increase around 10 GHz. This effect is mainly the result of the polarisation of water, which has a characteristic frequency of about 20 GHz (room temperature, pure water). Bound water (in tissue) may have relaxation frequencies as low as a few GHz, due to its larger size and smaller mobility. Additionally, there are contributions from cellular proteins. As the protein structure possesses a sufficient degree of freedom to rotate with the field, it also has the effect of broadening the tail of the β-dispersion overlapping with the γ-dispersion. In the γ-dispersion range, the voltage across the membrane decreases with increasing frequency and becomes of no significance at frequencies exceeding 100 MHz.

The main consequence of γ-dispersion is the production of heat.

3.2.1.3 Amplitude modulated interactions

Different biological effects of amplitude-modulated fields have been discussed in the scientific literature (eg, Merritt et al, 1995; Walters et al, 1995). However, for none of these microeffects (such as molecular and conformational changes, alterations in chemical reaction rates, local thermal damage, membrane effects or electroporation, and electrofusion) is it clear what relevance *in vitro* results have for *in vivo* systems.

Consequently, the origin of most macroscopic findings, for example, cognitive or perceptional functioning (Raslear et al, 1993) or degenerative changes in the eye (UNEP/WHO/IRPA, 1993) are unclear and the effects themselves have to be confirmed.

Recent research has given rise to the assumption that the demodulated low frequency components of amplitude-modulated high frequency fields may be crucial in non-thermal effects (Litovitz et al, 1996). Experiments are continuing and other hypotheses, such as the effect of incoherent noise fields, are being tested.

Theoretical models and laboratory studies indicated cell membranes as probably a major site of interaction with ELF-modulated fields (Adey, 1996). They have determined sequences in the coupling of cell surface signals to a cascade of enzymatic mechanisms inside cells. Effects of these fields have been noted as possibly playing a role in:

- regulation of the immune system
- modulation of brain and central nervous system functions, including regulation of the pineal gland and its hormone melatonin
- regulation of cell growth, through enzymatic mechanisms mediating DNA synthesis and repair
- apparently acting at cell membranes with chemical cancer promoters, or with the body's intrinsic hormonal mechanisms, as co-factors in tumour formation.

There is a need to research such effects further in order to understand their relevance, if any, to microwave exposure and human health.

3.2.2 Biological effects

3.2.2.1 Genetic effects studies

Possible effects on DNA or chromosome structure in somatic cells are considered to be very important as these changes can be associated with cell death or, possibly, with the development of cancer. Furthermore, such

effects in male or female germ cells may lead to surviving mutations passed on to the next generation. Many investigations of radiofrequency-induced genetic effects in somatic as well as in germ cells have thus been conducted in many different cell and animal systems (Léonard et al, 1983; Saunders et al, 1991; UNEP/WHO/IRPA, 1993; Brusick, 1995; Verschaeve, 1995; 1996). Here only the more recent or most relevant papers will be cited (see Tables 3.1 and 3.2). The Expert Group also considered published studies involving the use of bacteria and yeast and noted that the outcome of these was invariably negative (for example, Léonard et al, 1983). This large volume of data has therefore not been included in the tables of published studies. The Expert Group also notes an on-going study using yeast (Kohli) and any recommendation for further work using yeast should await the outcome of this study.

Published studies

In vitro studies Investigations on different cell systems provide evidence for a lack of direct genotoxic and mutagenic effects of continuous and pulsed microwave radiation at different power densities. Yet there have been a number of reports showing genetic damage in cells or organisms following radiofrequency exposure, but most often they could be ascribed to heating. Most positive effects referred to in Table 3.1 were clearly thermal in nature. The non-thermal positive responses were possibly due to so-called sporadic positive responses (Brusick, 1995). Reviews of assays used to detect DNA alterations have shown that such sporadic positive responses are, indeed, obtained from time to time. Additionally, as seen in Table 3.2, no synergistic effect was found between the applied field and a number of known mutagens (eg, mitomycin C, adriamycin, proflavin) when the exposures to microwave radiation and to mutagens were simultaneous. However, when radiofrequency exposure precedes the mutagen, a synergistic effect is sometimes found. This was the case with mitomycin C in a recent investigation (954 MHz GSM base station antenna, SAR = 1.5 W kg^{-1}). A synergistic effect is also being studied for exposures at 450 MHz or 937 MHz but so far the results are not clear. According to another investigation, exposure to microwave radiation also increased the mutagenic properties of ethyl methanesulphonate (EMS) in chinese hamster ovary (CHO) cells (Gillois et al, 1980). These investigations reporting a synergistic action of radiofrequency fields with chemical or physical agents corroborate the earlier finding that microwave radiation exposure enhances, in human cancers, the effects of some cytotoxic agents (Holt and Nelson, 1976). So far no mechanistic studies have been conducted to explain the reported synergism.

In vivo studies Most studies reporting positive results were performed at power levels sufficiently high to induce heating. Yet some positive effects were observed at low exposure levels. Changes in metaphase counts and translocation numbers were observed in Balb/c mice that were exposed for 2 weeks to pulsed 9.4 GHz microwave radiation. In male CBA/CAY mice exposed to 2.45 GHz microwave radiation, increased chromosome exchanges and other cytogenetic abnormalities were found in germ cells exposed as spermatocytes. Another study attempted to replicate these findings but found chromosome aberration frequencies lower than previously reported and no difference between sham-exposed and exposed animals. As spermatogonial cells represent the greatest risk of accumulating genetic damage, exposures at this cell stage are particularly important. No evidence was found of radiofrequency radiation-induced reciprocal translocations in the recycling stem cells after acute or chronic exposure at 5 W kg^{-1}. Increased dominant lethality has been reported in some but not all investigations following acute or chronic exposure to microwave radiation.

Chromosome aberrations in somatic cells from *in vivo*-exposed laboratory animals were found by some investigators but could not be confirmed by others. The mutagenic effect of microwave radiation was also investigated using DNA analysis with synthetic oligo probes. Male Swiss albino mice were exposed to 2.45 GHz

continuous waves, for 2 hours per day, over different periods. Hybridisation profiles demonstrated altered band patterns of brain and testes DNA from exposed mice.

Using the alkaline comet assay, which is a sensitive method for assessing DNA strand breaks, DNA damage was found in brain cells of rats exposed *in vivo* to 2.45 GHz radiation at SAR values of 0.6 and 1.2 W kg^{-1}. This may be of particular importance with regard to the possible, but to date unproven, association between microwave exposure and brain tumour.

The latter two investigations produced quantitative data which are subject to sources of inter-trial variation and experimental error, such as incomplete DNA digestion (Sarkar et al, 1994) or unusually high levels of background DNA fragmentation (Lai and Singh, 1995). These experiments should, therefore, be replicated before the results can be used in any health risk assessment, especially given the weight of evidence suggesting that radiofrequency fields are not genotoxic. According to the above (and other) cytogenetic investigations, it is clear that caution must be exercised in drawing any general conclusion on the clastogenicity and genotoxicity of radiofrequency/microwave radiation.

Few studies have been performed on people. An increased incidence in micronucleated white blood cells from occupationally-exposed subjects was found in one investigation but it is not clear to what extent they were also exposed to other environmental influences. A previous cytogenetic investigation of radio-linemen who were almost solely exposed to radiofrequency fields gave negative results. In another study on maintenance workers occupationally exposed to microwave radiation of different frequencies, no cytogenetic effect was found when compared with non-exposed control subjects.

On-going studies At present several studies are being conducted on the genetic effects of radiofrequency fields alone or in combination with other environmental factors. Most refer to the GSM frequency (about 900 MHz) but some also include higher frequencies (for example, 1.8 GHz) that are characteristic of current personal telecommunication systems. Some of them are represented in Table 3.3; see also Appendix 2 where listings are in alphabetical order by country and location.

3.2.2.2 Cancer-related studies

The evidence for a clastogenic (chromosome breaking) or genetic effect of microwave radiation exposure is contradictory and, overall, it may be concluded that radiofrequency/microwave radiation is not genotoxic. Therefore, it may also be concluded that radiofrequency/microwave radiation is not a tumour initiator and that, if it is somehow related to carcinogenicity, this has to be by some other mechanism (eg, by influencing tumour promotion). Tumour promotion may be influenced by increases in cell proliferation rate via effects mediated through changes in proliferative signalling pathways, leading to enhanced transcription and DNA synthesis.

Published studies

In vitro studies (Table 3.4) Some reports suggest that radiofrequency fields may affect ion fluxes through cell membranes (important signalling mechanisms) via effects on ion pumps such as Na^+K^+-ATPase in human red blood cells exposed to radiofrequency and microwave radiation. Athermal effects were also reported on gross transcription as measured by incorporation of specific RNA or DNA precursors, ^{3}H-uridine or ^{3}H-thymidine. According to a series of papers, low level, low frequency, amplitude-modulated microwave radiation may affect intracellular activities of enzymes involved in neoplastic promotion without measurable influence on overall DNA synthesis. For example, a number of investigations showed some evidence of an effect on intracellular levels of ornithine decarboxylase (ODC) an enzyme implicated in tumour promotion. Tumour promoters increase ODC

synthesis. Where such effects have been observed with microwave exposure, they have been much weaker and have occurred only for certain modulations of the carrier wave.

Assays of cell transformation were performed in order to detect changes consistent with carcinogenesis. For example, Balcer-Kubiczek and Harrison (1991) exposed cells to 120 Hz modulated microwave radiation followed by treatment with a phorbol ester tumour promoter. Cell transformation was induced in a dose-dependent way (increase with increasing SAR value). Overall, these results are in agreement with those from earlier studies although there were also some inconsistencies. To date, the significance of these results is not clear in terms of *in vivo* carcinogenesis.

In vivo studies (Table 3.5) Along with investigations carried out *in vitro*, a number of *in vivo* investigations have also been performed. Of particular interest is, for example, the study conducted by Szmigielski et al (1983), who observed faster development of benzo(a)pyrene-induced skin tumours in mice that were exposed for some months to subthermal 2450 MHz microwave radiation. Also of interest is a study where 100 rats were exposed from 2 to 27 months of age to pulsed microwave radiation (0.4 W kg^{-1}) (Guy et al, 1985). The exposed group had a significant increase in primary malignant lesions compared with the control group when lesions were pooled regardless of their location in the body. Yet, overall, there was no clear evidence of an increase in tumour incidence as a result of exposure to microwave radiation. In another study, the effects of exposure to electromagnetic fields on a rat brain glioma model was investigated. The exposure consisted of 915 MHz microwave radiation, both as continuous wave and ELF-modulated (Salford et al, 1993). The extensive daily exposure did not cause tumour promotion. However, the experimental model has sometimes been questioned as the experimental animals had a high rate of spontaneous tumours. In another investigation in which cancer cells (B16 melanoma) were injected into animals, a lack of effect of exposure to continuous wave and pulsed radiofrequency radiation on tumour progression was observed (Santini et al, 1988). Overall, evidence for a co-carcinogenic effect of microwave radiation on tumour progression is not substantiated. The few positive results which do exist are, however, sufficiently indicative to merit further investigation.

On-going studies As for genetic studies, there are a number of cancer studies presently being conducted. Available data (sometimes incomplete) are summarised in Table 3.6.

3.2.2.3 Immune system studies

In view of the important role of the immune system as a defence against micro-organisms, and cancer cells, the effects of radiofrequency/microwave radiation exposure on it have been studied actively.

The immune system is composed of two main components: the humoural system (antibodies and complement), and the cellular system (lymphoid and phagocytic cells). It may also be divided into natural and acquired mechanisms, the latter being mediated via the lymphocytes. Desirable consequences of immunity are well-known – natural resistance, recovery and acquired resistance – but there are also detrimental aspects – auto-immunity, graft rejection and hypersensitivity. There is plenty of adaptability and redundancy built in to the immune system via self-regulation and through interaction with the nervous and endocrine systems. The vast majority of cells in the immune system are derived from precursors in the bone marrow and circulate in the blood; this constitutes the haemopoeitic system. Since bone marrow is not particularly exposed to radiotelephone emissions, data on effects on the haemopoeitic system may not be very relevant. However, cutaneous elements of the immune system which are in close contact with foreign antigens may be modified by radiofrequency radiation exposure (Dhabhar and McEwan, 1995).

Very few experiments have been undertaken so far that are specifically designed to study relevant effects on the immune system of the microwave radiation from personal telecommunications. Most published studies considered whole body exposure corresponding to the use of radar and industrial equipment. The microwave radiation was either pulsed (radar) or continuous wave (ovens, etc) at high power levels. In contrast, exposure to handheld radiotelephones is such that the main target is the head, the emitted power is low, and the carrier frequency is in the GHz range, with amplitude, phase, or frequency modulation.

There have been many reviews of the effects of radiofrequency radiation on the immune system, such as those by Roberts (1983); Smialowicz (1984); Budd and Czerski (1985); Smialowicz (1987); Saunders et al (1991); Polson and Heynick (1994). More recent reviews have addressed the specific situation of personal telecommunications (Carlo et al, 1994; Barnett, 1994).

Since one of the main issues in health risk analysis has been cancer, and in view of the important role of the immune system in controlling the proliferation of cancer cells, numerous laboratory studies have been performed at various power levels and frequencies. Some of the results are collected in Tables 3.7–3.11. These selected publications correspond to either *in vitro* experiments conducted at the well-controlled temperature of the culture medium or, in the case of animals, to experiments in which there was no measurable or expected increase in core temperature.

Published studies

In vitro studies (Table 3.7) Most experiments have been performed on lymphocytes in culture, either activated with mitogens or not. Since most of these physiological processes are temperature-dependent (eg, B-lymphocyte capping), careful control of the temperature of the culture under exposure was of primary importance.

A very clear picture emerges from these data regarding the absence of effects on cells exposed to continuous wave microwave radiation. However, a few results obtained at low SAR were found to depend upon specific ELF amplitude modulation: the cytotoxicity of lymphocytes at 60 Hz (Lyle et al, 1983) and kinase activity in lymphocytes at 16–60 Hz modulation (Byus et al, 1984).

In conclusion, very few positive results have been obtained *in vitro* that are relevant to the effects of radiofrequency radiation on the immune system. ELF modulation appears to be a key factor but, in any case, the effects of microwave exposure on cellular systems are not great.

In vivo short-term experiments (Table 3.8) Several acute or subchronic studies have been performed at moderate or low power levels, and their results are summarised where only experiments corresponding to a small or negligible increase in core temperature are included (below about 5 W kg^{-1} for rats). At this exposure level, thermo-regulation can still be a source of stress. This points towards a possible role for the hypothalamus, which is a key element of thermo-regulation and could be a direct target for fields emitted by radiotelephones, albeit screened by the head.

Many of the positive effects are transient (Huang and Mold, 1980; Smialowicz et al, 1982b) and similar to those caused by thermal stress, being related to physiological changes related to thermo-regulation (Liddle et al, 1980). A good example is that of the effects on natural killer cells, which have a role in tumour surveillance and whose activity is temperature and/or stress-hormone dependent (Smialowicz et al, 1983; Yang et al, 1983).

Because of the natural complexity of the immune system, and the variety of biological models and exposure systems, it is difficult to unambiguously attribute published experimental effects to microwave exposure. Because of the many regulation processes built-in to the immune system, an adaptative response to the stimulus is expected. Therefore, a time dependence of the response is not unlikely (eg, Huang and Mold, 1980).

In vivo long-term experiments (Table 3.9 Guy (1994) has reviewed the few long-term experiments performed using microwave exposure. The main results are summarised in Table 3.9. It appears that such experiments yield few unambiguous effects of exposure on the immune system *per se*. The best example might be that of the major study by Chou et al (1992), using many animals. There is still a debate about tumour incidence at the end of exposure but immune parameters assessment showed a transient alteration half-way through exposure that was not reproduced in a subsequent experiment. This may show the high degree of adaptability of the immune system. However, it should not be concluded that such long-term experiments are unnecessary, since they correspond to health risk situations and are best suited to demonstrate effects on endpoints such as tumour incidence, which are related to immune surveillance.

On-going studies

In vitro studies (Table 3.10) Details of on-going studies for *in vitro* systems are given in Table 3.10.

In more recent on-going work, amplitude modulation was set according to the various TDMA systems (mainly GSM at 217 Hz and American TDMA at 50 Hz) and, under these conditions, most of the results obtained have been negative. There are new endpoints being used, such as measurement of intracellular calcium and ODC activity, which should soon yield some new information about early events in the interaction of cells with radiofrequency/microwave radiation.

In vivo studies (Table 3.11) Details of an on-going *in vivo* study is given in Table 3.11.

On-going work is mainly addressing the problem of cancer via tumour incidence. Recently, negative results were obtained (Chagnaud et al, 1995) on rats exposed to GSM-modulated microwave radiation.

In summary, while thermogenic levels have been shown to have an effect (on stimulation of B-lymphocytes but not T-lymphocytes (Wiktor Jedrzejczak et al, 1977)), low-level microwave exposure seems to have little direct effect on the immune system *in vivo*. However, the role that stress (due to either thermoregulation or confinement, or both) may play, in particular on the cell-mediated immune response (delayed type hypersensitivity), should be taken into account when interpreting results or planning experiments.

Table 3.1 Published studies on radiofrequency fields-induced genetic effects

Reference	Exposure characteristics	Biological model	Biological endpoint	Results	Comments
***IN VITRO* STUDIES**					
Hamrick,1973	2.45 GHz cw, 94 mW cm^{-2}	Commercialised calf thymus DNA	Analysis of thermal denaturation curves	No difference with unexposed DNA	Control and exposed DNA solutions were maintained at the same temperature
Yao, 1976	2.45 GHz, 15.2 W kg^{-1}	Rat kangaroo cells	Chromosome aberrations	Increased incidence of unstable chromosome aberrations	The observed aberrations are more commonly associated with ionising radiations
Alam et al, 1978	2.45 GHz, 0–200 mW cm^{-2}	Chinese hamster cell lines	Cytological effects	Cytological effects (nuclear vacuoles, pycnic and decondensed chromosomes, chromosome breakage) observed under elevated temperature conditions	
Yao, 1982	2.45 GHz, 15 W kg^{-1}, long-term exposure (over 320 d)	Rat kangaroo cells	Chromosome aberrations	Increased chromosome aberration frequency	A change in cell population by repeated passage of the cells and senescence may have influenced the results
Lloyd et al, 1984; 1986	2.45 GHz, cw, 20 min exposure, SAR: 104–200 W kg^{-1}	Human lymphocytes	Chromosome aberrations and sister chromatid exchanges	No evidence of cytogenetic damage	Mild hyperthermia
Garaj-Vrhovac et al, 1990	7.7 GHz, 2 W max. power output, SAR not reported	V79 chinese hamster cells	Cytogenetic effects	Increased [^{3}H] thymidine incorporation and chromosome aberrations	Thermal effect probable
Garaj-Vrhovac et al, 1991	As above	V79 chinese hamster cells	Cytogenetic effects	Effect on colony forming ability, chromosome aberrations and micronuclei	Thermal effect probable
Garaj-Vrhovac V et al, 1992	As above	Human lymphocytes	Cytogenetic effects	Chromosome aberrations and micronuclei	Thermal effect probable

min ≡ minutes; h ≡ hours; d ≡ days; w ≡ weeks; mo ≡ months; y ≡ years

Table 3.1 (continued)

Maes et al, 1993	2.45 GHz, 50 Hz modulated, 30 and 120 min exposure, 75 W kg^{-1}	Human lymphocytes	Chromosome aberrations, micronuclei and sister chromatid exchanges	Increased frequency of chromosome aberrations and micronuclei. No microwave induced sister chromatid exchange frequency or influence on the cell proliferation.	Temperature computer-controlled at 0.1 °C during the complete exposure time
Maes et al, 1995	0.954 GHz from a GSM base station, cw, 60–120 min exposure	Human lymphocytes	Chromosome aberrations	Slight increase in chromosome aberration frequency after exposure	No increased DNA damage according to the alkaline comet assay (unpublished results)
Eberle et al, 1996	TEM or GTEM-cells; 440, 900 and 1800 MHz, exposure at 37 °C over 39–70 h	Human lymphocytes	Chromosome aberrations, sister chromatid exchanges, micronuclei, cell proliferation, HGPRT-mutations	No indications of any radiofrequency-induced cytogenetic damage	
***IN VIVO* STUDIES**					
Mittler, 1976; 1977	29, 146.36 and 98.5 MHz	*Drosophila melanogaster*	Sex-linked recessive lethal mutations	No effect	
Huang et al, 1977	2.45 GHz, SAR up to 21 W kg^{-1}	Chinese hamsters	Chromosomal aberrations in blood lymphocytes	No effect	Rectal temperature increase of 1.6 °C in the high exposure group. Long cell cultivation time following exposure may disadvantage cells with cytogenic damage
Hamnerius et al, 1979	2.45 GHz, 6 h exposure at SAR = approx. 0.1 W kg^{-1}	*Drosophila melanogaster*	Somatic mutations for eye pigmentation in embryos	No effect	
Manikowska et al, 1979	9.4 GHz, pulse-modulated, 1–100 W m^{-2}, 1 h d^{-1} over 2 weeks	Male Balb/c mice	Chromosome aberrations in male germ cells exposed as spermatocytes	SAR dependent increase in the frequency of chromosome exchanges and other cytogenetic effects	
McRee et al, 1981	2.45 GHz, SAR = 21 W kg^{-1}, chronic exposure 8 h d^{-1} for 28 d	Mouse	Sister chromatid exchanges in bone marrow cells	No effect	
Hamnerius et al, 1985	27.12 MHz, cw and pulsed, SAR <0.05–110 W kg^{-1}, 6 h exposure at 25 °C	*Drosophila melanogaster*	Somatic mutations for eye pigmentation	No effect	Difference in temperature of treated and non exposed animals was less than 0.3 °C

min ≡ minutes; h ≡ hours; d ≡ days; w ≡ weeks; mo ≡ months; y ≡ years

Table 3.1 (continued)

Manikowska-Czerska et al, 1985	2.45 GHz, SAR = 0.05–20 W kg^{-1}, 6 h over a 2 week period	Male CBA mice	Chromosome aberrations in male germ cells exposed as spermatocytes	SAR dependent increase in the frequency of chromosome exchanges and other cytogenetic damage	
Marec et al, 1985	2.375 GHz, cw, 15 W cm^{-2}, 60 min, 20 W cm^{-2}, 10 min, 25 W cm^{-2}, 5 min for 5 d	*Drosophila melanogaster*	Sex-linked recessive lethal mutations	No effect, except a significant decrease in the number of offspring in the group exposed to 15 W cm^{-2}. No cumulative effect of repeated exposures on the mortality of treated males and no effect on the sex ratio of the offspring	The effect on the number of F1 offspring in the 15 W cm^{-2} exposed group was considered to be due to a negative thermal effect of the microwave radiation on the male germ cells
Beechey et al, 1986	2.45 GHz	Male $(C3Hx101)F_1$ mice	As above	No difference between sham-exposed and exposed animals	Rectal temperature in the highest exposed group rose by up to 3°C
Sarkar et al, 1994	2.45 GHz, cw, 2 h d^{-1}, 12, 150 & 200 d, 0.1 W m^{-2}, SAR = 1.2 W kg^{-1}	Male Swiss albino mice	DNA analysis with synthetic oligo probes	Altered band patterns of brain and testes DNA from exposed mice	
Lai & Singh, 1995; 1996	2.45 GHz, pulsed, 2 µs pulse width, 500 pps, or cw, 2 h exposure, SAR = 1.2 W kg^{-1}	Male Sprague-Dawley rats	DNA damage by the single cell gel electrophoresis assay	Increased DNA damage for both continuous and pulsed fields	
INVESTIGATIONS ON HUMANS					
Garson et al, 1991	Professionally exposed subjects; frequencies ranging from 400 kHz to 20 GHz	Human lymphocytes	Chromosome aberrations	No increase in chromosome damage found in radio-linemen working with radiofrequencies at or below occupational exposure limits	Exposure to radiofrequency-fields is relatively pure (no other occupational exposures known)
Fucic et al, 1992	Professionally-exposed subjects 10 µW cm^{-2}, frequencies ranging from 1250 to 1350 MHz	Human lymphocytes	Micronuclei	Increased micronucleus frequency in exposed subjects compared with controls	Workers exposed to other environmental influences?

min ≡ minutes; h ≡ hours; d ≡ days; w ≡ weeks; mo ≡ months; y ≡ years

Table 3.2 Published studies on the synergy between radiofrequency fields and known mutagens

Reference	Exposure characteristics	Biological model	Biological endpoint	Results
Ciaravino et al, 1987	2.45 GHz pulsed, 49 mW cm^{-2}, SAR = 34 W kg^{-1} Cells simultaneously irradiated and mytomycin C (MMC) exposed	CHO cells	Sister chromatid exchanges (SCEs)	No increased SCE frequency in cells exposed to radiofrequency radiation alone or with MMC compared with MMC alone
Meltz & Walker, 1987	350 MHz, 850 MHz and 1.2 GHz, pulsed 1–10 mW cm^{-2}, SAR = 0.39–4.5 W kg^{-1} Radiofrequency exposure of cells after ultraviolet radiation exposure	Human diploid fibroblasts	DNA repair	Radiofrequency radiation alone, either continuous or pulsed, has no effect on DNA repair. Radiofrequency exposure after ultraviolet damage also had no effect
Ciaravino et al, 1989	2.45 GHz pulsed, 49 mW cm^{-2}, SAR = 33.8 W kg^{-1} Cells simultaneously irradiated and adriamycin exposed	CHO cells	Cell cycle progression and SCEs	Radiofrequency exposure does not affect changes in cell progression caused by adriamycin. It does not change the number of SCEs induced by adriamycin
Meltz et al, 1989	2.45 GHz, pulsed, 48.8 mW cm^{-2} SAR = 30 W kg^{-1} Cells simultaneously irradiated and MMC exposed	L5178Y mouse leukaemia cells	Forward mutation assay (thymidine kinase locus)	Radiofrequency exposure alone is not mutagenic. It does not affect either inhibition of cell growth or the extent of mutagenesis resulting from treatment with MMC alone
Kerbacher et al, 1990	2.45 GHz, pulsed 49 mW cm^{-2}, SAR = 33.8 W kg^{-1} Cells simultaneously irradiated and exposed to MMC and adriamycin	CHO cells	Chromosome aberrations	Radiofrequency radiation alone does not enhance chromosome aberration frequency. No alteration in the extent of chromosome aberrations for the combined treatment compared with the chemicals alone
Meltz et al, 1990	2.45 GHz, pulsed, SAR ~ 40 W kg^{-1} Cells simultaneously exposed to proflavin	L5178Y mouse leukaemic cells	Forward mutations at the TK-locus	Radiofrequency radiation alone is not mutagenic. No increase in mutation frequency for combined treatment compared with proflavin alone. No difference in colony size distribution of mutant colonies
Maes et al, 1996	954 MHz, continuous, 15 W, 49 V m^{-1}, SAR = 1.56 W kg^{-1} Cells exposed to MMC following radiofrequency irradiation (during lymphocyte cultivation)	Human lymphocytes	SCEs	Radiofrequency radiation alone did not increase SCE frequency. SCE frequency for combined treatment was always higher than for MMC alone. No change in cell proliferation compared with control cultures

min ≡ minutes; h ≡ hours; d ≡ days; w ≡ weeks; mo ≡ months; y ≡ years

Table 3.3 On-going studies on radiofrequency fields-induced genotoxicity

Researchers	Exposure conditions	Biological model	Biological endpoint	Results	Comments
	837 MHz, specially constructed TEM cell	Bacteria (see endpoints)	Ames test, *E. coli* WP2*uvr*A reverse mutation assay, L5178Y TK-mouse lymphoma forward mutation assay		WTR sponsored research; will start in Autumn 1996 and last 15 months
Verschaeve L, Lai H, Tice R	837 MHz, specially constructed TEM cell	Human lymphocytes	Comet assay (single strand DNA breakage) and micronucleus test		WTR sponsored research; will start in Autumn 1996 and last approx. 6 months
Verschaeve et al	Occupational exposure. Telecommunication workers being exposed to several electromagnetic frequencies including 900 MHz frequency band	Peripheral blood lymphocytes	Chromosome aberrations and DNA damage (comet assay)	So far no cytogenetic damage found	Investigation ends Autumn 1996
Kohli G	900 MHz, 10 W max, GSM modulation. Two Faraday cages with exposed and sham parallel treatment	*Saccharomyces cerevisiae* constructs	Forward and reverse mutation, homologous recombination and 'petite' mutation		Investigation ends December 1997

min ≡ minutes; h ≡ hours; d ≡ days; w ≡ weeks; mo ≡ months; y ≡ years

Table 3.4 Published *in vitro* studies on cancer

Reference	Exposure conditions	Biological model	Biological endpoint	Results	Comments
Stofolnik-Baranska, 1967	Cells in test-tubes exposed for 3–5 d in anechoic chamber to pulsed 10 cm microwave radiation from a box horn antenna	Human lymphocytes	Lymphoblasto-EFd transformation	Induction of lymphoblasto-EFd transformation by microwave radiation	According to control experiments, the effects were not due to a heating effect
Balcer-Kubiczek & Harrison, 1985; 1989; 1991	Amplitude-modulated microwaves, SAR = 0.1–4.4 W kg^{-1}, eventually combined with X-rays, followed by treatment with TPA	C3H10$T^{1/2}$ cells	*In vitro* cell transformation	Enhanced cell transformation	Some inconsistency was found between the different studies. Furthermore, C3H10$T^{1/2}$ cells are chromosomally abnormal and their response to proliferative stimuli may be atypical
Allis & Sinha-Robinson, 1987	2.45 GHz	Human red blood cells	Na^+K^+-ATPase activity	Inhibition of Na^+K^+ ATPase activity	
Byus et al, 1988	Amplitude-modulated 450 MHz radiation, 10 W m^{-2}, eventually after TPA application	Reuber H35 hepatoma cells, CHO cells and 294T human melanoma cells	ODC activity	Increased ODC activity	
Krause et al, 1990; 1996	Amplitude -modulated microwaves, SAR = 3 W kg^{-1}	Mouse fibroblasts	ODC activity	Increased ODC activity	Increase is at much lower level than treatment with a chemical promoter
Cleary et al, 1990a; b	2.45 GHz, cw, SAR = 5–20 W kg^{-1}	Glioma cells or human lymphocytes	RNA precursor ^{3}H-uridine or DNA precursor ^{3}H-thymidine incorporation	Elevated transcription and proliferation at SAR = 25 W kg^{-1} but unchanged at higher SARs	
Cleary et al, 1996	27 MHz or 2.45 GHz cw, SAR = 5 or 25 W kg^{-1}	CHO cells	Cell cycle alterations	Cell cycle alterations found at both frequencies, 2.45 GHz being more effective in inducing alterations	Exposure under 'isothermal' conditions (37 ± 0.2 °C)

min ≡ minutes; h ≡ hours; d ≡ days; w ≡ weeks; mo ≡ months; y ≡ years

Table 3.5 Published studies on radiofrequency fields-exposed laboratory animals

Reference	Exposure characteristics	Biological model	Biological endpoint	Results	Comments
Prausnitz & Susskind, 1962	9.27 GHz, pulsed at 500 pps, 1000 W m^{-2} 4.5 min d^{-1}, 5 d w^{-1} for 59 w	Swiss mice	Post-mortem analysis	Microwave-induced leucosis	The investigation was criticised for several reasons
Spalding et al, 1971	800 MHz, 2 min d^{-1}; 5 d w^{-1} over a period of 25 w. SAR up to 1.5 W kg^{-1}	RFM adult mice	Effect on longevity	No significant increase in the life-span of the exposed mice compared with the controls. No significant changes in mean red and white blood cell counts	
Preskorn et al, 1978	2.45 GHz, 35 W kg^{-1}; 20 min d^{-1} during days 11–14 of gestation	CFW mice exposed *in utero*. Mice injected with lymphoreticular sarcoma cells at age 16 days and further irradiated or not	Tumour incidence	Significantly lower tumour incidence in mice irradiated *in utero* and irradiated or sham-irradiated postnatally. Mice irradiated *in utero* and followed for 36 months had a lower tumour development rate initially but then the rate increased to become similar	
Roszkowski et al, 1980	2.45 GHz, 500 W m^{-2} SAR = 25 W kg^{-1}; 2 h d^{-1} for 7 d	BALB/c mice injected with mouse sarcoma cells prior to irradiation	Tumour growth and lung metastases	Temporary tumour regression followed by renewed growth 12 days later. More lung metastases in the exposed group compared with controls but mean survival time greater in exposed animals (53 days vs 38 days)	
As above	As above	As above, but irradiation prior to injection of sarcoma cells	As above	Significantly accelerated tumour growth and increase in the number of lung metastases. Mean survival time shortened in irradiated mice	

min ≡ minutes; h ≡ hours; d ≡ days; w ≡ weeks; mo ≡ months; y ≡ years

Table 3.5 (continued)

Szmigielski et al, 1982	2.45 GHz, 50 or 150 W m^{-2}, SAR up to 3 and 8 W kg^{-1} respectively; 2 min d^{-1}, 6 min d^{-1}	C3H/He mice (irradiated at age 6 weeks to 12 months) or BALB/C mice irradiated 1 or 3 months prior to or simultaneously with exposure to benzo(a)pyrene	Effect of microwave radiation on tumour growth and lung cancer colony assay	SAR-dependent acceleration of both mammary tumours in C3H/HeA mice and skin tumours in BALB/c mice. Microwave exposure resulted in an increase in the number of L1-sarcoma cell colonies in the lungs of irradiated mice	C3H/HeA mice are genetically predisposed to mammary tumours. BABL/c mice were exposed to benzo(a)pyrene by skin painting (5 months treatment). 2–3 W kg^{-1} gave results similar to the effect of overcrowding (chronic stress). E-field orientation with respect to the animals unknown. Effect of confinement uncertain
Guy et al, 1985; Kunz et al, 1985	Low level pulsed 2.45 GHz waves, SAR up to 0.4 W kg^{-1}; exposure from 2 to 27 months of age	Sprague-Dawley rats	Life-time study including determination of cause of death, frequency and site of neoplastic and non-neoplastic lesions	No clear evidence of an increase in tumour incidence as a result of exposure to microwave radiation	
Santini et al, 1988	2.45 GHz, cw or pulsed (10 µs pulses for 10 ms repeated at 25 Hz); SAR=1.2 W kg^{-1}	C57BL/6J mice, irradiation 15 d exposure prior to injection of 3 x 10^6 B16 melanoma cells and during subsequent tumour development	Effect of microwave radiation on tumour progression	No effect on the rate of development of melanoma or on mean survival time (25 d)	
Salford et al, 1993	915 MHz, cw (1 W) and modulated with 4, 8, 16 and 200 Hz in 0.5 ms pulses, and 50 Hz in 6 ms pulses (2 W per pulse)	Male and female Fisher rats	Brain tumour development following injection of RG2-glioma cells	No significant difference in tumour size between animals exposed to 915 MHz microwave radiation and those not exposed. No evidence of tumour growth promotion	The study is sometimes criticised because of the high background level of tumours in the animals
Wu et al, 1994	2.45 GHz, 10 mW cm^{-2} in anechoic chamber, 3 h d^{-1}, 6 d w^{-1} over a 5 mo period. SAR = 10–12 W kg^{-1}	BALB/C mice, 4 w of age. Animals injected with dimethylhydrazine (DMH) once per week during the course of the microwave treatment. A group DMH treated animals were also exposed to TPA once per week for 10 weeks from the third week on after initial treatment	Colon tumour incidence	The 2.45 GHz microwave radiation at 10 mW m^{-2} power density did not promote DMH-induced colon cancers in young mice	

min ≡ minutes; h ≡ hours; d ≡ days; w ≡ weeks; mo ≡ months; y ≡ years

Table 3.6 On-going studies on radiofrequency fields and cancer

Researchers	Exposure characteristics	Biological model	Biological endpoint	Results	Comments
Juutilainen J	902.5 MHz, cw, SAR = 1.5 W kg^{-1}, or pulsed (1/8 duty cycle, 217 Hz repetition rate), peak SAR = 2.8 W kg^{-1}	CBA/S mice exposed to 4 Gy ionising radiations as the tumour initiator	Tumour growth and survival	So far no effects on growth or survival	End of the study December 1997
Fitzner R et al	GTEM-cell, 1.8 GHz field pulsed with 217 Hz	Human leukaemia HL-60 cells	Growth behaviour for the investigation of cancer promoting effects (doubling time and thymidine kinase activity)	Already transformed leukaemia cells show no multiple increase in growth speed compared with control cells	
Persson R R & Salford L G	Pulsed or cw microwave radiation. Exposure in anechoic chamber	Fisher rats	Tumour growth and promotion *in vivo*. ODC levels in rats and mice	No effect on the growth of brain tumours implanted in the brain of Fisher rats exposed daily to cw or pulsed microwave radiation. Preliminary results indicate an increase in ODC and spermine levels in the rat brains exposed to pulse-modulated fields but not in rats exposed to cw fields	On-going study (no fixed deadline)
Veyret et al	Plane wave exposure at 900 MHz in anechoic chambers, up to 200 µW cm^{-2} GSM signal, 2 h d^{-1} for 2 w, SAR = 0.27 W kg^{-1}	Rats exposed *in vivo* (benzo(a)pyrene as tumour initiator) or cells in culture (GH3, Molt4, C6 cell lines) exposed in thermostatic containers (37 °C, 5% CO_2)	Growth of chemically-induced tumours in rats. Proliferation of cells exposed for 4 h assessed 24 and 48 h post exposure	No changes in date of appearance of tumours nor in survival of rats bearing tumours. No effect on the proliferation of cells exposed	Study ended by now
Marino C	Modified TEM cell operating at 900 MHz; standard dipole and small anechoic chamber. Whole body exposure of inoculated animals: various overall and daily exposure durations	Murine adenocarcinoma C3H mice	Tumour growth rate, tumour growth delay, kinetic analysis and cell proliferation	No difference observed among non-exposed, exposed and sham-exposed animals in terms of volume uptake, tumour growth rate and tumour growth delay (around 500 animals exposed since 1994)	Non-thermal effect studies still on-going
Bartsch & Bartsch	Exposures to GSM waves in individual exposure chambers	Rats exposed to DMBA as initiator	Cancer promotion. Co-promoting role of microwave radiation, melatonin levels monitored in urine	None yet	

min ≡ minutes; h ≡ hours; d ≡ days; w ≡ weeks; mo ≡ months; y ≡ years

Table 3.6 (continued)

Kwee S & Raskmark P	TEM cell. 960 MHz. Calculated electric field: 0.75 V m^{-1}	Human epithelial amnionic cells (AMA)	Proliferation using the MTT assay	Changes depending on SAR and on cell concentration	Needs replication in a better TEM cell under construction
Cain et al	TEM cell. 836.55 MHz. TDMA. SAR 0.78 and 7.8 mW kg^{-1}	C3H/10T1/2 fibroblasts. C6 glioma cells	Ornithine decarboxylase (ODC) activity	Under some culture conditions, ODC activity decreased by 50% in fibroblasts. No effects on C6 cells	Sponsored by Motorola
Litovitz et al, 1996	TEM cell.10 W m^{-2} , Modulations: 60 Hz AM, 60 Hz FM, and 50 Hz square wave, cw . Analogue and TDMA sources	L929 murine cells in culture	ODC activity	FM and cw signals had no effects AM caused a decrease in ODC activity	Superposition of incoherent ELF noise field suppressed the effect on ODC
Motzkin S	Replication of experiments of Cleary et al (1985)		Cell proliferation	In progress	Sponsored by Motorola
Repacholi et al	Pulsed fields (900 MHz) 2 x 30 min exposure for up to 18 mo to 1/4 λ monopole antenna, far-field exposure. SAR 0.01–4.2 W kg^{-1}	Eμ-pim1 transgenic mice	Effects of pulsed radiofrequency fields (900 MHz) on lymphoma incidence in mice	In progress	To be published
Adey et al, 1996	836.35 MHz, TDMA signal. 1/3 duty cycle. 50 packets s^{-1}. Brain SAR in near-field exposure = 0.75–1.00 W kg^{-1}	Pregnant rats receive a single dose of the carcinogen ENU on pregnancy day 18. Exposure starts on day 19. Near field exposure of offspring (n = 236) starts after weaning at day 35 and lasted 22 mo (4 d w^{-1}, 2 h d^{-1}, 7.5 min ON and 7.5 min OFF)	Incidence, type, location of spontaneous and chemically-induced tumours. Death rates	Exposure appeared to reduce incidence of spontaneous and malignant tumours. Survival rates were in a consistent progression: exposed/sham-exposed/ ENU+exposed/ENU+sham-exposed	Funded by Motorola

min ≡ minutes; h ≡ hours; d ≡ days; w ≡ weeks; mo ≡ months; y ≡ years

Table 3.7 Published immune system studies *in vitro*

Reference	Exposure characteristics	Biological model	Biological endpoint	Results	Comments
Hamrick & Fox, 1977	2.45 GHz, cw. 50, 100 or 200 W m^{-2} 4, 24 or 44 h exposure 0.7, 1.4 or 2.8 W kg^{-1}	Rat lymphocytes. Activation with mitogen (PHA) during exposure	Blast transformation monitored with tritiated thymidine	No effects	
Lyle et al, 1983	450 MHz, cw or AM (3, 16, 40, 60, 80 or 100 Hz) 15 W m^{-2} for 2 or 4 h, estimated SAR 0.047 W kg^{-1}	Effector cells: murine T-cells. Target cells: murine myeloma cells	Cytotoxicity of effector cells	No effects with cw. 20 % decrease in cytotoxicity with AM at 60 Hz and lesser effect at other frequencies	Dependence of effect on AM frequency. Effect is on T-cells. Decrease with time after exposure
Roberts et al, 1983	2.45 GHz, cw, 2 h, 0.5–4 W kg^{-1}	Human mononuclear leukocytes	Viability. Production of interferon	No effects	
Roberts et al, 1984	2.45 GHz, cw or AM (16 or 60 Hz), 4 W kg^{-1}	Human mononuclear leukocytes infected with influenza virus	Viability. DNA synthesis from mitogen activation	No effects	
Byus et al, 1984	TEM cell, 450 MHz, cw or AM at 3, 6, 16, 40, 60, 80, 100 Hz for 15, 30, 45, 60 min 10 W m^{-2}, $\Delta T < 0.1°C$	Human tonsil lymphocytes	Activity of protein kinases	No effects of cw or AM at 3, 6, 80, 100 Hz. Transient decrease in cAMP independent kinase activity at frequencies between 16 and 60 Hz	Dependence of effect on AM frequency. Specific identity of kinase unknown
Cleary et al, 1985	100 MHz, cw or AM (20 Hz), 37 ± 0.2 °C, 120–341 W kg^{-1}, 30 or 60 min	Rabbit peritoneal polymorpho-nuclear leukocytes (PMN)	Viability and phagocytic activity of PMN	No effects	Careful control of temperature, but large variability among control groups
Brown & Marshall, 1986	1.18 GHz, 55, 110 and 220 W m^{-2}, 18, 36.5 and 69 W kg^{-1}, 37.4 °C, 48 h exposure	Mouse erythroleukaemic cell line cultured with HMBA to induce differentiation	Cell differentiation	No effects	
Czerska et al, 1992	2.45 GHz, cw or pulsed (1 µs at 100 or 1000 pps) < 12.3 W kg^{-1} or conventional heating	Human lymphocytes	Blast transformation	Increased transformation as a function of temperature, pulsed microwave radiation more efficient than cw	Visual assessment of blast transformation

min ≡ minutes; h ≡ hours; d ≡ days; w ≡ weeks; mo ≡ months; y ≡ years

Table 3.8 Published immune system studies *in vivo* (short-term experiments)

Reference	Exposure characteristics	Biological model	Biological endpoint	Results	Comments
Huang & Mold, 1980	2.45 GHz, 50–150 W m^{-2}, 1–17 d, 3 h d^{-1} Anechoic chambers, SAR 11 W kg^{-1}	Female Balb/c mice	Immune parameters: response of spleen lymphocytes to mitogens (PHA and ConA). Tumour cytotoxicity of killer lymphocytes	Fluctuating response to mitogens. Activation of macrophages. No change in cytotoxicity	Peculiar time profile of the immune response may be due to factors other than radiofrequency radiation
Liddle et al, 1980	9 GHz, pulsed, 100 W m^{-2} SAR 3.3–4.7 W kg^{-1}, 2 h d^{-1} for 5 d	Mice	Response against pneumococcal polysaccharide. Survival of mice challenged with *S. Pneumoniae*	Increase in level of antibody and in survival time	Results not confirmed later by Liddle et al (1986) at 10 W m^{-2}, SAR 0.47 W kg^{-1}
Ortner et al, 1981	2.45 GHz, 8 h exposure, 20 and 100 W m^{-2} SAR 0.44 and 2.2 W kg^{-1}	Rats	Histamine release by basophils and peritoneal mast cells following exposure. Cell counts	No effects	
Smialowicz et al, 1982a	425 MHz pulsed or cw, up to SAR 8.6 W kg^{-1}	Mice	Immune parameters: lymphocyte activation, response to SRBC	No effects	No differences in effects of pulsed and cw microwave radiation
Smialowicz et al, 1982b	425 MHz, 4 h d^{-1} for 41 d, SAR 3–7 W kg^{-1}	4 x 6 pregnant rats exposed from day 12 of pregnancy to parturition. 4 pups/dam exposed for 20 or 40 d	Lymphocyte activation with mitogens	Increases in T and B lymphocyte activation in half of the experiments in lymph nodes but not in blood	Replication experiment successful on a group of six pregnant rats
Smialowicz et al. (1983)	2.45 GHz, 50, 150 and 300 W m^{-2} SAR 3.5, 10.5 and 21 W kg^{-1}, 1.5 h d^{-1} for 2–9 d	Mice	*In vitro* NK activity against lymphoma cells	NK activity suppressed at 21 W kg^{-1} but not at lower levels. Macrophage phagocytosis increased at 21 W kg^{-1}	Hydrocortisone (stress hormone) also caused a decrease in NK activity
Yang et al, 1983	2.45 GHz, cw, 1 h exposure, SAR 8 and 13 W kg^{-1}	Hamsters	NK activity measured *in vitro*	NK activity suppressed 4 h after exposure at 13 W kg^{-1} only	May be due to heating-induced increase in glucocorticosteroids
Veyret et al, 1991	9.4 GHz, AM at approx 20 MHz. SAR 0.04 W kg^{-1}, 6 d exposure	Male Balb/c mice	Immune response against SRBC	Alterations of antibody levels depending on modulation frequency	High frequency of AM: 20 MHz
Elekes et al, 1996	2.45 GHz, cw or 50 Hz amplitude-modulated, SAR 0.14 W kg^{-1}, 6 d	Male and female Balb/c mice	Immune response against SRBC	Increase in antibody levels in male but not in female mice	Not statistically significant

min ≡ minutes; h ≡ hours; d ≡ days; w ≡ weeks; mo ≡ months; y ≡ years

Table 3.9 Published immune system studies *in vivo* (long-term experiments)

Reference	Exposure characteristics	Biological model	Biological endpoint	Results	Comments
Guy et al, 1980	2.45 GHz, 70–100 W m^{-2}, estimated average SAR 1.5 W kg^{-1}, 6 mo, 23 h d^{-1}	New Zealand white male rabbits	White cell count	No effects	
McRee et al, 1980	2.45 GHz, cw, 70–100 W m^{-2}, estimated average SAR 1.5 W kg^{-1}, 6 mo, 23 h d^{-1}	New Zealand white male rabbits	Activation of lymphocytes in the presence of mitogens (PHA, ConA, PWM)	Abnormal myeloid/ erythroid ratio. Significant reduction in activation of lymphocytes with PWM	Few animals
Smialowicz et al, 1981	970 MHz, 22 h d^{-1} for 70 d, 2.5 W kg^{-1}	16 rats	Immune parameters (lymphocyte activation) and blood chemistry	No effect on cell population but alterations in blood chemistry	Effect on the endocrine system
Chou et al, 1983	2.45 GHz, cw, 5–50 W m^{-2}, 13 w, 5 d w^{-1}, 7 h d^{-1} Average SAR approx 6 W kg^{-1}, 14 mo, 1 h d^{-1}, estimated SAR 0.075–0.75 W kg^{-1}	New Zealand white male rabbits (16 + 16)	Haematology, lymphocyte blast transformation, mitotic index	No effects	Non-uniform SAR: 0.55–5.5 W kg^{-1} in the head. Decrease in food consumption
Chou et al, 1992	Pulsed 2.45 GHz, 10 µs pulses at 800 pps, 8 Hz trains of 50 pulses, 5 W m^{-2} average, 1250 W m^{-2} peak, average SAR 0.15–0.4 W kg^{-1}, 13 or 25 mo, 21.5 h d^{-1}	Sprague-Dawley male rats (100 + 100)	Endocrinology, immunology (lymphocyte maturation), cancer	Transient changes in immunological parameters at month 13 (increase in B and T-cells in the spleen). No difference at 25 months	Failure of replication in a later study on 20 + 20 rats over 12 months

min ≡ minutes; h ≡ hours; d ≡ days; w ≡ weeks; mo ≡ months; y ≡ years

Table 3.10 On-going immune system studies *in vitro*

Authors	Exposure characteristics	Biological model	Biological endpoint	Results	Comments
Veyret & Chagnaud, 1996	Plane-wave exposure at 900 MHz in anechoic chambers, 2 W m^{-2}, GSM signal. Cells exposed once for 4 h in thermostatic containers (37°C, 5% CO_2)	GH3, Molt4, C6 cell lines	Proliferation of cells 24 h and 48 h post exposure assessed using the MTT assay	No effects	Sponsored by French Télécom. Only one exposure duration. To be submitted for publication shortly
Fitzner et al	GTEM-cell, 900 MHz and 1.8 GHz	Human leukaemia HL-60 cells	Proliferation and thymidine kinase activity	No effects	Sponsored by FGF
Meyer et al	TEM-cell	Excitable heart muscle cells and nonexcitable cultured Jurkat T-lymphocytes	Calcium concentration	No effects	Sponsored by FGF
Wood et al	900 MHz radiofrequency exposure. Laser scanning confocal fluorescence microscopy using calcium probes	Cultured cells	Free calcium concentration	In progress	
French	Mobile phone frequencies	Cultured mast cells	Histamine release	In progress	

min ≡ minutes; h ≡ hours; d ≡ days; w ≡ weeks; mo ≡ months; y ≡ years

Table 3.11 On-going immune system study *in vivo*

Authors	Exposure characteristics	Biological model	Biological endpoint	Results	Comments
Chagnaud et al, 1995	Plane-wave exposure at 900 MHz in anechoic chambers, 2 W m^{-2}, SAR 0.27 W kg^{-1}. GSM signal. 10 d, 2 h d^{-1}	Female Sprague-Dawley rats	Immunological parameters in splenic lymphocytes (lymphocyte subpopulations, lymphoblastoid transformation)	No effects	Sponsored by French Télécom. To be submitted for publication

min ≡ minutes; h ≡ hours; d ≡ days; w ≡ weeks; mo ≡ months; y ≡ years

3.2.2.4 Nervous system studies

Since the early development of radiotelephony, the possibility of potentially hazardous effects on the central nervous system has been a matter of concern.

In principle, microwave radiation exposure may affect the function of the central nervous system in a number of different ways. Examples of possible interactions are: the modulation of neurotransmitter binding to specific receptors, the modulation of ionic membrane conductances and interactions with free radicals produced by on-going biochemical reactions. It has also been suggested that modulation of sensitive enzymatic systems such as ornithine decarboxylase or nitric oxide synthase could directly or indirectly affect signal transduction pathways. These are linked to a host of regulatory processes leading to adaptive changes of neuronal function and, hence, long-lasting effects. However, at present, there is little experimental evidence for any significant adverse effect on the brain from exposure to microwave radiation at the levels of emission characteristic of radiotelephones.

Published studies

In vitro studies (Table 3.12) Electrophysiological investigations on the effects of microwave radiation exposure on isolated neurons have led to controversial results. Some studies suggested that neurons respond to continuous exposure with a decrease in spontaneous activity, an increase in membrane conductance or a prolongation of the refractory period following depolarisation. In other studies, using temperature-controlled experimental conditions, these effects could not be confirmed at all. In one study, a shortening of the survival time of frog sciatic nerves *in vitro* has been described following pulsed microwave radiation exposure.

Following acute exposure of chick brain tissue to sinusoidal amplitude-modulated microwave radiation, an increase in the release of calcium ions from the cell membrane to the extracellular space was reported for amplitude-modulation frequencies between 6 and 20 Hz, but not at higher or lower modulation frequencies. However, these findings were equivocal. Some studies suggested that increased release of calcium occurs only in certain 'power density windows', but not at higher or lower values. Other studies did not observe effects on calcium release.

Pulsed microwave radiation exposure of synaptosomes prepared from rat cerebral cortex led to an increase in ^{32}P incorporation into phosphoinositides, suggesting stimulation of inositol metabolism. Continuous microwave radiation exposure of rats resulted in changes in energy metabolism of cerebral cortex, as reflected by a decrease in adenosine triphosphate (ATP) and creatine phosphate concentration, and an increase in nicotinamide adenosine dinucleotide (NADH) concentration. These results have been interpreted as evidence for disturbances of mitochondrial electron transport; however, this also has to await confirmation by independent replication studies.

In vivo studies in animals (Tables 3.13 a/b/c)

Electrophysiological effects Acute exposure of rats to continuous microwave radiation for 30 minutes previously led to an increase in the total spectral EEG signal at high (30 mW cm^{-2}) but not at lower (10 mW cm^{-2}) power densities. Following acute and chronic microwave exposure of rats and rabbits, increased EEG alpha-, beta- and delta-activities have been reported. In a joint project in the USA and the former Soviet Union, rats were exposed to continuous microwave radiation for 7 hours. No consistent changes in EEG signal spectra were found in this study. A slight reduction in the spectral theta activity was observed by the Soviet but not by the American scientists after 2 hours of microwave radiation exposure.

During exposure of cats to pulsed microwave radiation, auditory responses were evoked in the eighth cranial nerve, the medial geniculate nucleus and the primary auditory cortex. The evoked responses were eliminated after destruction of the cochlea, indicating that it is this part of the auditory pathway that is sensitive to microwave

radiation exposure. Further experiments revealed that the incident energy per pulse and the peak pulse power are critical factors influencing evoked auditory responses.

Effects on neurotransmitters and neurohormones An increase in brain concentration of serotonin and 5-hydroxyindoleacetic acid was reported in rats following acute continuous microwave radiation exposure, whereas a decrease in serotonin and 5-hydroxyindoleacetic acid was observed following chronic exposure. Similarly, acute exposure of rats to continuous microwave radiation caused a decrease in hypothalamic norepinephrine concentration, whereas chronic exposure led to a slight increase. Since the serotonergic and noradrenergic systems are implicated in mechanisms of heat dissipation, these changes may reflect thermal effects of microwave exposure.

Following exposure of mice to single microwave radiation pulses which deposited 18.7 J and increased brain temperature by 2–4 °C, a decrease in whole brain acetylcholine concentration was observed, suggesting an increase in the release of acetylcholine. Acute exposure to pulsed microwave radiation also inhibited the activity of acetylcholinesterase, the degradation enzyme for acetylcholine, in the guinea-pig brain. By contrast, an increase in brain acetylcholinesterase activity was seen after chronic exposure. Finally, two studies reported that microwave radiation exposure did not affect acetylcholinesterase activity *in vitro* over a wide power range.

A decrease in sodium-dependent high-affinity uptake from brain tissue of choline, which is the rate limiting step in acetylcholine synthesis, was found in the frontal cortex and hippocampus of rats after acute exposure to pulsed microwave radiation for 45 minutes. Under these conditions an increase in the concentration of muscarinic cholinergic receptors was also seen in the rat brain. By contrast, after a shorter exposure of only 20 minutes, an increase in sodium-dependent high-affinity choline uptake and a reduction in the muscarinic receptor concentration was observed. The effects of microwave radiation exposure on sodium-dependent high-affinity choline uptake and muscarinic receptor concentration were blocked following pre-treatment with the opiate-antagonist naltrexone and corticotropin-releasing hormone. The combined evidence of these studies provides a diffuse and partly controversial picture of neurotransmitter changes which is difficult to reconcile with a common pattern of injury.

Effects on blood–brain barrier permeability Effects of microwave exposure on blood–brain barrier permeability have been studied either alone or in combination with static magnetic fields, as used in MRI. Disturbances of blood–brain barrier permeability were assessed by evaluating the extravasation of external tracers or of internal serum constituents. Most researchers agree that microwave radiation exposure increases blood–brain barrier permeability, but some studies reported difficulties in confirming these findings. The combination of microwave exposure with static magnetic fields resulted in increased barrier permeability mainly at low field strengths (up to 0.5 T) but less so at field strengths of more than 2 T.

It has been suggested that blood–brain barrier breakdown following microwave radiation exposure is mainly due to thermal effects, but some researchers have stressed that the disturbance may occur under thermally-controlled conditions. The relationship may even be more complex with a 'power window' of barrier disturbances between ranges of low and high power intensities, at which the barrier remains intact. As far as the mechanism of blood–brain barrier disturbance is concerned, pinocytotic (ie, vesicle) uptake is a possible mode of extravasation. An increase of ornithine decarboxylase activity also appears to correlate with barrier disturbances.

The investigation that relates most closely to radiotelephones has been carried out by Salford et al (1994). Using either cw or pulse-modulated 915 MHz electromagnetic radiation exposure at SARs of up to 5 W kg^{-1}, these authors observed multifocal albumin- but not fibrinogen-extravasations, the incidence of which rose significantly at SAR > 2.5 W kg^{-1}. The more pronounced permeability change of the low molecular weight albumin compared with the larger fibrinogen molecule points against a pinocytotic mechanism because pinocytosis does not differentiate between different molecular sizes. It is, therefore, conceivable that the observed barrier disturbances

are due to, or increased by, unspecific side-effects, such as stress-induced hypertensive episodes brought about by the immobilisation required for the exposure of animals.

An increase in the vascular permeability to fluorescein and horseradish peroxidase has not only been observed in the brain, but also the iris of the eye in M. mulatta and M. fascicularis monkeys following pulsed and continuous microwave radiation exposure at SARs of 2.6–3.9 W kg^{-1}. The threshold for the permeability increase could be reduced to 0.26 W kg^{-1} following topical pretreatment with timolol maleate.

In vivo studies in humans (Table 3.14) The acute effects of radiotelephone emissions on EEG activity have been studied in human volunteers. The subjects' heads were exposed to a handset for 15 minutes at a distance of 40 cm. In a first study, an increase in the alpha-activity was observed immediately after exposure. In a second study, an increase in the $alpha_2$ and beta signals was described 15 minutes later. These observations have been interpreted as in support of interference between the radiotelephone emissions and the electrophysiological function of the brain. However, similar changes can also be induced by spontaneous alterations of vigilance. More rigorously controlled studies with group comparisons are therefore required to substantiate these findings.

During nocturnal exposure to radiotelephone emissions over 8 hours, a shortening of sleep onset latency and a reduction in duration as well as percentage of REM sleep has been described. The total amount of sleep and the total amount of slow wave sleep were not influenced during that experiment. In another study, acute exposure of human subjects for only 15 minutes to amplitude-modulated microwave radiation led to a shortening of the sleep onset latency and to an increase in the duration of stage 2 sleep. Since such changes are of considerable interest, this topic warrants further investigation.

Table 3.12 Published studies on nervous system – *in vitro* effects

Reference	Exposure characteristics	Biological model	Biological endpoint	Results	Comments
Bawin et al, 1975; 1978	Amplitude-modulated 147 and 450 MHz, 10–20 Hz, 0.75 mW cm^{-2}	Chick brain tissue	Cellular calcium efflux	Increase in calcium ion efflux	
Wachtel et al, 1975; Seaman & Wachtel, 1978	1.5 and 2.45 GHz (cw), 10–50 W kg^{-1}	Isolated neurons from abdominal ganglion of marine gastropode aplysia	Spontaneous unit activity	Decrease in spontaneous activity	Exposure level above the safety limits relevant to radio telephones. Thermal effects probable
Chou & Guy, 1978	cw and pulsed (100 and 1000 pps) 2.45 GHz, 0.3–1500 W kg^{-1}	Isolated frog sciatic nerve, cat saphenous nerve and rabbit vagal nerve, superior cervical ganglion	Biophysical membrane characteristics	No significant biophysical changes	No change despite very high exposure intensity
Blackman et al, 1979; 1980; 1991	Amplitude-modulated 50 and 147 MHz, 16 Hz, > 750 µW cm^{-2}	Chick brain tissue	Cellular calcium efflux	Calcium efflux power density window at 0.75 mW cm^{-2}, influenced by experimental temperature and modulation frequency	
Sheppard et al, 1979	Amplitude-modulated 450 MHz, 16 Hz	Chick brain tissue	Cellular calcium efflux	Increased calcium efflux in power density window between 0.1 and 1 mW cm^{-2} but not at higher or lower power densities	
McRee & Wachtel, 1980; 1982	cw and pulsed (50 pps) 2.45 GHz, SAR 10 W kg^{-1}	Frog sciatic nerve	Compound action potential, refractory period, survival time	Prolongation of refractory period, amplitude decrease of compound action potential following continuous microwave irradiation, shortening of survival time following pulsed microwave irradiation	
Sanders et al, 1980; Sanders & Joines, 1984, Sanders et al, 1985	cw, pulsed (250 or 500 pps) and amplitude-modulated (4–32 Hz) 591 MHz, SAR 2.48–5.8 W kg^{-1}	Rat	Concentrations of adenosine triphosphate (ATP), creatine phosphate and nicotinamide adenosine dinucleotide (NADH)	Decrease in ATP and creatine phosphate concentration, increase in NADH concentration	
Shelton & Merritt, 1981; Merritt et al, 1982	Square-wave modulated 1 and 2.45 GHz, 16–32 Hz, SAR 0.3–2.9 W kg^{-1}	Rat brain tissue	Cellular calcium efflux	No changes	

min ≡ minutes; h ≡ hours; d ≡ days; w ≡ weeks; mo ≡ months; y ≡ years

Table 3.12 (continued)

Arber & Lin, 1984; 1985	Continuous and amplitude-modulated 2.45 GHz over 60 min, SAR 6.8–14.4 W kg^{-1}	Helix aspersa neurons	Membrane conductance, spontaneous activity	Increase in membrane conductance, decrease in spontaneous firing at 8 and 21 °C but not 28 °C, and at 12.9 W kg^{-1} but not 6.8 or 14.4 W kg^{-1}; effects abolished following intracellular calcium-chelation with EDTA
Gandhi & Ross, 1989	Pulsed 2.8 GHz, 350 pps, 10–30 mW cm^{-2}	Rat cerebral cortex synaptosomes	^{32}P-incorporation into phosphoinositides	Increase in ^{32}P-incorporation
Wang et al, 1991	2.45 GHz, cw, temperature-controlled conditions	Rat dorsal root ganglion cells	Biophysical membrane characteristics	No changes

min ≡ minutes; h ≡ hours; d ≡ days; w ≡ weeks; mo ≡ months; y ≡ years

Table 3.13a Published studies on nervous system – animal studies: electrophysiological effects

Reference	Exposure characteristics	Biological model	Biological endpoint	Results	Comments
Taylor & Ashleman, 1974	Pulsed 2.45 GHz, 1 Hz	Cat	Evoked auditory response	Suppression of evoked response after damage of cochlea	
Chou et al, 1975; 1982; Chou & Guy, 1979b	Pulsed 918 MHz, 5–10 mJ kg^{-1}, 10–500 µs pulse width	Guinea-pig	Evoked auditory response	Responses in eighth cranial nerve, medial geniculate nucleus and primary auditory cortex	
Chou & Guy, 1979a	2.45 GHz, cw	Rabbit	EEG, evoked auditory response, hypothalamic activity	No changes	
Shandala et al, 1979	2.375 GHz, cw, for 7 h d^{-1} over 30 d, 10–500 µW cm^{-2}	Rat, rabbit	Spectral EEG	Variable increase in spectral alpha- and delta-activities at single times during exposure.	Inconsistent changes might be provoked by accidental variations of vigilance
Takashima et al, 1979	15 Hz modulated, 1–10 MHz for 2 h d^{-1} over 6 w	Rabbit	EEG	Change in EEG pattern (increase in low frequency, decrease in high frequency bands)	Acute exposure did not produce changes
Chou et al, 1985	Pulsed 2.45 GHz, 10 pps	Rat	Evoked auditory response	Incident energy per pulse and peak pulse power as critical factors of evoked response, threshold 0.9–1.8 mJ kg^{-1} x pulse	
Mitchell et al, 1989 (US/Soviet Union joint programme)	2.45 GHz, cw, SAR 2.7 W kg^{-1} for 7 h	Rat	Spectral EEG	No consistent changes in EEG power spectra, reduction in theta-activity found by Soviet Union, but not American scientists after 2 h exposure	Inconsistent changes might be provoked by accidental variations of vigilance
Seaman & Lebowitz, 1989	915 MHz pulses, 20–700 µs duration, SAR 11.1 W kg^{-1} per pulse	Cat	Evoked auditory response	Cochlea sensitive to microwave radiation stimulation	
Thurcozy et al, 1994	2.45 GHz, cw, for 10 min, amplitude-modulated 4 GHz, 16 Hz for 30 min SAR 8.3–42 W kg^{-1}	Rat	Spectral EEG	Increase in total EEG spectral power following 30 mW cm^{-2} (25 W kg^{-1}), but not 10 mW cm^{-2} (8.3 W kg^{-1}) cw; increase in delta- and beta-powers following amplitude-modulated radiation	Increase in EEG spectral power might reflect thermal effects

min ≡ minutes; h ≡ hours; d ≡ days; w ≡ weeks; mo ≡ months; y ≡ years

Table 3.13b Published studies on nervous system – animal studies: effects on neurotransmitters and neurohormones

Reference	Exposure characteristics	Biological model	Biological endpoint	Results	Comments
Snyder, 1971	3 GHz, cw	Rat	Concentrations of serotonin and 5-hydroxyindoleacetic acid in the brain	Serotonin and 5-hydroxyindoleacetic acid increase following acute exposure, decrease following chronic exposure over 7 d for 8 h d^{-1} at 10 mW cm^{-2}	In this and the following studies, thermal effects are possible, because the serotenergic and noradrenergic systems are implicated in thermoregulation
Baranski, 1972	3 GHz, cw and pulsed, 400 pps)	Guinea-pig, rabbit	Activity of acetylcholinesterase	Activity decrease following acute exposure at 25 mW cm^{-2}, activity increase following chronic exposure at 3.5 mW cm^{-2} over 3 mo for 3 h d^{-1}	No effect in more recent studies (see Millar et al, 1984; Galvin et al, 1981)
Grin, 1974	2.375 GHz, cw, 50 or 500 μW cm^{-2}	Rat	Hypothalamic norepinephrine concentration	Slight norepinephrine increase following chronic exposure over 20 d for 7 h d^{-1}	
Merritt et al, 1977	1.6 GHz, cw, 20 or 80 μW cm^{-2}	Rat	Hypothalamic norepinephrine concentration	Norepinephrine decrease following acute exposure	
Galvin et al, 1981	2.45 GHz, cw, SAR 1–100 W kg^{-1}	Purified enzymatic preparation	Activity of acetylcholinesterase and creative phosphatase	No effects	
Millar et al, 1984	Pulsed 2.45 GHz, 10–90 pps, SAR 2.46–4.29 W kg^{-1}	Enzymatic preparation from ray fish	Activity of acetylcholinesterase	No effects	
Lai et al, 1987a; b; 1989; 1990; 1991; 1993	Pulsed 2.45 GHz, 500 pps, SAR 0.6 W kg^{-1}	Rat	Sodium-dependent high affinity choline uptake, muscarinic cholinergic receptor concentration	Decrease in sodium-dependent high-affinity choline uptake and increase in concentration of muscarinic cholinergic receptors following 45 min exposure, but increase in sodium-dependent high-affinity choline uptake and decrease in muscarinic cholinergic receptor concentration following 20 min exposure. Effects blocked by naltrexone and corticotropin-releasing hormone	No plausible explanation for the time-dependence of changes
Inaba et al, 1992	2.45 GHz, cw, 5–10 mW cm^{-2}	Rat	Norepinephrine and hydroxyindoleacetic acid concentrations in the cortex and hypothalamus	Decrease in hypothalamic norepinephrine, increase in cortical 5-hydroxyindoleacetic acid following acute exposure	Increase in body temperature

min ≡ minutes; h ≡ hours; d ≡ days; w ≡ weeks; mo ≡ months; y ≡ years

Table 3.13c Published studies on nervous system – animal studies: effects on blood–brain barrier permeability

Reference	Exposure characteristics	Biological model	Biological endpoint	Results	Comments
Frey et al, 1975	1.2 GHz, cw and pulsed, 1000 pps, 0.2–2.4 mW cm^{-2}	Rat	Blood–brain barrier permeability to fluorescein	Permeability increase	
Oscar & Hawkins, 1977	1.3 GHz, cw and pulsed, 50–1000 pps, 0.3–2 mW cm^{-2}	Rat	Blood–brain permeability to mannitol, inulin and dextran	Permeability increase to mannitol and inulin, but not to dextran	
Merritt et al, 1978	1.2 GHz, cw and pulsed, 1000 pps, 2–75 mW cm^{-2}	Rat	Blood–brain barrier permeability to fluorescein and [^{14}C]-mannitol	Permeability increase in hyperthermic rats, not in thermally controlled animals	
Preston et al, 1979	2.45 GHz, cw, 0.1–30 mW cm^{-2}	Rat	Blood–brain barrier permeability to [^{14}C]-mannitol	No permeability increase	
Sutton & Carroll, 1979	2.45 GHz, cw	Rat	Blood–brain barrier permeability to horseradish peroxidase	Permeability increase accompanied by brain temperature increase	
Lin & Lin, 1980; 1982	Pulsed 2.45 GHz, 25–500 pps, SAR 0.08–240 W kg^{-1}	Rat	Blood–brain barrier permeability to Evans blue and fluorescein	Permeability increase at SAR of 240 W kg^{-1}, but not at lower absorption rates	Increased permeability at high SAR probably related to temperature effect
Albert & Kerns, 1981	2.45 GHz, cw, SAR 2.5 W kg^{-1}	Hamster	Blood–brain barrier permeability to horseradish peroxidase	Permeability increase	
Gruenau et al, 1982	2.8 GHz, cw and pulsed, 500 pps, 1–40 mW cm^{-2}	Rat	Blood–brain barrier permeability to [^{14}C]-sucrose	No permeability increase	
Ward et al, 1982	2.45 GHz, cw, SAR 2–6 W kg^{-1}	Rat	Blood–brain barrier permeability to [^{14}C]-sucrose and [^{3}H]-inulin	No permeability increase	
Goldman et al, 1984	Pulsed 2.45 GHz, 500 pps, SAR 240 W kg^{-1}	Rat	Blood–brain barrier permeability to ^{86}Rb	Permeability increase accompanied by brain temperature increase	
Neubauer et al, 1990	Pulsed 2.45 GHz, 100 pps, SAR 2 W kg^{-1}	Rat	Blood–brain barrier permeability to rhodamine-ferritin	Permeability increase which is blocked following colchicine treatment	Blocked by colchicine points to pinocytotic mechanism of blood–brain barrier injury
Moriyama et al, 1991	2.45 GHz, cw	Rat	Blood–brain barrier permeability to horseradish peroxidase	Permeability increase accompanied by brain temperature increase	

min ≡ minutes; h ≡ hours; d ≡ days; w ≡ weeks; mo ≡ months; y ≡ years

Table 3.13c (continued)

Kues et al, 1992	2.45 GHz, cw and pulsed (100 pps), 0.052–3.9 W kg^{-1} for 4 h d^{-1} over 3 d	Monkey	Iris endothelial permeability to fluorescein and horseradish peroxidase	Permeability increase	
Persson et al, 1992	MRI gradient field (2.35 T) and cw/pulsed (8–215 pps) 915 MHz	Rat	Blood–brain barrier permeability to Evans blue, albumin and fibrogen	Permeability increase	
Salford et al, 1994	915 MHz, cw and pulsed, 8–200 pps, SAR 0.016–5 W kg^{-1}	Rat	Blood–brain barrier permeability to albumin and fibrinogen	Increased leakage of albumin, but not fibrinogen leakage	Selective increase of proteins with low molecular weight points to (stress-induced) hypertensive episodes, rather than to activation of pinocytosis

min ≡ minutes; h ≡ hours; d ≡ days; w ≡ weeks; mo ≡ months; y ≡ years

Table 3.14 Published studies on nervous system – *in vivo* effects in humans

Reference	Exposure characteristics	Biological endpoint	Results	Comments
Reite et al, 1994	Amplitude-modulated 27.12 MHz, 42.7 Hz over 15 min, SAR 0.1–100 mW kg^{-1}	EEG sleep pattern	Decrease in sleep onset latency to stage 2 sleep, increase in total amount of stage 2 sleep	No control experiment to exclude spontaneous vigilance changes of EEG
Von Klitzing, 1995	Pulsed 900 MHz, 217 pps	EEG	Changes in alpha-activity immediately after exposure	Spontaneous vigilance change cannot be excluded
Reiser et al, 1995	Pulsed 900 MHz, 217 pps, telephone device 40 cm from head, 15 min exposure	EEG	Increase in $alpha_2$- and beta-power 15 min after exposure	
Mann & Röschke, 1996	Pulsed 900 MHz, 217 pps, 50 mW cm^{-2} (telephone device 40 cm distant from head), 8 h exposure during nocturnal sleep	EEG sleep pattern	Shortening of sleep onset latency, reduction of REM sleep duration, no changes in total sleep time and total amount of slow wave sleep	Only 12 subjects

min ≡ minutes; h ≡ hours; d ≡ days; w ≡ weeks; mo ≡ months; y ≡ years

On-going research

In vitro studies (Table 3.15) At present, scientific studies on the interactions of microwave radiation with the nervous system are being carried out at all three scientific levels of complexity described previously. Due to the growing concern about the possible health risks of the use of radiotelephones, the specific electromagnetic characteristics of radiotelephone signals are taken into account. Sensitive molecular biological tools that have recently become available in neurobiology are applied to study putative cellular and subcellular changes following microwave exposure. For example, the localisation of calcium and calcium-ATPases within the cytoskeleton is currently being investigated by a group led by Somozy. Their results suggest an increase in cyclic AMP and cyclic GMP levels as well as an increase in adenylate cyclase activity following exposure to 16 Hz amplitude-modulated 2.45 GHz microwave radiation.

In vivo studies in animals (Table 3.16) The concentrations of ornithine decarboxylase and spermine in the brain as well as the permeability of the blood–brain barrier are currently being investigated in rats and mice exposed to 915 MHz microwave radiation by Persson and Salford. Preliminary results indicate that there is an increase in both ornithine decarboxylase and spermine levels following exposure to pulsed, but not to continuous microwave radiation. Moreover, there seems to be an increase in the permeability of the blood–brain barrier to albumin following exposure to both pulsed and cw microwave radiation. A minor increase of the blood–brain barrier permeability to albumin was also observed in a study by Fritze et al. However, these changes appeared at SAR levels well above the range associated with mobile telephone use. Pulsed and, at higher intensity, cw microwave radiation exposure also caused minor expression of the mRNAs of immediate-early genes and heat stress proteins. These changes have mainly been related to the confinement required for exposure as well as to thermal stress, but a possible field effect cannot be fully excluded.

The effects of long-term exposure to radiotelephone emissions on neurotransmitter concentrations, such as dopamine, noradrenaline and GABA, are being examined in rats by de Seze. However, no differences have been reported so far between exposed and sham-exposed animals. The effects of 2.45 GHz microwave radiation exposure on the activity of aminoacyl-tRNA synthetase are currently being studied in embryonic mice by Kubinyi. A significant decrease in the activity of aminoacyl-tRNA synthetase was found following cw, but not following amplitude-modulated microwave radiation exposure.

In vivo studies in humans (Table 3.17) The effects of radiotelephone radiation exposure on endocrine and electrophysiological parameters are being investigated by de Seze. Following 4 weeks of exposure for 2 hours per day over 5 days per week a slight decrease in the pituitary hormone, TSH, was found. This finding needs to be confirmed in future studies. Electrophysiological and neuropsychological recordings in human volunteers are being carried out by Spittler. So far, no significant electrophysiological and neuropsychological differences have been detected between microwave radiation and sham-exposed human subjects at SARs typical of radiotelephone use.

Table 3.15 On-going research on nervous system: *in vitro* effects

Reference	Exposure characteristics	Biological model	Biological endpoint	Funding agency
P Semm & W Wiltschko	Pulsed 900 MHz, 217 Hz, 100 μW cm^{-2}, cw and modulated 900 MHz	Bobolink and pigeon visual neurons and ophthalmicus nerve, insect neurons. Isolated mouse, bird and insect neurons	Electrophysiological changes	Deutsche Telekom
Z Somosy	Amplitude modulated 2.45 GHz, 16 Hz, SAR 1.4 W kg^{-1}	Epithelial and neuroblastoma cell culture	Distribution of Ca^{2+} and Ca^{2+}-ATPases, cytoskeletal ultrastructure	Hungarian Ministry of Welfare

min ≡ minutes; h ≡ hours; d ≡ days; w ≡ weeks; mo ≡ months; y ≡ years

Table 3.16 On-going research on nervous system: *in vivo* effects in animals

Reference	Exposure characteristics	Biological model	Biological endpoint	Funding agency
G Thuroczy	Amplitude-modulated 2.45 GHz, SAR 0.3 W kg^{-1}	Anaesthetised and awake, freely moving rats	Visual evoked potential latencies	Hungarian Ministry of Welfare
H Lai	2.45 GHz, cw and pulsed, various power densities	Rats	Central cholinergic activity and maze performance	National Institutes of Health
BRR Persson & LG Salford	915 MHz, cw and pulsed	Rats and mice	Ornithine decarboxylase and spermine concentrations, blood-brain barrier permeability	Lund University
K Fritze et al	Pulsed 915 MHz, 217 Hz, SAR 0.4–10 W kg^{-1}	Rats	Permeability of blood–brain barrier, expression of immediate early genes and heat shock proteins	Motorola
R de Seze	Pulsed 900 MHz, 217 Hz, 200 μW cm^{-2}	Rats	Effects of long-term exposure on neurotransmitter concentrations	France Télécom, CNET
G Kubinyi	2.45 GHz, cw and amplitude-modulated, 217 Hz, SAR 4.2 W kg^{-1}	Mice embryos *in utero*	Effects on aminoacyl-tRNA synthetase in brain tissue	Hungarian Ministry of Welfare
J Bohl & L Vollrath	Pulsed 900 MHz, 217 Hz	Mice	Histological changes	Deutsche Telekom

min ≡ minutes; h ≡ hours; d ≡ days; w ≡ weeks; mo ≡ months; y ≡ years

Table 3.17 On-going research on nervous system: *in vivo* effects in humans

Reference	Exposure characteristics	Biological endpoint	Funding agency
R de Seze	Pulsed 900 MHz, 217 Hz, radiotelephone exposure for 1 h	Electrophysiological recording	France Télécom, CNET
JF Spittler	Pulsed 915 MHz, 217 Hz	Electrophysiological recording, neuropsychological testing	Forschungsgemeinschaft Funk
M Hietanen et al	Pulsed 900 MHz, radiotelephone exposure for 20 min	Electrophysiological recording	Various
R de Seze	Pulsed 900 MHz, 217 Hz, radiotelephone exposure 2 h d^{-1}, 5 d w^{-1} for 4 weeks	Secretion of pituitary hormones (ACTH, TSH, FSH, GH, LH, prolactin)	France Télécom, CNET
L Vollrath	Pulsed 900 MHz, 217 Hz	Immune parameters, melatonin secretion	Deutsche Telekom
G Thuroczy	GSM signal (1 W)	Cerebral circulation, EEG	Hungarian Ministry of Welfare

min ≡ minutes; h ≡ hours; d ≡ days; w ≡ weeks; mo ≡ months; y ≡ years

3.2.2.5 Other studies

Published and on-going studies There have been reports that people occupationally exposed to microwave radiation have complained of heavy feeling in their heads, headaches, fatigue, drowsiness in the daytime, irritability, poor memory, nausea, vertigo, and sleep disturbances more often than control groups (Marha et al, 1971; Baranski and Czerski, 1976; WHO, 1977). Skin rashes have also been mentioned in this connection. The overall symptoms have often been described as neurasthenic syndrome. Cohen and White (1972, quoted in WHO, 1977) noted that the onset of the syndrome in predisposed individuals was usually precipitated or made worse by emotion-provoking circumstances and medical illness.

The problems regarding the neurasthenic syndrome have not been solved. The question has not been addressed since the mid-1970s, when it was dismissed because of lack of control of confounding factors.

In this context, it should be noted that experiments were done in the 1960s on 'microwave hearing' using intensities below 1 mW cm^{-2} and similar problems were encountered. It is reported that the experiments were discontinued because some of the volunteers reported headaches (Frey, 1996 – personal communication).

Facial skin rashes have been reported by visual display unit users. ELF electric and magnetic fields in the work environment have been suggested as a possible cause (Sandström et al, 1995), but stress factors and psychosocial factors have also been found to be relevant (Eriksson, 1996).

Altpeter et al (1995) found a high frequency of disorders of 'neurovegetative nature' among residents near a short-wave transmitter. Sleep interruptions were directly associated with the electromagnetic field strengths of the transmitter. Sleep quality apparently improved after interruption of broadcasting. No effect was seen on melatonin metabolism.

The question of subjective disorders linked with the use of radiotelephone handsets has recently been raised. Users have contacted manufacturers, sales organisations and research institutes. The problem has been raised in Sweden, Norway (Oftedahl, 1996), UK (Cox, 1996), Australia (Hocking, 1996), and USA (Lotz, 1996) – all references refer to personal communications to Hansson Mild. Complaints are usually about headaches, difficulties in concentrating, nausea, and sometimes also a stinging sensation and a feeling of heat in the facial skin that appear to be similar in some respects to the neurasthenic syndrome mentioned above. The problems often occur on that side of the head where the handset is held. Complaints seem to be more common among GSM users than among users of analogue radiotelephones. A joint Norwegian–Swedish study of these problems is currently being undertaken. Recently, Johansson (1995) carried out a study with twelve people claiming sensitivity to radiotelephones. He exposed them to radiotelephones contained in a bag. It is reported that one person out of the twelve could correctly tell in nine out of nine trials if the telephones were on or off. The study is presented as an institutional report and lacks details regarding exposure. The results were inconclusive.

There have also been reports of people claiming to be 'hypersensitive' to electromagnetic fields in general. The most common symptoms are headaches, insomnia, seizures, tingling of the skin, difficulty in concentrating, and dizziness. Rea et al (1991) performed a provocation study among 100 such patients. Exposure to magnetic fields at certain frequencies from a few Hz up to a few MHz provoked the symptoms for some of these patients. However, it is not clear how the exposure was made or to which field strengths the subjects were exposed. Other studies, mainly from Scandinavia, have not been able to confirm such relationships between field exposure and symptoms.

3.3 Conclusions and recommendations for biophysical and biological research

In order not to exclude any worthwhile research proposal, the recommendations for biological (and epidemiological) research made by the Expert Group are not specifically prescriptive but rather indicative of the

areas of research that should be addressed and prioritised. These, together with recommended criteria for selection of research proposals, should both encourage the submission of proposals from suitably qualified research groups and aid the prioritisation and selection of the proposals for funding.

The Expert Group agrees that only *in vivo* biological studies are able to provide convincing evidence of whether microwave radiation exposure confers increased health risks, because many complex features of the living organism cannot be replicated *in vitro*. Thus, *in vivo* studies, using either experimental animals or human volunteers, should play the major role in any European research programme. Nonetheless, *in vitro* studies provide insight into the cellular and subcellular mechanisms underlying the interactions between electromagnetic radiation and biological systems. The understanding of these mechanisms contributes to the improvement of specific working hypotheses both in animal and human research and results in better designed *in vivo* studies. Therefore, *in vivo* and *in vitro* experiments should be supported in a complementary and balanced way.

It is important to consider possible synergism between microwave radiation exposure and other factors.

3.3.1 Biophysical interaction studies

Studies on basic interaction mechanisms should have a low priority compared with research more directly related to human health. However, because several hypotheses for the demodulation of amplitude-modulated fields exist, the Expert Group noted that it is important to address basic interaction mechanisms in this research programme. Furthermore, the biophysical interaction paths described in Section 3.2.1 lead to the need to consider a limited number of issues.

The Expert Group recommends that the following be considered:

- mechanisms of signal detection and the role of electromagnetic 'noise' in biological structures
- molecular dynamics of proteins under electromagnetic exposure
- microdosimetry.

3.3.2 Biological effects – *in vitro* studies

Cellular models are becoming more and more popular in toxicology although *in vitro* experiments lack the most fundamental interactions between body organs and systems. However, many new models and techniques have made *in vitro* research very informative. They provide insight into the cellular and subcellular mechanisms underlying the interactions of radiofrequency radiation and biological systems. Within the scope of this programme, these new models and techniques should be used in two complementary directions: towards better designed animal models (promotion, cellular or humoral components, stress, ageing, etc) and towards mechanisms of possible effects (role of ELF modulation, of membrane function and signal transduction, of free radicals, of gap junctions, etc).

One of the primary examples of *in vitro* experiments is that of calcium efflux in cells exposed to ELF-modulated microwave radiation. The calcium ion is now recognised as a possible direct or indirect target of electromagnetic fields. However, there is currently no experimental evidence for an influence of exposure to microwave radiation on calcium ion concentration. The Expert Group views further investigations of this type of phenomenon, which is of importance for a number of biological processes, as being worthwhile. The effects of microwave radiation exposure on biochemical species such as nitric oxide, which is of major biological importance, should also be studied, together with other cases such as lymphocyte activation and effects on the phases of the cell cycle. Overall, the role of cellular stress (and, in particular, oxidative stress) in the elicitation of microwave radiation *in vitro* effects, should be emphasised in further investigations.

Three categories of electromagnetic interactions deserve particular attention:

- effects on membrane function and signal transduction pathways
- effects on biochemical reactions including genomic responses
- effects on cell cycle and proliferation.

Examples of membrane-associated processes are effects on ions movement (and, in particular, calcium), on the sensitivity of receptors, on the electrical properties of gap junctions and on the transduction of external stimuli to second and third messenger systems.

With respect to effects on biochemical reactions, attention should be given to sensitive regulatory enzymes, as well as specific genomic responses such as the induction of immediate/early genes or stress proteins. Effects on cell cycle relate mainly to tumour proliferation. Of particular concern is the possibility that microwave radiation exposure may modulate independent pathological processes which involve free radical reactions or disturbances of neuroreceptor sensitivity or ion channel conductances.

In vitro models that could be used for such studies include primary neuronal and glial cultures, organotypic cultures, subcellular fractions or slices from various parts of the brain. The methodologies for electrophysiological, biophysical and biochemical measurements, as well as for the induction of the various pathological states, are well established and can be directly applied to these or related research problems.

3.3.3 Biological effects – animal studies

Dosimetry and standardisation of experimental procedures, as well as the avoidance of stress or other unspecific side-effects, are mandatory for any meaningful experimentation and represent methodological research projects in themselves.

Some of the research topics proposed here involve various sensitive methods which may be able to detect even minor abnormalities. It is now possible to use transgenic and 'knock-out' animals as well as animal strains especially prone to develop specific diseases. Therefore, the Expert Group strongly advises that the severity of such changes should be compared with those induced by other known pathologies in order to allow the objective evaluation of possible health risks. In order to ascertain the existence of 'non-thermal' effects of microwave radiation, animal studies should be carried out to determine the SAR threshold for such effects.

Genetic and cancer-related effects As there is no convincing evidence that microwave radiation is directly genotoxic or carcinogenic (under athermal or non-thermal conditions), investigations on genetic and cancer-related effects should be directed particularly toward their possible promotional, co-promotional and synergistic properties.

Effects on the immune system Most *in vivo* results in the literature are either not relevant to personal telecommunication emissions or contradictory. The database for this important biological system is thus poorly defined. There seems to be no consistent finding of alteration of the immune system of animals acutely exposed to microwave radiation at moderate power levels (corresponding to SARs below a few W kg^{-1}). Some recommendations can thus be made for further research, keeping in mind that effects on the immune system cannot be studied independently of other systems such as the haematopoietic, nervous and endocrine systems.

Since few long-term exposure studies at low levels have been performed, well-designed experiments should be undertaken, linked to cancer promotion studies.

The possible role of amplitude modulation in the elicitation of effects on the immune system is still uncertain. In view of the amplitude-modulation of some of personal telecommunications equipment, further investigation of the role of ELF modulation is needed. The results of experiments on effects of ELF magnetic field exposure of animals should also be carefully analysed in this respect.

As exposure to radiotelephone emissions includes the skin, the possibility that there is a local immune response, such as sequestration of leukocytes in the skin, should be considered.

Nervous system-related effects For the evaluation of the effects of microwave radiation exposure, investigations on integrated neuronal function, cochlear function, sleep pattern analyses and neurobehavioural studies would be appropriate. The effect on electrophysiological function should be carried out not only by recording conventional EEG and evoked potentials (these studies were essentially negative in the past) but also by magnetoencephalography because this method allows much finer spatial and temporal resolution than earlier recording techniques. Such studies can be complemented by testing memory acquisition and storage before and after microwave radiation exposure.

With regard to neurohumoural and neurotransmitter interactions, the effect on pineal melatonin secretion requires further investigation. If previous ELF findings could be replicated by cw or pulsed microwave radiation exposure, such effects would be of considerable importance not only for tumour proliferation but also for alterations of sleep pattern.

The possibility that incidental pathologies are aggravated by microwave radiation exposure is an important health issue. This is already under investigation in regard to tumour proliferation but it should also include other pathological states, such as epilepsy, inflammation or ischaemia. Appropriate experimental models would be reperfusion injury after global ischaemia (for possible interference with free radical reactions), permanent or reversible focal ischaemia (to study complicating inflammatory responses) or kainate-induced kindling (for the investigation of hippocampal seizures).

A sensitive way to address possible effects on signal transduction pathways is the study of the genomic response of the brain. If microwave radiation exposure exerts any relevant pathophysiological effects on the brain, short or long-term changes of the genomic expression pattern of neurons and/or glial cells should occur. Such genomic changes can be studied by *in situ* hybridisation, reaction or immunocytochemical techniques, which allow the detection of even minor abnormalities.

Finally, the effect of microwave radiation exposure on permeability changes of the blood–brain barrier should be addressed, in particular, whether previously described permeability changes are the direct consequence of exposure or are side-effects of the experimental procedure, such as immobilisation stress or cryptic thermal effects.

The Expert Group recommends the following lines of *in vivo* biological research:

Genetic studies

- studies of genotoxicity on microwave-irradiated animals, including irradiation following or preceding administration of established chemical mutagens/carcinogens
- studies of genetic effects and morphological changes in brain cells from microwave radiation-exposed animals (for example, DNA damage)

Cancer studies

- studies of long-term carcinogenicity in normal or sensitised/transgenic animals
- studies of the influence of microwave radiation on growth of existing tumours

Immune system studies

- long-term studies (because of the difficulties and high cost, it would be advisable to conduct such studies together with cancer-oriented studies)
- studies of the possible role of ELF-modulation

Nervous system studies

- electrophysiological and neurobehavioural studies
- investigations of signal transduction pathways by study of the genomic response of the brain

- effects of microwave radiation exposure on permeability changes of the blood–brain barrier
- aggravation of incidental brain pathologies other than cancer (inflammation, ischaemia, seizures).

3.3.4 Human (laboratory) studies

The design and construction of handsets leads to energy absorption in the brain and neck tissues near the antenna. Structures such as the vestibulum, cochlea and acoustic nerve, other cranial nerves including vagus, facialis, trigeminus, etc, the meninges, the carotids and salivary glands may be exposed under these circumstances.

Most laboratory and clinical projects focus on carcinogenesis, tumour promotion and mutagenic effects. However, potential health effects might also be seen as non-cancer disorders of the above mentioned structures, and physiological investigations and clinical examinations are needed to complement cancer-oriented research.

Four types of possible effects might be considered:

- acute, functional disturbances (presumably reversible) during the exposure, ie, telephone use
- stable impairment of functions due to long-term use of a handset
- progression of existing neurological symptoms (migraine, hearing deficit, trigeminal neuralgia, cerebro-vascular disorders, etc) in patients using handsets
- increase in subjective symptoms in people complaining of 'hypersensitivity' to electromagnetic fields.

Acute, functional disturbances could be investigated by provocation studies including standardised exposure facilities and experimental protocols. Investigations on healthy volunteers are closest to the real situation and address directly public concern.

The stable impairment of functions owing to long-term usage of handsets is based on the outcome of the epidemiological study on subjective disorders connected with radiotelephone use. If this finds a relatively high number of people with complaints, which they relate to handset use, then it would be of interest to test some of these individuals in the laboratory using objective physiological examinations under controlled exposure conditions.

The fourth type of possible effect is based on the small fraction of the population claiming a general electrical hypersensitivity. It would be of interest to perform provocation experiments under strictly controlled conditions. For this group, in particular, it is necessary to consider the provocation protocol carefully and to take into consideration previous experience from studies on such patients (Sandström, 1996).

Studies should be based on standard clinical examinations, tests and objective psycho-physiological methods commonly accepted in laboratory and clinical practice.

Lateralisation of exposure should be take into account where relevant. It is expected that the side of main radiofrequency exposure depends on right- or left-handedness. In these circumstances, the 'rarely' stimulated side might be considered as a control.

Although the main concern is the energy absorption in tissue near the antenna, some other mechanisms cannot be excluded *a priori*. Consideration of the possible non-thermal effects of radiofrequency radiation as well as focal stimulation of crucial acupuncture sites of the ears could also be of importance for a more complete picture.

The study of stress in combination with microwave radiation exposure is important because of the findings of Dhabhar and McEwen (1995). They found that tube restraint of mice was followed by a 50–80% fall in blood leukocyte levels within 2 h, and recovery in 3 h. The results suggests that acute stress induces a redistribution of leukocytes (seen as an influx of leukocytes to the skin). They also reported delayed hypersensitivity in the skin of the ear pinnae of stressed mice, measuring inflammation by increased pinna thickness and histological quantification of leukocytes. In view of the strong near-fields generated in superficial tissues of the heads of cell-phone users, it may be useful to examine local tissue immune status and blood flow changes.

In view of the results of the studies on the connection between sleep disturbance and mobile telephone exposure (Mann and Röschke, 1996) and short-wave transmitters (Altpeter et al, 1995), it is also of interest to continue this line of research with more and well-controlled laboratory experiments on sleep quality during exposure. Even long-term exposure experiments may be needed for some groups.

The Expert Group recommends that laboratory studies on volunteers should be carried out as follows:

- acute exposure of healthy volunteers to radiofrequency fields from handsets and investigations of possible neurophysiological effects including neurotransmitter levels
- provocation studies, involving the acute exposure of people claiming neurological symptoms associated with radiotelephone use, to the emissions from handsets and/or base stations
- disturbance of sleep patterns in people exposed to radiofrequency fields associated with personal telecommunications
- acute exposure of healthy volunteers to radiofrequency fields from handsets and investigations of possible effects on the immune system (lymphocytes – sub-populations, etc).

All experiments using volunteers should be 'double blind' where appropriate.

4 Epidemiology

4.1 The role of epidemiological research

Epidemiological research can be used to investigate directly the question of whether or not radiotelephone use is a determinant of risk of disease in people. By comparison, biological *in vitro* research investigates whether there are cellular or physiological mechanisms by which disease could be caused, and biological animal research investigates whether disease can be caused in species other than humans (and by extrapolation, whether disease would be caused in humans **if** the same outcomes occur in humans as in the animal model, which they may not). The input of biological and dosimetric research findings will be critical to designing epidemiological studies.

Epidemiological studies, unlike most laboratory studies, tend to take several years and to be based on data arising from populations of many thousands or even millions of individuals. Hence, epidemiological studies are not likely to give the 'first warning' of any ill effects of radiotelephones. They need to be initiated, however, while appreciating that they will take several years to give an answer, to provide in a few years' time the most direct information on whether hazards to people exist.

Also, unlike laboratory studies, epidemiological studies can only give information on exposures that have already occurred in people, and on the levels of exposure that they have experienced. Thus, for instance, although an experiment might be conducted in mice to discover whether constant exposure to radiotelephones for a period of life equivalent to, say, 30 years in people produces carcinogenic effects (but with uncertainty as to whether such information can be transposed to humans), an epidemiological study of this question would not at present be possible since there are no people who have been exposed to radiotelephones for 30 years. This limitation means that, for instance, epidemiological studies can only show whether or not risk is raised for latent periods of effect shorter than those since radiotelephones were introduced, and at levels of use up to those that are prevalent in the heaviest users. There is no alternative method to be sure about the effects of use for longer or at higher levels than those that have actually occurred: this will only be known when there are groups of people who have been exposed at higher levels or longer, and whose morbidity and mortality can be measured. Since, at the time studies are conducted, radiotelephones will have been in use in Western Europe for about 14 years, and on a fairly large scale for about 10 years, studies initiated in the next few years will only give information on risks with induction

periods from first use, and for durations of use of about this length, and such studies will be most powerful for shorter periods, of a few years, for which much larger numbers of users exist. Many known instances of cancer causation, including certain effects of ionising radiation, are first seen well within this period (van Leeuwen, 1996), so it is reasonable that epidemiological studies should now be conducted to examine the risks from radiotelephones. However, there are also many carcinogens for which the usual induction period is known to be as long as 15–40 years (Schottenfeld and Fraumeni, 1982), so that negative results from current studies would not rule out the possibility of carcinogenicity with a long induction period: this could only be addressed by waiting several more years before conducting further studies (or for cohorts, re-analyses).

A similar, but slightly different, issue arises with regard to changing technology – the use of analogue versus digital transmission, the frequencies in use, and the power outputs of radiotelephones, have changed over time and will change in future. Again only the effects of those types of technology that have been reasonably widely used for several years can be studied, but since the trend is for new technologies to **reduce** the power output of radiotelephones, this may not be a great limitation to drawing conclusions: if no effect were found from higher power older technologies this would provide substantial reassurance that more recent lower power outputs were unlikely to be harmful. Conversely, if any effect were found from exposure to older, higher power instruments, this would indicate a likely limit on the effect of newer, lower power radiotelephones.

Another limitation of epidemiological research is that it is almost impossible to tell with certainty whether weak associations (ie, slightly elevated relative risks) are caused by exposure. Again this is a limitation not solely of epidemiology, but of scientific research overall. If weak associations are found in rodent experiments, it will be uncertain whether they transpose to humans, so that again there is uncertainty about the effects in people. The reasons why epidemiological studies cannot with certainty identify weak causal associations are both statistical – increasing sample size is needed as the elevation in risk becomes smaller, to the point where study of very slight elevations of risk requires impossibly large studies – and interpretational – for slight associations alternative explanations cannot be satisfactorily ruled out from 'confounding' (ie, there may be other causal variables for the disease that are associated with mobile telephone use and are the true cause of the raised risk and bias). In contrast, for stronger associations (larger relative risks), it is practical to attain statistical power to determine whether results are due to chance, and if a risk is found, it is reasonably certain that it is due to radiotelephone exposure rather than to confounding factors. The greater certainty of results for strong rather than weak associations is not entirely a problem from a public health perspective, however: the public health consequences, and the public perception of risk and need for action, will be greater for large relative risks, which are exactly the ones that the research will be best able to identify.

Taking account of the above limitations, the Expert Group considers that epidemiological studies are a crucial component in determining whether radiotelephone emissions cause adverse health effects, and for the reasons given below they should form a significant component of a funded research programme. Epidemiology is the only way to determine directly whether disease is caused in people, whereas animal experiments and biological/cellular research give a very uncertain prediction of the human effects. There are numerous examples where causes of cancer in animals, or mutagens *in vitro*, have proved not to be material carcinogens in people, and, conversely, where substances not carcinogenic in animal experiments have proved to be human carcinogens. For instance, recently large trials of carotene supplementation in man have been stopped because more deaths occurred in the treated than the placebo group, even though animal studies had shown clear benefits of carotene. Similarly, arsenic and asbestos, which have been found to be powerful carcinogens in humans, are not carcinogens in animal experiments.

Also, the question of whether radiotelephones have adverse health effects is a suitable one for epidemiological enquiry, particularly since their use is widespread in the population. Indeed, certain features of radiotelephone use make it likely that epidemiological investigation could successfully come to a conclusion. The large number of users gives the potential for studies of considerable power, based on hundreds of thousands or even millions of exposed individuals (although not, in the near future, for large numbers with very long-term exposure). The existence of quantified, recorded and dated data about exposures, from billing records (compared with the far more imprecise data usually available for many other epidemiological exposures, for instance, diet) gives a basis from which exposures can be estimated with some precision (although for the reasons given in Section 4.3.2 below, further data, beyond those from the billing records, would be needed to maximise the quality of exposure estimates). The exposure has laterality (users will either hold the handset to the left or right ear), which would be expected to result in laterality of any local effects – again, few other epidemiologically studied exposures have this characteristic.

4.2 Epidemiological studies relevant to human health and mobile telephones

There is, to our knowledge, no published epidemiological research on cause-specific morbidity or mortality in relation to radiotelephone use. However, one recent study from the USA reported preliminary findings regarding overall mortality rates of customers of a large radiotelephone operator (Rothman et al, 1996a). In this on-going prospective cohort study of 255,868 radiotelephone users, age-specific total mortality rates at 1 year follow-up were very similar for users of hand-held telephones and users of other radiotelephones (with the former type of telephones – antenna in the handset – resulting in higher exposure to microwave radiation than the latter type). For customers listed as continuous users for at least 3 years, the overall mortality rate ratio for hand-held versus other radiotelephone use was 0.86 (95% CI, 0.47–1.53). The extremely short follow-up and the unavailability of cause-specific mortality data are strong limitations to meaningful interpretations of these results. There have been a number of investigations of health outcomes of radiofrequency radiation exposure in various circumstances other than radiotelephone use. These studies provide background information of interest in the context of radiotelephone use, but no direct information on its possible hazards. Furthermore, these studies of other exposures to radiofrequency radiation have been small, lacking in data on potentially confounding variables, and had poor data on radiofrequency exposures, so that their results cannot be interpreted conclusively. These studies have related to occupational exposures to radar, occupational and other exposures to radiofrequency and microwave radiation, populations living near military installations and near broadcasting towers, telecommunications workers, workers using radiofrequency radiation for heating, sealing, and plastic welding, groups with medical exposure to radiofrequency radiation, amateur radio operators ('radio hams'), users of hand-held traffic radar devices, and police and military users of hand-held radios. For information, the design and results of selected studies of cancer risk in relation to radiofrequency radiation exposures are summarised in Tables 4.1 and 4.2. These studies all have exposures differing in frequency, type and anatomical distribution from those received from radiotelephones (Rothman et al, 1996b). No conclusion can be drawn from them on the possible effects of the emissions from radiotelephones. For several studies, the link between the occupations investigated and actual exposure is questionable and, in case of exposure to radiofrequency energy, study participants may also have been exposed to ELF radiation. Tables 4.1 and 4.2 show that the results of the various epidemiological studies are inconsistent, both with regard to brain cancer risk and risk of leukaemia. So far, there is certainly no persuasive evidence that low power microwave radio communications emissions adversely affect human cancer risk.

The Expert Group was able to ascertain what epidemiological studies are currently being undertaken on possible radiotelephone health effects. In the USA, Rothman and associates will conduct further follow-up of their cohort of over 250,000 portable and radiotelephone customers (see above for preliminary findings; Rothman et al, 1996a). The Danish Cancer Society, Division of Cancer Epidemiology, is planning a nationwide cohort study of radiotelephone users (estimated cohort size, n = 800,000). Furthermore, in the USA, there are two on-going case-control studies, one conducted by the National Cancer Institute, and one by the American Health Foundation, examining brain tumour risk in relation to radiotelephone use. Both studies have a specific interest in the risk of acoustic neuromas (see Section 4.3.1.1). Plans for case-control studies of brain cancer, cancer of the salivary gland and adult-onset leukaemia have been made in Denmark and Finland. It will take several years before any of these studies will produce results.

In Sweden and Norway, epidemiological studies are now being carried out to discover the prevalence of headaches, and other subjective disorders among radiotelephone users. This will be done by using a questionnaire study. As a first estimate, about 5000 questionnaires will be sent out to each group, ie, analogue and GSM users. This will be followed by a case-control study based on the outcome of the questionnaire, and which will include assessments of SAR values and ELF magnetic fields from the different models in question. Thereby, it might be possible to find out what, if any, parameter(s) are the ones of most interest for these disorders. The case-control studies will also include psychosocial and stress factors as possible risk indicators.

The preliminary results from the questionnaire part of these studies will be ready in Spring 1997, and will give an indication of the prevalence of these disorders. These results can then be used as guidance for the need for an enlargement of the studies.

Table 4.1 Selected results of epidemiological studies related to brain cancer and occupational or recreational exposure to electromagnetic energy (adapted from Rothman et al, 1996b)

Authors	Study type	Disease	Occupational group	RR	95% CI
Beall et al, 1996	Case-control	Brain and CNS cancer (mortality)	Electronics industry (≥ 20 y cf < 10 y)	1.6	0.7–3.3
Gallagher et al, 1991	Cohort	Brain cancer	Radio/TV announcers, technicians, electronic repairman, assemblers	1.6 0.8	0.3–4.8 0.1–2.8
Grayson et al, 1996	Case-control	Brain cancer	US Air Force Radiofrequency/microwave radiation exposures	1.4	1.0–1.9
Hill, 1988	Cohort	Brain and CNS cancer	MIT radar lab workers	1.1	0.2–3.1
Lilienfeld et al, 1978	Cohort	Brain and CNS cancer	Moscow US embassy staff	0.0	0.0–3.3
Milham, 1985	Cohort	Brain cancer	Radio/telegraph operators	0.4	0.0–1.9
Milham, 1988	Cohort	Brain cancer	Ham radio operators	1.4	0.9–2.0
Preston-Martin et al, 1989	Case-control	Glioma	Various high-exposure groups	1.8	0.7–4.8
Speers et al, 1988	Case-control	Brain cancer	Utilities, communications, transportation	2.3	1.2–4.3
Szmigielski, 1996	Cohort	Brain and CNS cancer	Military personnel	1.9	1.1–3.5
Thomas et al, 1987	Case-control	Astrocytoma	Electronics manufacture and repair	4.6	1.9–12.2

RR, Relative risk; CI, Confidence intervals

Table 4.2 Selected results of epidemiological studies relevant to leukaemia and occupational or recreational exposure to electromagnetic energy (adapted from Rothman et al, 1996b)

Authors	Study type	Disease	Occupational group	RR	95% CI
Calle & Savitz, 1985	Cohort	Leukaemia	Radio/telegraph operators, radio/TV repairmen	2.4	0.9–5.1
Coleman et al, 1982	Cohort	Leukaemia	Radio/radar mechanics, telegraph/radio operators	0.2	0.0–1.1
Garland et al, 1990	Cohort	Leukaemia	Electronics technicians	1.1	0.4–2.6
Hill, 1988	Cohort	Leukaemia	MIT radar laboratory workers	0.6	0.1–2.3
Lilienfield et al, 1978	Cohort	Leukaemia	Moscow embassy staff	2.5	0.3–9.0
McDowall, 1983	Cohort	Leukaemia	Telegraph/radio operators, radio/radar mechanics	2.5	1.0–5.2
Milham, 1985	Cohort	Lymphatic, haematopoietic	Radio/telegraph operators, radio/TV repairmen, electronics technicians	1.4	0.8–2.2
Milham, 1988	Cohort	Leukaemia	Ham radio operators	1.2	0.9–1.7
Milham, 1988	Cohort	Lymphatic, haematopoietic, other lymphatic malignancy	Ham radio operators	1.2	1.0–1.5
Pearce et al, 1985	Case-control	Leukaemia	Radio/TV repairmen	4.8	1.6–14.2
Pearce et al, 1989	Case-control	Leukaemia	Radio/TV repairmen	7.9	2.2–28.1
Robinette et al, 1980	Cohort	Lymphatic, haematopoietic	Military radar exposed	1.2	0.8–1.7
Robinson et al, 1991	Cohort	Leukaemia	Telegraph/telephone operators	1.9	0.6–4.6
Szmigielski, 1996	Cohort	Lymphatic, haematopoietic	Military personnel	6.3	3.1–14.3
Wiklund et al, 1981	Cohort	Leukaemia	Telephone operators	1.0	0.6–1.7
Wright et al, 1982	Cohort	Leukaemia	Electronic technicians, radio/TV repairmen	1.0	0.3–2.3 0.1–6.1

RR, Relative risk; CI, Confidence interval

4.3 Research options

4.3.1 Diseases to be studied

As noted above, the current epidemiological literature on the effects of radiotelephones (or indeed of radiofrequency radiation exposure in general) is insufficient to give guidance on which diseases, if any, need epidemiological investigation as possible consequences of radiotelephone exposure. Decisions must, therefore, be based on available information of dosimetry for different anatomical locations in the body, biological research, background knowledge on the incidence, prognosis, and general epidemiology and known risk factors for specific cancer sites, and public concerns. In addition, since rigorous and competent epidemiological studies will take several years to carry out, plans need to take account of likely future public concerns and areas likely to be highlighted by current and planned biological and dosimetric research. To obtain a coherent plan of research overall, therefore, the epidemiological research needs to be planned to take account of the direction of the proposed biological research and to address the prime issues and research questions that this biological research is likely to bring forward.

4.3.1.1 Cancer

On the above grounds, the Expert Group considers that studies should be inaugurated of risks in relation to radiotelephone use of certain cancers originating in parts of the head that receive radiation exposures from handsets, namely: tumours of the brain and cerebral meninges; acoustic neuromas; salivary gland tumours; and leukaemia in adults. Brain cancer is the issue on which public concern about radiotelephones has focused and, although the radiation exposure of the brain is low, the brain is one of the sites receiving some irradiation.

Acoustic neuroma and salivary gland cancers are less common tumours but with direct exposure from handsets. Leukaemia in adults is considered worth investigation because of the suggested sensitivity of the haemopoietic system to electromagnetic energy, Table 4.2. Childhood leukaemia was considered by the Expert Group; these malignancies have been a focus of concern with regard to ELF fields from power lines, although this is not an established aetiological relationship. It does not seem reasonable, however, to initiate studies of childhood leukaemia in relation to radiotelephones since they are not used appreciably by children at the ages at which leukaemia principally occurs.

The Expert Group considered whether breast cancer risk should be investigated epidemiologically, because of suggestions that radiofrequency radiation may affect melatonin secretion by the pineal gland, and that high levels of melatonin might reduce the risk of breast cancer. The Group concluded, however, that there was insufficient dosimetric, biological or epidemiological evidence for these hypotheses at present to justify any epidemiological investigation; if the proposed biological research should prove positive, the need for epidemiological studies would then need to be re-considered.

The Expert Group also considered whether studies should be inaugurated of cancer risk in relation to residential proximity to base stations. It was considered that there was neither dosimetric (Section 1.2), biological or epidemiological justification for such studies. Furthermore, because of methodological difficulty, epidemiological studies based on currently available methods would be most unlikely to give decisive results. The Expert Group do not recommend that such epidemiological studies be inaugurated.

4.3.1.2 Non-malignant diseases and subjective disorders

Apart from the cancers mentioned above, the Expert Group considered that there were no other diseases for which epidemiological studies would be worthwhile, based on current or foreseeable knowledge and concerns. There have been case-reports claiming that radiotelephone use causes various subjective disorders, but study of this

is methodologically very difficult because of the subjectivity of the outcomes. Studies currently underway in Sweden and Norway, described in Section 4.2, should greatly improve understanding of the best ways to attempt to overcome these difficulties; the Expert Group recommend that further research should not be called for until the results of the Swedish and Norwegian studies are known.

4.3.2 Study designs

Long-term trials to determine whether mobile telephones can cause cancer would be neither ethical nor practical. There are two main study designs that could be used to investigate epidemiologically whether radiotelephones can cause cancer. To a large extent their comparative advantages and disadvantages are complementary. In essence, either a *cohort* study could be performed, in which data on handset use would be collected from large numbers of individuals and then these individuals would be followed up over time to ascertain whether users were at greater risk of cancer than non-users, and whether degree and duration of use were related to degree of risk; or a *case-control* study could be conducted, in which individuals with a particular cancer (the 'cases'), and individuals who did not have this cancer (the 'controls'), were compared with regard to their handset use. A hybrid design termed a *nested case-control study* is also possible, in which individuals with and without exposure are followed as in a cohort study and, when cancers have occurred, more detailed data on exposures are collected only for the cancer cases and for a sample of the remainder of the cohort, as controls; this economises on the number of individuals within the cohort for whom the detailed exposure data need to be collected.

Cohort studies have the strength that, since all persons within the study population (the cohort) are included in the analysis, there can be no bias in the selection of the people with cancer and the people without cancer included. Also, since exposure data are collected **before** disease occurs, these data cannot be biased by knowledge of the presence/absence of disease. Cohort studies can give information on multiple outcomes from the exposure studied, and thus a cohort study of cancer incidence could readily provide data on incidence of all cancers and mortality from all causes. By using billing records, if they have been retained and are accessible, important exposure information could potentially be obtained for a large number of people (Funch et al, 1996). The disadvantages of a cohort study are that it would need to be extremely large and to continue for a large number of years (or gain data retrospectively for a large number of years) to gain sufficient cases. As a consequence, in most circumstances it would be very expensive, and in many countries it would be completely impractical, because of the scale and difficulty of the necessary follow-up. Also, importantly, it could not realistically collect data for the whole cohort on confounding variables or exposure variables requiring enquiry to the user. For instance, the side of use (left-handed, right-handed) of handsets would be important in relation to side of brain cancers, but could only be determined by asking the user. The extent to which a radiotelephone billed to an individual was actually used by that person, rather than by, say, their family or colleagues, would also be evident only from enquiry to the subject, not from routine billing records. A recent United States study by Funch et al (1996) showed that 48% of account holders of a large radiotelephone company were sole users of the telephone, while 69% were the primary user. A further limitation of billing records is that much business use, especially by intensive users, has been billed to the company rather than the individual user. Also, the extent to which a handset has been used for conversation (and hence held to the head) or in computer modem mode (and hence not close to the head and, indeed not necessarily close to the user at all), and if used for conversation has been hand-held rather than, for instance, used in a vehicle-holder at a distance from the body, would only be evident from direct enquiry to the subject.

A further difficulty of a cohort design is that radiotelephone use is changing rapidly over time; consequently, any prospective element in a cohort study would need to include repeated re-collection of exposure information for the surviving cohort, at considerable expense.

Case-control studies have in general opposite strengths and weaknesses to cohort studies. They tend to be cheaper and quicker to conduct than cohort studies, because information only needs to be obtained for hundreds of cases and controls, rather than hundreds of thousands of people in a cohort, few of whom will eventually get the cancer of interest. It is therefore practical to gain detailed information from the individuals – for instance, on the side of the head that the individual holds their handset, who truly uses the radiotelephone registered in their name, and on confounding variables, which could not realistically be collected in a cohort study of hundreds of thousands of subjects. However, case-control studies are notoriously prone to bias which, depending on the circumstances, may or may not be possible to avoid (although one important potential bias, in recall of telephone use, could in part be avoided by gaining permission to use billing records for cases and controls, to give recorded data on use). Case-control studies also focus on one specific disease (the 'cases') under study, although this does not preclude conducting simultaneously and with similar methods in the same country, parallel case-control studies of several diseases.

A *nested case-control* design potentially could give the merits of both cohort and case-control methods, by identifying cases and controls, in an unbiased way, from within a defined cohort population, and then collecting detailed exposure information (for example, both from billing records and from enquiry to the cases and controls). The main problem with this design is that it is likely to be impossible in practice to conduct in most (or perhaps all) EU countries (and, indeed, in countries outside the EU). The major difficulties would be, first, that in many countries large-scale routine follow-up systems for cancer and mortality do not exist, and *ad hoc* individual follow-up would be extremely costly; and, second, that privacy and local ethical constraints, and commercial confidentiality constraints, might make this design impossible to carry out in many countries.

The relative merits and practicalities of the study designs described above are highly dependent on local circumstances. Unlike laboratory studies, the best design in one country might be less satisfactory, or completely impractical, in another.

4.3.3 Number of studies

The results of individual epidemiological studies need confirmation from other such studies elsewhere if they are to be regarded as a basis for reassurance or action. In common with laboratory studies, there is a possibility that the play of chance might lead to an apparently significant result in a particular study, when no true relationship exists. There is also a problem not normally of importance in laboratory studies, however: since epidemiology is based on observation of the complex, individually-chosen behaviour patterns and exposures of the genetically different human beings making up a population, differences in genetic susceptibility or in confounding factors between those who have the disease of interest (eg, brain cancer) and those who do not, might explain apparent differences in risk between users and non-users in any individual study. Efforts can be made to minimise confounding, as noted above, but there is no certainty that in any particular study that they have been entirely successful. In contrast, in a laboratory experiment, randomisation, use of a uniform environment for all animals, and breeding of animals for experimentation can remove or largely eliminate these problems. A further reason to need repetition of epidemiological studies at several locations is the ability to generalise: although it usually the case that external aetiological factors for disease in people are causes in both sexes and all populations (if they are exposed), it helps to confirm that this is true for a particular exposure, both in terms of scientific credibility and for public belief of the results, if the result has been shown in several different populations.

4.4 Recommendations for epidemiological research

Specific cancers

For the reasons given in the previous section, the Expert Group recommend that three or four studies be funded, in different countries (or groups of countries), on the risk of brain tumours in relation to use of radiotelephones. Each of the studies needs to be large enough to give independently substantial results, but also they need to be designed in such a way that eventual combined and comparative analyses are possible. Since radiotelephone use in the EU has been highly uneven between countries, substantial studies within a single country, especially with regard to longer term use and longer induction periods, would only be possible in a small number of countries; for instance, only the UK, Sweden and Norway had more than 100,000 subscribers before 1988. Multicountry collaborations within a single study may therefore be a valuable route to allow for participation by countries with lower prevalence of long-term use.

Studies should also be conducted of risks of acoustic neuroma, salivary gland tumours and leukaemia in adults. For acoustic neuroma and salivary gland tumours, it may well be that multicountry collaborations would be needed to gain a study of sufficient power, and that only one or two such studies, at most, would be practical within Europe.

At least some, and preferably all, of the studies funded should have personal as well as records-based data sources, in order to be able to include data on exposure variables not included in records, and on potential confounding variables. Since an important way to decide whether any associations with radiotelephone use are causal will be to examine whether dose-response and duration-response relationships exist, it is essential that the proposals to be funded should include collection of quantified information on amount and duration of use.

The evaluations of risks of specific cancers recommended above are likely to be best investigated by studies of case-control design. While case-control studies would address these specific outcomes, however, they would not address any public anxiety that might arise about general mortality or cancer incidence in relation to radiotelephone use, or such anxieties in relation to diseases other than those for which the scientific evidence is strongest. In order to give reassurance on these, there is, therefore, an argument for conducting one (or more) cohort studies of cause-specific mortality and cancer incidence in relation to radiotelephone use. For the various reasons outlined above, it would not be easy to conduct a pure cohort study of high quality, especially in relation to data on exposures and potential confounders, and such a study might well need to contain a nested case-control component.

In summary, the Expert Group recommends that:

- several studies of risk of brain cancer should be conducted, in different countries
- at least one study each of risk of acoustic neuroma, salivary gland tumours and leukaemia in adults should be conducted. Acoustic neuroma and salivary gland studies may well need to be multicountry in order to obtain sufficient power
- the above studies should use personal data, from the study subjects, on exposures and confounding variables, and should not be based solely on billing records
- at least one cohort study of cause-specific mortality and cancer incidence should be conducted, if proposals of sufficient power and quality are put forward. Such a study should preferably be followed by a nested case-control study.

5 Research management

5.1 Introduction

This chapter provides a structure for the selection and management of appropriate research.

In respect of its recommendations, the Expert Group recognises the need for the management structure to harmonise with existing administrative and financial procedures and customs within the European Commission. The recommendations made should therefore be regarded in part, or in whole, as one option, but the final management structure should be consistent with the following principles.

- The research should be of the highest quality and should be directly relevant to the question of possible human health effects related to the use of radiotelephones.
- The research should be carried out and managed in a manner such that the work is and is seen to be clearly independent of industry. Industry and other funding agencies should deposit agreed funding. Having deposited the finance, the funding agencies should have no further control over it or its use. Industry and other funding agencies should be provided with regular updates on the general progress of the research programme.
- The research programme should be coordinated and managed by a ***Research Management Team***. The management costs thereby incurred should be regarded for funding purposes as part of the research programme. Management and other administrative costs should be closely monitored and kept to a minimum consistent with maintaining the high quality of the research.
- The assessment and selection of specific research proposals should be carried out by an independent scientific panel – ***Proposals Assessment Panel***.
- The disbursement of research funds should be carried out on the advice of the ***Proposals Assessment Panel***.
- The call for research proposals should be widely advertised.
- The progress of the funded research studies should be monitored by a ***Research Monitoring Panel*** comprising *ad hoc* independent scientific experts.
- The results of the scientific research should be submitted for publication in the peer reviewed scientific literature.

5.2 Research Management Team

The ***Research Management Team*** should be responsible for the overall day-to-day administration and technical management of the entire research programme. This ***Research Management Team*** could be, for example, formed from existing administrative arrangements within the European Commission. Specific duties of the ***Research Management Team*** could include:

- the provision of Secretariat services to the ***Proposals Assessments Panel*** and the ***Research Monitoring Panel***
- handling all correspondence between research teams, the ***Proposals Assessments Panel***, the ***Research Monitoring Panel,*** the European Commission, the industrial and other funders, and the media and other interested parties
- organising all meetings in relation to the research projects including, as appropriate, visits by members of the ***Proposals Assessment Panel*** and the ***Research Monitoring Panel*** to research laboratories, etc.

5.3 Research funding

5.3.1 Firewall

A fundamental requirement of the funding mechanism is that industry and other funding bodies should be provided with the opportunity to contribute funding and materials in kind to the research programme, but should neither have nor be seen to have any influence over the choice of research studies funded, the conduct or the outcome of such studies, or the publication of the results.

The Expert Group recommends that funding for the research programme should be sought from the personal telecommunications industry and other interested parties. Contributions should be used for the sole purpose of funding the scientific research programme and its management. Public acknowledgement of individual contributions for funding and materials in kind should be at the mutual agreement of the funding body and the European Commission. All donations or loans of materials in kind should be arranged through the programme management and not given directly to the research teams. A contribution to the funding or of materials in kind should confer no rights to the contributor other than acknowledgement(s) of the contribution made (where agreed) and information about the progress of the study, as detailed in Section 5.8.

The allocation of funds to specific research projects should be decided according to the recommendations for research funding of the ***Proposals Assessment Panel*** and without consultation with industry or other funding bodies unless required by the Commission.

Legally binding contracts covering the research should be between the European Commission and each of the research teams carrying out the research. Sub- and/or cross-contractual arrangements may be made in respect of collaborative research between two or more research teams.

5.3.2 Budgetary considerations

Estimates of funding required to carry out a research programme in accordance with the recommendations of the Expert Group are provided in Table 5.1.

Table 5.1 Estimates of funding (kECUs)

Area of research	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Biological studies	**6,951**	**3,571**	**3,571**	**1,530**	**0**	**15,623**
Biophysical	708	368	368			1,444
In vitro	2,655	1,305	1,305			5,265
In vivo	2,880	1,530	1,530	1,530		7,470
Human	708	368	368			1,444
Epidemiology	1,400	1,750	1,700	1,500	1,150	**7,500**
Management, etc.	150	150	150	120	120	**690**
Total						**23,813**

The estimates have necessarily been compiled using representative staffing, overheads, laboratory supplies and travel costs for research carried out in a European academic establishment. The costs for biological (including biophysical) research allow for dosimetry and exposure systems necessary for the study.

The costs of the recommended epidemiological studies are particularly dependent on the countries in which they are conducted. Unlike laboratory studies, the difficulty of conducting a particular epidemiological study is likely to vary with location. For instance, obtaining follow-up in cohort studies of a fixed size would entail costs probably varying more than ten-fold in different European countries: in certain countries, such follow-up can be

obtained, relatively cheaply, by a routine computer linkage to files, using national ID numbers to link individuals on these files; in other countries, routine follow-up is possible, but only by linkage paid for on a *per capita* basis, and therefore very costly for large cohorts; and in other countries, no routine follow-up system exists, and each cohort member must separately be followed by letters to the individual, inspection of local or central mortality registers, and other time-consuming and costly methods. The variation in costs for case-control studies, although probably not quite as large, would still be very substantial; for instance, the costs of ascertainment of cases would generally be very much lower in those parts of Europe with efficient cancer registration than in those parts where no cancer registration exists. Case-control studies for less common cancers are likely to need to cover a much larger geographical area, probably in several countries, than studies of more common cancers.

5.4 Call for research proposals

It is envisaged that the timescale of the biophysical and biological research programme will be 4 years with individual research studies of duration between 1 and 4 years. By necessity, the epidemiological (cohort) programme may extend beyond this period and, with regard to the sources of uncertainty in the costs outlined above, further funding may be necessary. It is important that there is flexibility so that studies can be phased in as the programme develops. For example, it may be appropriate to identify further projects in the mid-to-latter part of the programme to elucidate aspects arising from the results of studies completed in the early part of the programme.

Calls for specific research proposals based on the recommendations of the Expert Group should be published. A first call for research proposals should invite applications for proformas. Interested research teams should complete these proformas providing, as appropriate, details of their proposed research, the facilities afforded by their laboratory, the qualifications and experience of the researchers, and details of the funding required for the research. Proposals should be assessed by the ***Proposals Assessment Panel***, who should recommend which research studies should be supported. The ***Proposals Assessment Panel*** should also indicate where collaborative projects appear either necessary or desirable.

5.5 Proposals Assessment Panel

The ***Proposals Assessment Panel*** should comprise *ad hoc* appointed experts in the fields of scientific/technical expertise required for the assessment of specific studies in respect of potential funding within the scientific programme. The ***Research Management Team*** should act as the Secretariat for the ***Proposals Assessment Panel*** and should make all administrative and other arrangements necessary for it to carry out its functions. Specific tasks of the ***Proposals Assessment Panel*** should include:

- critical review of proposals for research submitted for funding
- making initial visit(s) to and having discussion(s) with prospective research teams, as appropriate
- advising on the acceptability of specific project proposals in respect of funding
- recommending changes to proposals for research studies and collaborations between research teams where identified as being necessary and beneficial to the overall research programme.

5.6 Research proposals selection criteria

5.6.1 Exposure and dosimetry studies

The Expert Group notes the importance of providing guidance in respect of assessing proposals for research. It therefore recommends the following criteria in this respect.

- Laboratories and researchers must have proven experience in carrying out and publishing the results of scientific work in the specific area of microwave exposure and dosimetry of living systems.
- Exposure and dosimetry studies should form a collaborative part of a biological research study.
- Each laboratory should specify the nature of the quality assurance programme that it intends to follow in respect of its proposed research, and quality assurance documentation specifically related to the investigation should be made available to the ***Proposals Assessment Panel.***
- Where relevant, proven experience of dosimetric modelling using numerical codes is necessary.

5.6.2 Biophysical and biological studies

The selection criteria in respect of proposals for biophysical and biological studies may be summarised as follows.

- Laboratories and researchers must have proven experience in carrying out and publishing the results of scientific work in the specific area of biophysical/biological research.
- The researchers must have proven experience of electromagnetic fields dosimetry and exposure systems appropriate to microwave radiation exposure or enter into a collaborative arrangement with a laboratory with a proven record of experience in the field.
- Proposals for research should:

⇒ address issues relevant to human health

⇒ set out to investigate exposure–response relationships

⇒ allow differentiation between cw and amplitude-modulated effects

⇒ allow differentiation between thermal and non-thermal microwave radiation effects

⇒ characterise experimental conditions with radiotelephones such that comparison can be made with radiotelephones

⇒ employ appropriate negative and positive controls.

- The researchers should have access to and obtain statistical advice in respect of planning, carrying out and analysing the results of the experimental work.
- For biological effects studies, priority will be given to funding studies where the biological model is exposed to a range of exposures representing different radiotelephone systems.
- The protocols for studies should be produced at the outset of each study and should be regularly updated where appropriate in order to assist future replication of the study.
- Each laboratory should specify the nature of the quality assurance programme that it intends to follow in respect of its proposed research, and quality assurance documentation specifically related to the investigation should be made available on request to the ***Research Management Team.***
- Experimental studies involving the use of laboratory animals should be carried out in strict accordance with relevant regulations applicable to such use.

5.6.3 Epidemiological studies

The Expert Group considers that the following criteria are desirable and should be applied when selecting studies for funding. It is recognised that not all may be practical in any particular circumstance and judgement will be needed on whether sufficient are met to make a study worthwhile. It is suggested, however, that applicants should state the extent to which their proposals meet the criteria, viz,

- proven track record of applicants in successful conduct and publication of high quality case-control/cohort studies. Availability of expertise on statistics and exposure assessments either among the applicants or from collaborators
- if case-control design: appropriate non-biased control group; non-biased methods for data collection, applied in same way to cases and controls
- if cohort design, methods that will give:
  - ⇒ complete follow-up for cause-specific mortality and preferably also for site-specific cancer incidence
  - ⇒ data on changes of exposure over time for the full period of follow-up to be analysed
  - ⇒ comparison of cancer incidence in the cohort with that in a non-exposed cohort or from the appropriate general population (from population-based cancer registration)
- use of recorded quantified exposure data from billing records and also personal exposure data from individuals
- adequate data on confounding variables, and method(s) to control for confounding
- for brain tumour study – diagnostic confirmation of cases
  for acoustic neuroma, salivary gland and leukaemia studies – histological/haematological diagnosis of cases
  for brain tumour, acoustic neuroma and salivary gland studies – data on laterality of tumour
- for a case-control study, geographic and demographic choice of study population to obtain a high prevalence of use, and especially long-term and long-ago use, in controls. Calculation of power for a 5-year and for a 10-year induction period (since first use)
- experience of applicants in collaborative multicentre studies and willingness to make data collection compatible with parallel studies funded in other European countries
- willingness to enter data into meta-analysis and to agree mechanisms to prevent inappropriate preliminary publication.

5.7 Research Monitoring Panel

The Expert Group recommends the appointment of a ***Research Monitoring Panel*** consisting of *ad hoc* appointed experts in the fields of scientific/technical expertise required for monitoring the progress of specific studies. It is recommended that the ***Research Management Team*** should act as the Secretariat for the ***Research Monitoring Panel*** and should make all administrative and other arrangements necessary for it to carry out its functions.

The Expert Group recommends that the functions of the ***Research Monitoring Panel*** should include:

- making site visits to the research laboratories to monitor progress on specific studies
- discussing progress and points of concern with the research teams

- advising the ***Research Management Team*** on the acceptability of progress made on specific projects in respect of continuity of funding
- recommending changes to research studies (including curtailment, extension, redirection and collaboration), as appropriate
- critically reviewing progress reports from the research teams and material intended for publication.

5.8 Information channels

The Expert Group recognises the importance of good communications among all of the stakeholders in the research programme. It therefore recommends that the ***Research Management Team*** should be responsible for communications and dissemination of information between the funding agencies, the European Commission, the research teams, the broader scientific community, the media and the general public. The ***Research Management Team*** should prepare a report of overall research progress with a recommended frequency of twice per year. Annual open meetings could provide an opportunity for the Commission and the funding bodies to learn of progress and to provide feedback.

It is recommended that a scientific research newsletter and, if possible, Internet homepage should be available to the public and to all interested parties. The newsletter and Internet homepage should be prepared and updated regularly by the ***Research Management Team***. For completed research studies, statements, written for non-scientists, should be published in the newsletter (and Internet homepage), summarising their key findings.

5.9 Publication of results

It is the recommendation of the Expert Group that the results of all the research should be placed in the public arena without undue impediment. It is, however, recognised that in the interest of sustaining a consistent high standard and quality of presentations for the entire research programme, some editorial control may be necessary.

It is therefore recommended that draft reports of all studies or intended presentations at meetings should be subject to comment by the ***Research Monitoring Panel***. However, it is emphasised that their final content should rest with the authors of the studies reports. Results of the biological research of an interim or preliminary nature should not be presented at public or scientific meetings without the prior approval of the ***Research Monitoring Panel***.

The results of the scientific research must be submitted for publication in peer-reviewed scientific journals.

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Funding Agency	Telstra Co and National Health Medical Research Council
Main topic	Effects of pulsed radiofrequency fields (900 MHz) on lymphoma incidence in Eμ-pim1 mice
Dates (start-end)	From November 1992
Exposure systems and protocols	2 x 30 min exposure for up to 18 months to 1/4 λ monopole antenna, far-field exposure to SAR of 0.01–4.2 W kg^{-1}
Biological models	Eμ-pim1 transgenic mice
Results	Not yet available
Publications	Submitted to Radiation Research
Collaborations within programme	
outside programme	

Location	Melbourne (Australia)
Name(s) of project leader(s)	WOOD, JOYNER, ANDERSON
Full address	Swinburne University of Technology, John St, Hawthorn, VIC 3122, Australia
Email	andrewwood@swin.edu.au k.joyner@telstra.com.au v.anderson@trl.telstra.com.au
Funding Agency	Swinburne University and Telstra
Main topic	Effects of radiofrequency radiation on cell function
Dates (start-end)	March 1996 – December 1997
Exposure systems and protocols	Purpose designed cell chamber that allows simultaneous 900 MHz radiofrequency exposure and viewing by a laser scanning confocal microscope. Fluorescence microscopy particularly using calcium probes.

Results	In progress
Publications	None
Collaborations within programme	Swinburne University of Technology and Telstra Research Laboratories
outside programme	None

Location	Mol (Belgium)
Project leader (s)	VERSCHAEVE
Full address	VITO, Boeretang 200, 2400 Mol, Belgium.
Email	verschal@vitooosf1.vito.be
Funding Agency	BELGACOM
Main topic	Genetic effects of mobile telephones microwaves radiation
Dates (start-end)	August 1995 to August 1998
Exposure systems and protocols	Radiofrequency generator + TEM cell at various power levels; GSM base station antenna, cw; Other exposure systems (450 MHz antenna, etc).
Biological models	Cytogenetics and comet assay on human lymphocytes *in vitro* and on lymphocytes of exposed rats and workers.
Results	Usually no genotoxic effects except for effects observed under thermal conditions. Synergistic effects with some chemical/physical mutagens under specific conditions (eg, radiofrequency irradiation prior to mutagen exposure).
Publications	◆ Verschaeve (1994), Proc. COST 244 Meeting Bled. ◆ Maes et al (1995), Electromagnetiobiology, 14: 91–98. ◆ Maes et al (1996), Environ Molec Mutagen, in press. ◆ Verschaeve (1996), Proc. 3rd Int. Symp. on Gen. Health and Disease, Amritsar, India. ◆ Verschaeve (1996), Proc. WTR State of the Science Colloquium, Rome.
Collaborations within programme	Dr. L. Martens, University of Ghent, Belgium.

	Dr. D. Slaets, Gezondheid en Arbeid, Brussels, Belgium.

Location	Aalborg (Denmark)
Project leader(s)	KWEE[1] and RASKMARK[2]
Full Address	1. Institute of Medical Biochemistry, University of Aarhus, 8000 Denmark 2. Institute of Communication Technology, Aalborg University, 9220, Denmark.
Email	
Funding Agency	
Main Topic	Cell proliferation
Dates(start-end)	
Exposure systems and protocols	TEM cells in incubators. 960 MHz. 30 min exposure.
Biological models	Cells cultured in 96-multiwell plates. Log phase. Cell proliferation was assayed 24 h after exposure using the mTT test.
Results	Alteration of proliferation depending on SAR and on confluence of the cells.
Publications	Proceedings of the COST 244 workshop in Kuopio, Finland, September 1995.
Collaborations	

Location	Helsinki (Finland)
Project leader (s)	HIETANEN
Full address	FIOH, Laajaniityntie 1, 01620 Vantaa, Finland
Email	Mhie@occuphealth.fi
Funding Agency	Finnish Work Environment Fund Technology Development Centre Nokia Mobile phones

	Benefon Telecom Finland Helsingin Puhelin
Main topic	Effects of mobile communication microwaves on EEG in humans.
Dates (start-end)	1994 – 1996
Exposure systems and protocols	Quantitative analysis of EEG was taken for 19 volunteers (10 men and 9 women). Six EEG recordings were taken for each volunteer. Total time of recording was 30 min, of which exposure duration was 20 min.
Biological models	
Results	No statistically significant changes in EEG were observed.
Publications	None yet
Collaborations within programme	Nokia Mobile phones Benefon, Ericsson.
outside programme	

Location	Kuopio (Finland)
Project leader (s)	JUUTILAINEN
Full address	Department of Environmental Sciences, University of Kupio, PO Box 1627, 70211 Kuopio, Finland.
Email	jukka.juutilainen@uku.fi
Funding Agency	Several Finnish agencies and companies
Main topic	Possible cancer-promoting effects of pulsed or continuous 900 MHz radiation in mice.
Dates (start-end)	January 1995 to December 1997
Exposure systems and protocols	A rectangular waveguide is used for exposure (24.8 x 20 cm). Animals are exposed 1.5 h d^{-1}, 5 d w^{-1}. During exposure, mice are immobilised by keeping them in small acrylic tubes. 50 animals per group are exposed, divided into the following groups: A. cage controls, B. sham radiofrequency exposure, C. Continuous exposure

	902.5 MHz, (SAR 1.5 W kg^{-1}), D. pulsed radiofrequency radiation 902.4 MHz, 1/8 duty cycle, 217 Hz repetition rate (peak SAR 2.8 W kg^{-1}). In addition, there is a 'potentially positive control group' exposed to 50 Hz magnetic fields (24 h d^{-1}) and a sham 50 Hz exposed group.
Biological models	Female CBA/S mice exposed to ionising radiation (4 Gy in three subdoses) to initiate the development of tumours. These mice are prone to develop lymphomas when exposed to ionising radiation.
Results	Thus far, no effects of radiofrequency radiation on growth or survival.
Publications	Juutilainen J, Heikkinen P, Hongisto T, Huuskonen H, Komulainen, Kosma V-M, Kumlin T, Lahtinen T, Lang S, Penttilä I, Väänäen A (1996). A study of the effects of pulsed or CW 900-MHz radiation on the development of cancer in mice. 3rd Congress of the EBEA, Nancy, France.
Collaborations within programme	Finnish Centre for Radiation and Nuclear Safety (STUK), National Public Health Institute, Kuopio University Hospital

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Location	Bordeaux (France)
Project leader (s)	VEYRET, CHAGNAUD and MOREAU
Full address	Laboratoire PIOM, ENSCPB, BP 108, 33402 Talence cedex, France.
Email	veyret@hugo.lmaster.u-bordeaux.fr
Funding Agency	CNET (research centre of France Télécom).
Main topic	*In vivo* and *in vitro* effects of microwave radiation used in mobile communications.
Dates (start-end)	January 1994 to December 1995
Exposure systems and protocols	Plane-wave exposure at 900 MHz in anechoic chambers, up to 200 µW cm^{-2}. GSM signal. Rats exposed parallel to the electric field by groups of 10. (2 h d^{-1} for 2 weeks SAR 0.27 W kg^{-1}). Cells in culture exposed in thermostatically controlled containers (37 °C, 5% CO2) exposed once for 4 h.

Biological models	Growth of chemically induced tumours (benzo(a)pyrene) in rats. Two-week exposures at three dates before tumour appearance. Immunological parameters in the spleen lymphocytes of rats exposed for 10 days (lymphocyte subpopulations, lymphoblastoid transformation, etc), Proliferation of cells exposed for 4 h (GH3, Molt4, C6 cell lines) assessed 24 and 48 h post exposure.
Results	No changes in date of appearance of tumours nor on survival of rats bearing tumours. No changes in immunological parameters in exposed rats. No effect on the proliferation of cells exposed.
Publications	◆ Chagnaud JL, Després B and Veyret B (1995). Effects of pulsed microwaves on the immune system and on chemically-induced tumors in rats. In: Proceedings of the COST 244 workshop on Biological effects relevant to amplitude modulated RF fields, Kuopio, Finland, D. Simunic ed. ◆ Veyret B and Chagnaud JL (1996). Effects of GSM-Modulated Microwaves on the Proliferation of Tumour Cells *In Vitro*. 3rd Congress of the European Bioelectromagnetics Association, Nancy, France. ◆ 3 manuscripts in preparation.
Collaborations within programme	B. Després and J. Wiart, CNET, Several departments of the Medical School in Bordeaux, R. de Seze and L. Miro, Medical Biophysics Department, University of Nîmes, France.
outside programme	C. Marino, G. Lovisolo and G. D'Inzeo, ENEA and La Sapienza University, Rome, Italy, P. Raskmark, Aalborg, Denmark.

Location	Nîmes (France)
Project leader (s)	de SEZE and MIRO
Full address	Laboratoire de Biophysique Médicale, Faculté de Médecine, Avenue Kennedy, 30900 Nîmes, France
Email	biomed@zeus.sc.univ-montp1.fr
Funding Agency	CNET, France Télécom

Main topic	Biological effects of mobile telephones on the endocrine system in humans
Dates (start-end)	September 1994 to June 1995
Exposure systems and protocols	Volunteers using mobile phones while watching TV. 2 h d^{-1}, 5 d w^{-1} for 4 w.
Biological models	Weekly sampling and dosage of ACTH, TSH, FSH, GH, LH and PRL for 9 w, 3 before exposure period, 4 during and 2 after.
Results	Slight TSH decrease on week 4 of exposure. Needs to be confirmed with sham-exposed groups.
Publications	In progress
Collaborations within programme	Dr. Baudin, Radioimmunologie, CHU Gaston Doumergue, BP 26, 30029 Nîmes, France
outside programme	B. Veyret, laboratoire PIOM, ENSCPB, BP 108, 33402 Talence, France.

Location	Nîmes (France)
Project leader (s)	MIRO, AYOUB, de SEZE and THIMONNIER
Full address	Laboratoire de Biophysique Médicale, Faculté de Médecine, Avenue Kennedy, 30900 Nîmes, France.
Email	biomed@zeus.sc.univ-montp1.fr
Funding Agency	CNET, France Télécom
Main topic	Biological effects of mobile telephones on cerebral and auditive electrophysiology in humans.
Dates (start-end)	January 1996 to June 1996
Exposure systems and protocols	1 h listening to mobile phones. Electrophysiological recording before and after exposure.
Biological models	20 healthy young volunteers: 10 males and 10 females.
Results	—

Publications	—
Collaborations within programme	Drs. Chabert-Lallemand, Otoneurologie, CHU Gaston Doumergue, BP 26, 30029 Nîmes, France
outside programme	B. Veyret, laboratoire PIOM, ENSCPB, BP 108, 33402 Talence, France.

Location	Nîmes (France)
Project leader (s)	de SEZE and PRIVAT
Full address	Laboratoire de Biophysique Médicale, Faculté de Médecine, Avenue Kennedy, 30900 Nîmes, France.
Email	biomed@zeus.sc.univ-montp1.fr
Funding Agency	CNET, France Télécom
Main topic	Biological effects of mobile telephones on the nervous system in rats.
Dates (start-end)	September 1994 to September 1995
Exposure systems and protocols	6 h d^{-1}, 5 d w^{-1} for 4 w. Far-field exposure at 900 MHz (GSM modulation). Average incident power density: 200 $\mu W\ cm^{-2}$.
Biological models	Immunocytochemical detection of neurotransmitters: GABA, DA, NA, 5HT and GFAP in rat brains. Quantification by image analysis.
Results	No differences between exposed and sham-exposed groups.
Publications	In progress
Collaborations within programme	Dr. Privat, INSERM U-336, DPVSN-USTL-106 Box- Place Eugène Bataillon, 34095 Montpellier cedex 05, France.
outside programme	Drs. M. Geffard and B. Veyret, laboratoire PIOM, ENSCPB, BP 108, 33402 Talence, France.

Location	Berlin (Germany)
Name(s) of project leader	FITZNER, LANGER, ZEMANN
Full address	Institut fur Klinische Chemie und Klinische Biochemie Universitäts-

	klinikum Benjamin Franklin der Freien Universität Berlin Hindenburgdamm 30 D-122ûO Berlin
Email	
Funding Agency	Forschungsgemeinschaft Funk (FGF)
Main topic	Growth behaviour of human leukaemia HL-60 cells influenced by high frequency electromagnetic fields for the investigation of cancer promoting effects (Wachstumsverhalten von humanen Leukamiezellen)
Dates (start-end)	September 1993–December 1994
Exposure systems and protocols	GTEM-cell, model 5302, made by EMCO; USA; signal generator, type SMT 03, by Rhode 8 Schwarz, Germany; band amplifier for the frequency range of 900 MHz and 1.8 GHz
Biological models	*In vitro*, human leukaemia origin HL-60 cultured in RPMI 1640 medium
Results	Already transformed human white blood cells (leukaemia cells), which were exposed to high frequency fields (900 MHz and 1.8 GHz, pulsed with 217 Hz) show no multiple increase in growth speed compared with identical control cells not exposed, because doubling time and thymidine kinase activity, measured in the cell culture supernatants, do not differ essentially from each other.
Publications	Newsletter Edition Wissenschaft Nr 11/95
Collaborations within programme	Dipl-Ing. U Neibig, Institut fur Nachrichtentechnik, Technische Universitat Braunschweig and Prof Dr.-Ing EHK Brinkmann, Institut fur Hochspannungstechnik, Technische Universitat Braunschweig
outside programme	

Location	Bochum-Langendreer (Germany)
Name(s) of project leader(s)	GEHLEN, SPITTLER, CALABRESE, HANSEN
Full address	Neurologische Universitätsklinik, Knappschafts-Krankenhaus Ruhr Universität Bochum, In der Schornau 23-25, 44892 Bochum
Email	

Funding Agency	Forschungsgemeinschaft Funk (FGF)
Main topic	Cerebrobiological effects in low-frequency-pulsed radiofrequency fields
Dates (start-end)	September 1994–September 1995
Exposure systems and protocols	Mobile telephone with 914.2 MHz frequency, EEG, neuropsychological testing
Biological models	*In vivo*
Results	In a controlled study with 52 normal adult subjects, no significant impact of the transmitting field generated by a mobile telephone could be observed on the human EEG or on cognitive performance.
Publications	
Collaborations within programme	V Hansen, Lehrstuhl fur Theoretische Elektrotechnik Bergische Universitat, Wuppertal
outside programme	

Location	Bonn (Germany)
Name(s) of project leader(s)	MEYER, WOLKE
Full Address	Institute of Physiology, Rheinische-Friedrich-Wilhelms- Universität, Bonn (D)
Email	
Funding Agency	FGF
Main Topic	Cell physiology
Dates(start-end)	
Exposure systems and protocols	TEM cell, 900 and 1800 MHz, AM (0, 16, 50, 217, 30000 Hz), SAR: 9-559 mW kg^{-1}
Biological models	Isolated heart muscle cells and Jurkat T-cells.
Results	So far no effects on either type of cells.

Publications

Collaborations

Location	Bonn (Germany)
Name(s) of project leader	MEYER, GOLLNICK, WOLKE
Full address	Physiologisches Institut der Rheinischen-Friedrich-Wilhelms-Universität Bonn Wilhelmstr 31, D-53111 Bonn phone û228/28723-11, fax -13
Email	meyer@snphysio2.wilhelm.uni-bonn.de
Funding Agency	Forschungsgemeinschaft Funk (FGF)
Main topic	The influence of high-frequency electromagnetic fields on the intra-cellular calcium concentration of excitable and non-excitable cells
Dates(start-end)	September 1993–December 1994
Exposure systems and protocols	TEM-cell; signal generator, type SLRD, by Rhode & Schwarz, Germany, with extended pulse modulation; image analysis system based on an intensified CCD-camera and a frame grabber with appropriate software
Biological models	*In vitro*, (excitable) isolated heart muscle cells of the guinea pig and (non-excitable) cell cultured T-lymphocytes of the cell line Jurkat
Results	The field exposure did not influence the calcium concentration in any case.
Publications	Newsletter Edition Wissenschaft Nr 2, December 1995
Collaborations within programme	Dipl -Ing. U Neibig, TU Braunschweig
outside programme	

Location	Braunschweig (Germany)
Name(s) of project leader	NEIBIG, ELSNER
Full address	Institut fur Nachrichtentechnik, Technische Universitat

	Braunschweig
Email	
Funding Agency	Forschungsgemeinschaft Funk (FGF)
Main topic	Experimental set-up for studying electromagnetic alternating fields
Dates (start-end)	September 1993–December 1994
Exposure systems and protocols	Various TEM cells with 400 MHz and 900 MHz, and GTEM cells up to 1.8 GHz
Biological models	
Publications	Newsletter Edition Wissenschaft Nr. 3, January 1996
Collaborations within programme	Dr med R Fitzner, E Langer, FU Berlin; Dr. rer nat R Meyer, Universitat Bonn Dr. rer nat S. Diener, Prof Dr. rer nat P Eberle, TU Braunschweig:
outside programme	

Location	Braunschweig (Germany)
Name(s) of project leader(s)	EBERLE, DIENER, ERDTMANN-VOURLIOTIS, FINKE, LOFFELHOLZ, SCHNOR, SCHRADER
Full address	Institut fur Humanbiologie, Abt Humangenetik und Cytogenetik.Technische Universitat Braunschweig Gaul3str 17, D-38106 Braunschweig
Email	
Funding Agency	Forschungsgemeinschaft Funk (FGF)
Main topic	Cytogenic studies of the effects of mobile telephone radio waves
Dates (start-end)	September 1993–December 1994
Exposure systems and protocols	TEM or GTEM-cells
Biological models	*In vitro:* cell proliferation, SCE, chromosome aberrations, micronuclei and mutation rates.
Results	There were no indications whatsoever that the processes recorded in

	the test parameter were affected by high frequency electromagnetic fields.
Publications	Newsletter Edition Wissenschaft Nr 4, February 1996
Collaborations within programme	U Neibig, TU Braunschweig
outside programme	

Location	Braunschweig (Germany)
Project leader (s)	KULLNICK
Full address	Technical University of Braunschweig
Email	
Funding Agency	Deutsche Telekom
Main topic	Neurophysiological investigations on humans
Dates (start-end)	1993–1994
Exposure systems and protocols	
Biological models	Volunteers
Results	None
Publications	Yes
Collaborations within programme	
outside programme	

Location	Cologne (Germany)
Name(s) of project leader(s)	HOSSMANN
Full Address	Max Planck Institute Für Neurologische Forschung 50931 Köln (Lindenthal), Gleueler Strasse 50 Germany
Email	

Funding Agency	Motorola
Main Topic	*In vivo* testing of the GSM signal
Dates(start-end)	August 1994–1996
Exposure systems and protocols	Near-field head exposure of rats.
Biological models	Rats
Results	None yet
Publications	None yet
Collaborations within programme	Prof. M. Kiessling, University of Heidelberg. Prof. N. Kuster, Zurich, Switzerland

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Location	Frankfurt (Germany)
Project leader (s)	SEMM
Full address	Dept of Zoology, University of Frankfurt, Siesmayerstrasse 70, Frankfurt, Germany. Phone +49 69 798 232 86; fax +49 69 798 235 85
Email	semm@zoology.uni-franfurt.de
Funding Agency	Deutsche Telekom
Main topic	Behaviour
Dates (start-end)	1992–1994
Exposure systems and protocols	GSM — 900 MHz — 100 $\mu W\ cm^{-2}$
Biological models	Effects of radiofrequency fields on the spontaneous activity of single fibres of the nervous ophthalmicus of bobolink and pigeon, single visual neurons of the visual system of birds and insects and melatonin synthesis in birds and humans.
Results	Effects found
Publications	No

Collaborations	
within programme	
outside programme	

Location	Frankfurt (Germany)
Project leader (s)	THALAU
Full address	Dept of Zoology, University of Frankfurt, Siesmayerstrasse 70, 6000 60323 Frankfurt, Germany. Phone +49 69 798 232 86; fax +49 69 798 235 85
Email	semm@zoology.uni-franfurt.de
Funding Agency	Deutsche Telekom
Main topic	Development
Dates (start-end)	1995–1996
Exposure systems and protocols	GSM — special exposure chambers with computer controlled egg rolling, temperature, and exposure, 1.2 GHz, 5 mW cm^{-2}
Biological models	Chicken and pigeon eggs — survival of embryos — melatonin levels — histopathological examination
Results	None yet
Publications	
Collaborations within programme	
outside programme	

Location	Frankfurt (Germany)
Project leader (s)	SEMM, WILTSCHIKO
Full address	University of Frankfurt
Email	

Funding Agency	Deutsche Telekom
Main topic	Neurophysiological investigations on insects
Dates (start-end)	1995
Exposure systems and protocols	RFR
Biological models	Electrophysiological reactions of single cells of the CNS of insects on exposure to modulated and unmodulated radiofrequency radiation.
Results	Yes
Publications	None
Collaborations within programme	
outside programme	

Location	Heidelberg (Germany)
Name(s) of project leader(s)	KIESSLING
Full Address	Rupercht-Karls-Universitat , Heidelberg IM Neuenheimer Feld 220 D-69120 Heidelberg, Germany
Email	
Funding Agency	Motorola
Main Topic	*In vivo* testing of the GSM signal
Dates (start-end)	August 1994–1996
Exposure systems and protocols	Near-field head exposure of rats.
Biological models	Rats
Results	None yet
Publications	None yet

Collaborations within programme	Prof. K. Hossmann, Cologne, Germany Prof. N. Kuster, Zurich, Switzerland

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Location	Leipzig (Germany)
Project leader (s)	THOSS
Full address	University of Leipzig
Email	
Funding Agency	Deutsche Telekom
Main topic	Neurophysiological investigations on humans
Dates (start-end)	1993–1994
Exposure systems and protocols	
Biological models	Volunteers
Results	None
Publications	None
Collaborations within programme	
outside programme	

Location	Linden (Germany)
Project leader (s)	DIMPFEL
Full address	Pro-Science, Private Research Institute Kurt-Schumacher Str. 9, 35440 Linden 2, Germany
Email	
Funding Agency	Deutsche Telekom
Main topic	Neurophysiological investigations on humans

Dates (start-end)	1993–1994
Exposure systems and protocols	GSM telephone, near-field conditions, 30 μW cm^{-2}
Biological models	Effects in volunteers
Results	Weak effects
Publications	Reiser H-P, Dimpfel W and Schober F (1995/96). The influence of electromagnetic fields on human brain activity. European Journal of Medical Research, 1: 27-32.
Collaborations within programme	
outside programme	

Location	Linden (Germany)
Project leader (s)	DIMPFEL
Full address	Pro-Science, Private Research Institute Kurt-Schumacher Str. 9, 35440 Linden 2, Germany
Email	
Funding Agency	Deutsche Telekom
Main topic	Neurophysiological investigations on humans
Dates (start-end)	1994–1995
Exposure systems and protocols	GSM telephone, far-field conditions, 30 μW cm^{-2}
Biological models	Effects on EEG in volunteers
Results	No effects
Publications	None
Collaborations within programme	
outside programme	

Location	Mainz (Germany)

Project leader (s)	BOHL
Full address	University of Mainz
Email	
Funding Agency	Deutsche Telekom
Main topic	Effects on brains of mice
Dates (start-end)	1995–1996
Exposure systems and protocols	
Biological models	Histological and microscopic studies of possible morphological changes in the brains of mice caused by radiofrequency radiation.
Results	
Publications	
Collaborations within programme	
outside programme	

Location	Mainz (Germany)
Project leader (s)	MANN and RÖSCHKE
Full address	Department of Psychiatry, University Clinic of Mainz, Untore Zahlbacher Str. 8, 55131 Mainz, Germany
Email	
Funding Agency	Deutsche Telekom
Main topic	Effects of electromagnetic fields on sleep parameters.
Dates (start-end)	1995
Exposure systems and protocols	GSM telephone, near-field conditions, 0.04 mW cm^{-2}
Biological models	Measurements of EEG in volunteers
Results	Alterations of sleep patterns

Publications	(1996) Neuropsychobiology 33, 41–47.
Collaborations within programme	
outside programme	

Location	Mainz (Germany)
Project leader (s)	VOLLRATH
Full address	Universität Mainz, Anatomisches Institut, Postfach 3980, 55099 Mainz, Germany.
Email	
Funding Agency	Deutsche Telekom
Main topic	Biological effects on melatonin synthesis
Dates (start-end)	1993–1994 (rats) 1996–1997 (humans)
Exposure systems and protocols	Rats exposed in chambers (0.5 mW cm^{-2}) Humans exposed in free space conditions, GSM signal, 0.05 mW cm^{-2}
Biological models	Melatonin measurements
Results	No effects in rats, No results in humans yet
Publications	Submitted
Collaborations within programme	
outside programme	

Location	Tübingen (Germany)
Project leader (s)	BARTSCH and BARTSCH
Full address	Universitäts Frauenklinik, Scheichetr. 4, 72076 Tübingen, Germany.

Email	
Funding Agency	Deutsche Telekom
Main topic	Cancer promotion in rats
Dates (start-end)	In progress
Exposure systems and protocols	Individual exposure chambers, 900 MHz, 217 Hz pulsed, 0.4 mW cm^{-2}
Biological models	Co-promoting role of microwave radiation — DMBA chemically induced tumours in rats — melatonin levels monitored in urine
Results	
Publications	
Collaborations within programme	
outside programme	

Location	Witten (Germany)
Project leader (s)	DAVID
Full address	Private University of Witten/Herdecke
Email	
Funding Agency	Deutsche Telekom
Main topic	Long-term effects on organisms
Dates (start-end)	1993–1994
Exposure systems and protocols	
Biological models	Rabbits and other animals, tissue and cell cultures
Results	None
Publications	None

Collaborations within programme

outside programme

Location	Budapest (Hungary)
Project leader (s)	ELEKES
Full address	National Research Institute for Radiobiology and Radiohygiene H-1221 Budapest, Anna.u.5, Hungary; mail: H-1775 Budapest, POB.101, Hungary; phone/fax: +36 1 226 5331
Email	e-mail: h10904thu@ella.hu
Funding Agency	Hungarian Ministry of Welfare
Main topic	Immune response of mice exposed chronically to amplitude modulated microwaves radiation.
Dates (start-end)	1992 to 1997
Exposure systems and protocols	Mice were exposed for six subsequent days for one and half, three, six or twelve hours per day with average power density 0.1 mW cm^{-2} , and whole body SAR 0.l4l W kg^{-1} (50 Hz amplitude-modulated (AM) 2.45 GHz).
Biological models	Balb/C mice were immunised on the second day of exposure with sheep red blood cells. Mice were bled on the 5th day of the immune response. Body mass, spleen weight, spleen index, number of spleen cells, number of antibody producing cells (PFC) and IgG level were measured.
Results	Chronic (cw) exposures (6 d, 3 h d^{-1}) induced elevations (+37%) of the number of antibody producing cells in the spleen of male mice. AM microwave radiation exposures induced elevation of the spleen index (+15%) and antibody producing cell number (+56%) in the spleen of male mice. No elevations were observed in female mice. In female mice, 1.5 h AM exposures significantly depressed spleen weight and the number of spleen cells and 12 h exposures nearly significantly depressed the number of spleen cells and the number of antibody producing cells. Serum haemagglutinin titre was hardly altered by the exposure. Both cw and AM exposure for 6 h d^{-1} significantly elevated haemolysin titre in male mice. In female mice after 1.5 h exposure a significant depression occurred. The IgG level was not altered.

Publications	• E. Elekes, Gy. Thuroczy, L.D. Szabo: Effect on the immune system of mice exposed chronically to 50 Hz amplitude-modulated 2.45 GHz microwaves, Bioelectromagnetics, 1996, 17, 246-248. • Thuroczy G., Elekes E., Kubinyi G., Bakos J. and Szabo D.L.: Biological Effects of Modulated and CW Microwave Exposure: *In vivo* Experiments in the Immunology, Embryology and Neurophysiology, Transactions of COST 244 "Mobile Communications and Extremely Low Frequency Fields" ed: D.Simunic, Brussels DG XIII, pp.64-74, 1995. • Thuroczy G., Kubinyi G., E.Elekes, N.Nagy., J.Bakos and Szabo D.L.: *In-vivo* Studies on Biological Effects of ELF Amplitude Modulated Microwave Exposure, in: D.Simunic (ed): Biological Effects Relevant to Amplitude Modulated RF Fields, Proc. of COST 244, Brussels DG XIII, pp.88-93, 1995.
Collaborations within programme	Gyorgyi THUROCZY
outside programme	

Location	Budapest (Hungary)
Project leader (s)	KUBINYI
Full address	National Research Institute for Radiobiology and Radiohygiene H-1221 Budapest, Anna.u.5, Hungary; mail: H-1775 Budapest, POB.101, Hungary; phone/fax: +36 1 226 5331
Email	e-mail: h10904thu@ella.hu
Funding Agency	Hungarian Ministry of Welfare
Main topic	Effect of cw and AM 2.45 GHz microwave radiation on the liver and brain aminoacyl-tRNA synthetases of *in utero*-exposed mice
Dates (start-end)	1992 to 1997
Exposure systems and protocols	CFLP mice were exposed to microwave radiation daily for 100 min during the whole gestation period (19 days). Exposures were performed in anechoic rooms. The frequency was 2.45 GHz, 217 Hz AM, rectangular wave form (on/off ratio 1/8). The averaged power density was 3 mW cm^{-2}, whole body SAR 4.23 ± 0.63 W kg^{-1}. The exposure protocol will be extended to 900 MHz GSM-type modulation with $\lambda/4$ monopole antenna.

Biological models	The progenies of females, 50–60 day old CFLP mice were used in the experiments. The weight and mortality of the progenies of exposed pregnant females were followed until the 24th postnatal day. Aminoacyl-tRNA synthetase enzymes and transfer ribonucleic acid (tRNA) from brains and livers of the offspring mice were isolated. The aminoacyl-tRNA synthetase activities were determined.
Results	Postnatal increase of body weight and organ weight was not influenced by prenatal microwave radiation exposure. Activity of enzyme isolated from brain showed a significant decrease with cw microwave exposure, but the changes were not significant with AM microwave exposure. The activity of enzyme isolated from liver increased both with cw and AM microwave exposure. Our study did not support the suggestions that there are strong differences between cw and AM modulated microwave exposure.
Publications	◆ Kubinyi G., Thuroczy G., Bakos J., Sinay H. and Szabo L.D.: Effect of Continuous wave and Amplitude Modulated 2.45 GHz Microwave Radiation on the Liver and Brain Aminoacyl-tRNA Synthetases of in utero Exposed mice, Bioelectromagnetics, Willey-Liss, (in press). ◆ Thuroczy G., Elekes E., Kubinyi G., Bakos J. and Szabo D.L.: Biological Effects of Modulated and CW Microwave Exposure: In-vivo Experiments in the Immunology, Embryology and Neurophysiology, Transactions of COST 244 "Mobile Communications and Extremely Low Frequency Fields" ed: D.Simuic, Brussels DG XIII, pp.64-74, 1995. ◆ Thuroczy G., Kubinyi G., E.Elekes, N.Nagy., J.Bakos and Szabo D.L.: *In-vivo* Studies on Biological Effects of ELF Amplitude Modulated Microwave Exposure, in: D.Simunic (ed): Biological Effects Relevant to Amplitude Modulated RF Fields, Proc. of COST 244, Brussels DG XIII, pp.88-93, 1995.
Collaborations within programme	Gyorgyi THUROCZY, Jozsef BAKOS, Noemi NAGY

Location	Budapest (Hungary)
Project leader (s)	SOMOSY
Full address	National Research Institute for Radiobiology and Radiohygiene H-1221 Budapest, Anna.u.5, Hungary; mail: H-1775 Budapest, POB.101, Hungary; phone/fax: +36 1 226 5331
Email	e-mail: h10904thu@ella.hu

Funding Agency	Hungarian Ministry of Welfare
Main topic	Localisation of calcium and Ca^{2+}-ATPases, immunohistochemistry of cytoskeletal system, ultrastructure and micromorphology, measurement of cAMP content by RIA, cytochemistry and biochemistry of adenylate cyclase, cell surface charges, apoptosis tests
Dates (start-end)	1993 to 1998
Exposure systems and protocols	Exposures were performed in anechoic rooms. Frequency was 2.45 GHz, the amplitude modulation was 16 Hz rectangular wave (on/off ratio 50-50%). Average power density was 1 mW cm^{-2}, whole-body SAR was 1.41 ± 0.21 W kg^{-1}. The exposure protocol will be extended to 900 MHz GSM-type modulation with λ/4 monopole antenna on restrained animals.
Biological models	*In vivo*: habenule, rat temporal cortex; *in vitro*: epithelial cell culture (HT-29 cells), neuroblastoma cell culture
Results	Modulated microwave irradiation (2.45 GHz, 16 Hz AM, 1 mW cm^{-2}) caused changes of cell surface negative charges in cell culture, induced redistribution of pyroantimonate precipitable calcium in HT-29 cells and habenule without changes of Ca-activated ecto-ATPase activity and an elevation in cyclic GMP and cyclic AMP level as well as adenylate cyclase activity were observed in small intestine.
Publications	◆ Z.Somosy (1995) Morphological and histochemical investigations on cell junctional complex of *in vivo* and *in vitro* systems upon low doses of continuous and low frequency modulated microwave irradiations final report of phare accord Program H 9112-0472 ◆ Z. Somosy, G. Thuroczy, J Kovacs: (1993) Effects of modulated and continuous microwave irradiation on pyroantimonate perceptible calcium content in junctional complex of mouse small intestine. Scanning Microscopy. 7: 1255-1261. ◆ Agnes Kittel, L. Siklos, Gy. Thuroczy, Z. Somosy (1996) Qualitative enzyme histochemistry and microanalysis reveals changes in ultrastructural distribution of calcium and calcium-activated ATPases after microwave irradiation of medial habenula. Acta Neurophathol. in press ◆ Z. Somosy, G. Thuroczy, T. Kubasova, J Kovacs, LD Szabo (1991) Effects of modulated and continuous microwave irradiation on the morphology and cell surface negative charge of 3T3 fibroblasts. Scanning Microsc. 5, 1145-1155.

Collaborations within programme	Gyorgyi THUROCZY, Agnes KITTEL, Attila TAKACS, Gabriella BOGNAR, M SASS, E MADARSZ
outside programme	

Location	Budapest (Hungary)
Project leader (s)	THUROCZY
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Email	e-mail: h10904thu@ella.hu
Funding Agency	Hungarian Ministry of Welfare
Main topic	Neurophysiological response to GSM-type microwave radiation of anaesthetised awake freely moving rats.
Dates (start-end)	1994 to 1997
Exposure systems	0.31 ± 0.11 W kg^{-1}. The exposures were performed in anechoic chambers (2.55m x 1.8m x 2.9m) under standard horn antenna (G=14 dB). The freely moving animals were exposed in circular plastic cage (23 cm diameter, 15 cm high). After 30 min, 3 mW cm^{-2} whole-body exposures of rats to 2.45 GHz (GSM-type) microwave radiation, the response of the CNS was observed by quantitative EEG and visual evoked potentials (VEP) recordings. The average SAR measured in phantom models in the head was exposure protocol will be extended to 900 MHz GSM-type modulation with $\lambda/4$ monopole antenna on restrained rats and to human electrophysiology using GSM, NMT mobile phones.
Biological models	On Wistar female (180–250 g) standard electrophysiological procedures were performed. The EEG (70 Hz/0.3 s) and VEP recordings were performed on freely moving animals by using flash lamp stimuli. The electrodes were placed over the visual cortex below the skull on the dura mater. Bipolar and monopolar EEG were recorded simultaneously. The VEP responses (n = 40) of bipolar and monopolar EEG recordings were averaged (512 ms) and the latency time (N1, P2, N3) and amplitude were evaluated by computer. Between the light stimuli EEG power spectral analysis was calculated by FFT processing on 5120 ms epoch. The 40 power spectrum was averaged and the common EEG frequency bands were

separated.

Results

In the 5 min post exposure, the bipolar P2 latency time decreased significantly. No changes were observed in the other early (P0, N1) nor late (N3) latency times of bipolar and monopolar VEP. The delta bands of monopolar EEG power spectrum was increased significantly, the alpha and beta bands were decreased in the 5th min after exposure. These alterations had disappeared by 20 min after exposure. The bipolar EEG spectral components were changed mostly after 20 min of exposure.

Publications

- Thuroczy G., G.Kubinyi, N.Nagy, L.D.Szabo: Measurements of Visual Evoked Potentials (VEP) and Brain Electrical Activity (EEG) after GSM-type Modulated Microwave Exposure on Rats, in: T.Honma (ed): Adv Computational Applied Electromagnetics, Elsevier Press, pp. 384–395, 1995.
- Thuroczy G., Kubinyi G., Bodo M., Bakos J. and Szabo L.D.: Simultaneous Response of Brain Electrical Activity (EEG) and Cerebral Circulation (REG) to Microwave Exposure in Rats, Reviews on Environmental Health, Vol.10., No.2., pp: 135–148, 1994.
- M.Bodo, G.Thuroczy, I.Nagy, J.Peredi, K.Sipos, P.Harcos, Y.Nagy, J.Voros, L.Zoltay, L.Ozsvald: A Complex Cerebrovascular Screening System, J. of Medical Progress Through Technology, Kluwer Academic Publ., Vol.21., pp.53–66. 1995.
- Bakos J., Nagy Noemi, Thuroczy Gy., Szabo LD: Sinusoidal 500 þT, 50 Hz magnetic field has no acute effect on urinary 6-sulphatoxymelatonin production of Wistar rats, Bioelectromagnetics, Willey-Liss, Vol.16. pp. 377–380, 1995

Collaborations within programme

Gyorgyi KUBINYI, Noemi NAGY

outside programme

Location

Budapest (Hungary)

Project leader(s)

THUROCZY

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Email

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Funding Agency

Hungarian Ministry of Welfare

Main topic	Human studies on potential influence of cellular phone exposure on cerebral circulation and EEG.
Dates (start-end)	1996 to 1997
Exposure systems	Exposures were performed in anechoic chambers. Volunteers with closed eyes were exposed to computer controlled GSM phones (1 W) twice for 7.5 min. Exposure was blind. Polygraphic curves were recorded before, during and after exposure.
Biological models	Healthy volunteers (44 women and 29 men)
Results	Analysis in progress.
Publications	M. Bodo, G. Thuroczy, I. Nagy, J. Peredi, K. Sipos, P. Harcos, Y. Nagy, J. Voros, L. Zoltay, L. Ozsvald (1995), A complex cerebrovascular screening system. J. of Medical Progress through Technology. Kluwer Academic Publ., 21, pp. 53–66.
Collaborations within programme	Hungarian Stroke Institute, Budapest : Prof. Z. Nagy Hungarian University of Physical Education, Budapest: Dr. K. Sipos NASA, Ames Res. Center, CA, YSA : Dr. L. Montgomery
outside programme	

Location	Naples (Italy)
Project leader (s)	SCARFI
Full address	CNR-IRECE ; Via Diocleziano 328, 80124 Naples, Italy
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Funding Agency	Center for Devices and Radiological Health, FDA, USA
Main topic	Effects at the cytogenetic level (micronuclei) and on enzymes
Dates (start-end)	
Exposure systems	9 GHz (waveguide, SAR 70W kg^{-1}, exposure duration 10 min 10.4 GHz (waveguide), SAR 1.1-1.7 W kg^{-1}, 1.88 GHz
Biological models	Mammalian lymphocytes

	Thermophilic enzymes
Results	Induction of micronuclei in bovine lymphocytes Decrease in enzyme activity.
Publications	• G. D'Ambrosio et al (1995) Electro and magnetobiology, 14: 157–164. • M.R. Scarfi et al. (1996) Electro and magnetobiology, 15: 99–107. • F. La Cara, M.R. Scarfi, S. D'Auria, R. Massa, G. D'Ambrosio, G. Franceschetti, M. Rossi and M. de Rosa (1996) Analysis of the effects of microwave energy on a thermophilic b-galactosidase from Bacillus acidocololarius. Bioelectromagnetics (submitted).
Collaborations within programme	Dept. of Electronics, Univ. of Naples 'Federico II'
outside programme	CNR-Inst. Biochemistry and Enzymology, Naples, Italy. Dept of Animal Sciences, Univ. of Basilicata, Italy.

Location	Rome (Italy)
Project leader (s	MARINO
Full address	Department of the Environment, ENEA Casaccia, Via Anguillarese 301, 00060 Roma, Italy.
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Funding Agency	National Agency for New Technologies, Energy and Environment
Main topic	Effects of electromagnetic fields at mobile phone frequencies on cellular proliferation rate in an experimental tumour model.
Dates (start-end)	From 1992 to 1994 on thermal effects; from 1993 on nonthermal effects
Exposure systems and protocols	Modified TEM cell (operating at 900 MHz); standard dipole and small anechoic chamber. Whole body exposure of inoculated animals: various overall and daily exposure durations.
Biological models	Mice — Murine adenocarcinoma C3H — Tumour growth rate, tumour growth delay, kinetic analysis and index of cellular proliferation.
Results	No differences observed among non-exposed, exposed and sham exposed animals in terms of volume uptake, tumour growth rate and

tumour growth delay (around 500 animals exposed since 1994).

Publications

- Marino C (1994). Preliminary studies on biological effects of microwaves: *in vivo* experimental model. 16th Bioelectromagnetics Society Annual Meeting, Copenhagen, Denmark.
- Marino C, Antonini F, Avella B, Galloni L, Scacchi P (1994). Models in the study of biological effects of electromagnetic radiation: tumour induction and proliferation in *in vivo* systems. Proceedings of the VIIth Annual Meeting of the Italian Society for Radiation Research, Pisa, in press.
- Marino C, Antonini F, Avella B, Galloni L, Scacchi P (1995). 900 MHz effects on tumoral growth in *in vivo* systems. 17th Bioelectromagnetics Society Annual Meeting, Boston, USA.
- Marino C (1995). Thermal and non-thermal effects of non ionising radiations. Proceedings of the Italian Japanese Workshop on radiation effects and biomedical applications, Roma, Italy.
- Avella B, Galloni L, Marino C (1996). Effects on murine kidney and liver of a single dose of deep hyperthermia. Int J of Hyperthermia, submitted.

Collaborations within programme

University La Sapienza, Department of Electronics, Rome, Italy, Laboratoire PIOM, University of Bordeaux I, Talence, France.

outside programme

University of Tor Vergata, DISP, Rome, Italy
University of L'Aquila, DIE, L'Aquila, Italy.

Location

Lund (Sweden)

Project leader (s)

PERSSON and SALFORD

Full address

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Funding Agency

Lund University

Main topic

Potential health effects from exposure to specific electromagnetic fields.

Dates (start-end)

From 1987, on-going

Exposure systems and protocols	TEM cells for microwave exposure with pulse-modulation or continuous wave. Anechoic chamber for radiofrequency exposure.
Biological models	Permeability of the blood–brain barrier. Tumour growth and promotion *in vivo*. Ornithine decarboxylase (ODC) levels in rats and mice.
Results	Significant increase in the permeability of albumin through the blood–brain barrier at various power levels for cw or pulsed fields. No effect on the growth of brain tumours (RG2 and N32) implanted in the brain of Fisher rats exposed daily to cw or pulsed microwaves. Preliminary results indicate an increase in ODC and spermine levels in the rat brains exposed to pulse-modulated electromagnetic fields but not in rats exposed to cw fields.
Publications	◆ Persson BRR, Salford LG, Brun A (1996). Albumin leakage through the blood-brain-barrier in rats induced by cw and pulse modulated 915-MHz electromagnetic radiation exposure in TEM cells. 3rd Congress of the European Bioelectromagnetics Association, Nancy, France. ◆ Salford LG, Persson BRR, Brun A (1996). Experimental studies of brain tumour development in rats during exposure to cw and pulse-modulated 915-MHz electromagnetic radiation in TEM-cells. 3rd Congress of the European Bioelectromagnetics Association, Nancy, France. ◆ Persson BRR, Salford LG, Brun A (1996). Blood–brain barrier permeability in rats exposed to electromagnetic fields used in wireless communications. Wireless Networks Journal (submitted). ◆ Salford LG, Brun A, Persson BRR (1996). Brain tumour development in rats exposed to electromagnetic fields used in wireless communications. Wireless Networks Journal (submitted). ◆ Persson BRR, Salford LG, Persson L (1996). Increased ornithine decarboxylase activity in brain tissue of rats induced by GSM-modulated electromagnetic fields. In: Progress report BEEF/ODC 1996/02 Lund University, Sweden.
Collaborations within programme	University of Ghent (Belgium) for radiofrequency radiation dosimetry. Several Departments at Lund University.

Location	Zurich (Switzerland)
Project leader (s)	KUSTER
Full address	Laboratory for EMF and Microwave Electronics, ETH Zurich, 8092

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Funding Agency	ETH, Swiss Telecom PTT
Main topic	Evaluation, design and dosimetric assessment of *in vitro* exposure systems: the systems will be optimised with respect to the uniformity of exposure of the cell layers cultured in commercial Petri dishes.
Dates (start-end)	From June 1995
Exposure systems and protocols	
Biological models	None
Results	
Publications	M. Burkhardt, Katja Pkovic, M. Gnos, T. Schmid and N. Kuster (1996). Numerical and experimental dosimetry of Petri dishes exposure setups. Bioelectromagnetics, in press.
Collaborations within programme	
outside programme	

Location	Bern (Switzerland)
Project leader (s)	KOHLI
Full address	Institute of General Microbiology
Email	kohli@imb.unibe.ch
Funding Agency	Swiss and German Telecom
Main topic	Effects on yeast cells
Dates (start-end)	January 1996 – December 1997
Exposure systems and protocols	Directional antenna (900 MHz, 10 W max, GSM modulation). Two Faraday cages with exposed and sham parallel treatment.
Biological models	*Sccharomyces cerevisiae* constructs tested for short term carcinogen identification. Assays: Forward and reverse mutation, homologous

	recombination and 'petite' mutation
Results	
Publications	
Collaborations within programme	
outside programme	

Location	Zurich (Switzerland)
Project leader (s)	WIESER, HELLER, KUSTER
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Funding Agency	Swiss National Foundation
Main topic	Iron biomineralisation in the human brain and the effect of magnetic fields on EEG-recorded brain wave activity.
Dates (start-end)	From June 1994
Exposure systems and protocols	DC/ELF exposure using a computer-controlled Helmholtz coil setup. Pulsed microwave radiation conditions are planned.
Biological models	EEG evaluation
Results	
Publications	P.P. Grassi, J.P. Dobson, F. Heller, and N. Kuster (1995). Assessment of ferrimagnetic material in the hippocampus: elimination of artifact sources. 15th Annual Meeting of BEMS, Boston, P. 42.
Collaborations within programme	
outside programme	

Location	Loma Linda (USA)
Project leader(s)	ADEY
Full Address	V.A. Medical Center 11201 Benton Street Res Serv-151 Loma Linda, CA 92357, USA
Email	rossadey@opm.gov
Funding Agency	Motorola
Main Topic	*In vitro* testing of TDMA signal & iDen signal
Dates(start-end)	TDMA: January 1991–1996 iDEN: November 1995–1996
Exposure systems and protocols	TDMA radiofrequency exposures were carried out in four identical TEM transmission line chambers. 836.55 MHz radiofrequency supplied by a prototype TDMA transmitter (Motorola Corp.) and linear amplifier. The TDMA protocol required a carrier that was on 6.67 ms out of a 20 ms frame for a 33% duty cycle. Each resulting carrier burst was further modulated utilising D/4 QPSK modulation. Packet frequency was 50 Hz. Power densities used were 0.84 and 84 W m^{-2} with the carrier on. Average SARs were 0.78 and 7.8 mW kg^{-1}.
Biological models	Ornithine decarboxylase (ODC) activity of C3H/10T1/2 fibroblasts. Cells were exposed in 60-mm Petri dishes in 5 ml of medium
Results	At 8.40 mW cm^{-2} exposure did not affect the ODC activity response at 2 h after change-of-medium. However, at 3 and 4 h after change-of-medium, TDMA RF exposure inhibited the ODC activity response by 50%. At the lower power density of 0.84 mW cm^{-2}, TDMA RF exposure did not affect the ODC activity response at any of the time points, 2, 3 and 4 h after change-of-medium. There was no effect on C6 glioma cells at 8.40 mW cm^{-2}.
Publications	C.D. Cain, D.L. Thomas, M. Ghaffari and W.R. Adey. 837 MHz digital cellular telephone RF fields and induced ornithine decarboxylase activity in C3H10T1/2 cells. B-2-1 Eighteenth Annual Meeting of the Bioelectromagnetics Society, Victoria, Canada, June 1996.
Collaborations	Prof. Kuster, Zurich, Switzerland

Location	Loma Linda (USA)
Project leader(s)	Adey
Full Address	V.A. Medical Center 11201 Benton Street Res Serv-151 Loma Linda, CA 92357, USA
Email	rossadey@opm.gov
Funding Agency	Motorola
Main Topic	*In vitro* Testing of TDMA signal & iDen signal
Dates (start-end)	TDMA: January 1991–1996 iDEN: November 1995–1996
Exposure systems and protocols	Radiofrequency radiation exposures were carried out in TEM cells at 836.55 MHz. The carrier was FM by recorded speech, with a maximum deviation of 9 kHz. A 6 kHz tone (required for the existing FM cellular telephone system) was superimposed on the speech. Power densities used were 0.76, 7.6, and 76 W m^{-2}. SAR values were 0.41, 4.1, and 41 mW kg^{-1}.
Biological models	Expression of c-fos AND c-jun genes in NGF-responsive subclone of PC12 cells.
Results	No consistent alterations in the expression of either c-fos or c-jun as compared to control, unexposed cells under any condition of NGF concentration or radiofrequency radiation exposure tested.
Publications	O. Ivaschuk, T. Ishida-Jones, W. Haggren, W.R. Adey and J.L. Phillips. Exposure of nerve growth factor-treated PC12 cells to an 836.55 MHz frequency-modulated radio frequency field: effect on expression of c-fos and c-jun. A.4.3. Eighteenth Annual Meeting of the Bioelectromagnetics Society, Victoria, Canada, June 1996.
Collaborations	Prof. Kuster, Zurich, Switzerland

Location	Loma Linda (USA)
Project leader(s)	ADEY
Full Address	V.A. Medical Center, 11201 Benton Street, Res Serv-151 Loma Linda, CA 92357, USA

Email	rossadey@opm.gov
Funding Agency	Motorola
Main Topic	*In vivo* testing of TDMA signal & iDen signal
Dates(start-end)	TDMA: January 1991–1996 iDEN: November 1995–1996
Exposure systems and protocols	836.55 MHz signal was a 3:1 multiplexed TDMA. Far-field exposures (horn radiator, 836-MHz circularly polarised) began on Day 19 and continued after parturition until weaning at age 23 days. Offspring (n = 236) of the four maternal groups then became treatment cohorts: 1) ENU/Field (EF), n=56, 30M, 26F); 2) ENU/Sham (ES), n=60, 30M, 30F; 3) Sham/Field (SF), n=60, 30M, 30F; 4) Sham/Sham (SS), n=60, 30M, 30F. Near-field exposures began at 35 days, and continued for the next 22 months, 4 days weekly. Exposures were for 2 h daily, field-on 7.5 min, field-off 7.5 min. Far-field time-averaged SARs (modelled): pregnant dam (uterus) 0.3 W kg^{-1}; fetus (brain) 0.29 W kg^{-1}; isolated pup (brain) 0.035 W kg^{-1}; young rat (brain) 0.13 W kg^{-1}. Time-averaged near-field SARs: larger males, 0.75 W kg^{-1} (1.0 W kg^{-1} localised max); smaller females, 0.58 W kg^{-1} (0.75 W kg^{-1} localised maximum).
Biological models	Pregnant Fischer 344 rats were randomly assigned to four groups. They received either a single tail-vein injection of the carcinogen ethyl nitrosourea (ENU, 4 mg kg^{-1}) or inert buffer solution on pregnancy day 18.
Results	Radiofrequency radiation exposure had no enhancing effect on incidence, type or location of spontaneous nervous system tumours. At experiment termination, the TDMA field appeared to reduce incidence of brain malignant glial cell tumours in Group EF vs Group ES (4 vs 13). The TDMA field also appeared to reduce incidence of spontaneous glial tumours in Group SF vs Group SS (2 vs 7). Tumours in exposed rats were smaller in volume. In rats not surviving to full term (n = 54, 22%), the TDMA field appeared to prolong latency of appearance of both spontaneous and ENU-induced glial cell tumours, but did not alter histological criteria of tumour types. Higher death rates were in a progression SF-SS-EF-ES.
Publications	W.R. Adey, C.V. Byus, C.D. Cain, W. Haggren, R.J. Higgins, R.A. Jones, C.J. Kean, N. Kuster, A. MacMurray, J.L. Phillips, R.B. Stagg and G. Zimmerman. Brain tumour incidence in rats chronically

	exposed to digital cellular telephone fields in an initiation-promotion model. A-7-3. Eighteenth Annual Meeting of the Bioelectromagnetics Society, Victoria, Canada, June 1996. See also paper P-67A (BEMS 96) for a description of the *in vivo* systems
Collaborations	University of California, Riverside, California 92521, USA. University of California, Davis, California 95616, USA. Loma Linda University School of Allied Health Professions, California 92350, USA. Central Technological Institute, Zurich, Switzerland

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Location	New York (USA)
Name(s) of project leader(s)	MOTZKIN
Full Address	Polytechnic University, Chemistry/Life Science Dept., Six Metrotech Center, Brooklyn, NY 11201, USA
Email	
Funding Agency	Motorola
Main Topic	Replication of cell proliferation
Dates(start-end)	August 1995–1998
Exposure systems and protocols	Those used by original investigator, Dr. Steven Cleary
Biological models	Cells
Results	None yet
Publications	None yet
Collaborations	None

Location	Plantation (USA)
Name(s) of project leader(s)	DAUPHINEE
Full Address	Goodwin Institute for Cancer Research, 1850 NW 69th Avenue Plantation, FL 33313

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Funding Agency	Motorola
Main Topic	*In vivo* testing of IRIDIUM signal
Dates(start-end)	November 1993–1996
Exposure systems and protocols	Near-field exposure to head of animal
Biological models	Mice
Results	None yet
Publications	None yet
Collaborations	None

Location	Rockville (USA)
Project leader (s)	CRESS, CZERSKA, OWEN.
Full address	5600 Fishers Lane (HFZ-114), Rockville, Maryland, USA 20853
Email	rdo@fdadr.cdrh.fda.gov
Funding Agency	Center for Devices and Radiological Health, FDA, USA
Main topic	Effects of cell phone electromagnetic fields exposure on cell biology
Dates (start-end)	From 1995
Exposure systems and protocols	Crawford Cell and dummy Crawford Cell with signal generated by a digital or analogue cellular phone.
Results	Preliminary results suggest the possibility of a shift on cell distribution toward G2/M phase of the cell cycle when glioblastoma cells are exposed for 24 hours. Other aspects of analysis are to begin in 1997.
Publications	None yet
Collaborations within programme	
outside programme	

Location	St. Louis (USA)

Name(s) of project leader(s)	ROTI-ROTI
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Email	rotiroti@smtpgate.ustl.edu
Funding Agency	Motorola
Main Topic	*In vivo* and *in vitro* testing of CDMA Signal Replication of DNA single strand breaks
Dates (start-end)	CDMA: Jan 1994–1997
Exposure systems and protocols	835 MHz (frequency modulated, FMCW, or code domain multiple access, CDMA) MW in specially-designed radial transmission lines. SAR was calculated to be 0.8 W kg^{-1}.
Biological models	Alkaline comet assay in C3H 10T1/2 mouse fibroblasts.
Results	No effects
Publications	R.S. Malyapa, E.W. Ahern, C.H. Cheng, W.D. Wright and J.L. Roti Roti (1996). Measurement of DNA damage by the alkaline comet assay after *in vitro* exposure to 835 MHz electromagnetic radiation. Eighteenth Annual Meeting of the Bioelectromagnetics Society, Victoria, Canada, B-2-3.
Collaborations	None

Location:	Seattle (USA)
Project leader:	LAI
Full address:	Bioelectromagnetics Research Laboratory, Center for Bioengineering, Box 357962, University of Washington, Seattle, WA 98195, USA
E-Mail:	hlai@u.washington.edu
Funding agency:	National Institute of Health, USA
Main topic:	Neurological effects of low-level microwave radiation.

Dates: 1985–1996

Exposure systems and protocols: Circular waveguide and miniature anechoic chamber exposure to 2450 MHz pulsed or continuous-wave microwave radiation at various power densities. Controls were sham-exposed.

Results: Decrease in central cholinergic activity in the rat.
Alterations of radial-arm maze performance in the rat.
Increase in DNA single- and double-strand breaks in rat brain cells.

Publications:

- Lai H, Carino MA, Horita A and Guy AW. Single vs. Repeated microwave exposure: effects on benzodiazepine receptors in the brain of the rat. Bioelectromagnetics 13:57–66, 1992.
- Lai H, Carino MA, Horita A and Guy AW. Opioid receptor subtypes that mediate a microwave-induced decrease in central cholinergic activity in the rat. Bioelectromagnetics 13:237–246, 1992.
- Lai H. Research on the neurological effects of nonionizing radiation at the University of Washington. In: Past Perspectives and Future Directions on Bioelectromagnetics- the Contribution of Dr Arthur W Guy. Bioelectromagnetics 13:513–526, 1992. (Invited paper)
- Lai H, Horita A and Guy AW. Microwave irradiation affects radial-arm maze performance in the rat. Bioelectromagnetics 15:95–104, 1994.
- Lai H. Neurological effects of microwave irradiation In: Advances in Electromagnetic Fields in Living Systems, Vol. 1. JC Lin (ed.), Plenum Press, New York, 1994, pp. 27–80.
- Lai H and Singh NP. Acute low-intensity microwave exposure increases DNA single-strand breaks in rat brain cells. Bioelectromagnetics 16:207–210, 1995.
- Lai H, Carino MA, Horita A and Guy AW. Intraseptal β-funaltrexamine injection blocked microwave-induced decrease in hippocampal cholinergic activity in the rat. Pharmacol. Biochem. Behav. 53:613–616, 1996.
- Lai H and Singh NP. DNA Single- and double-strand breaks in rat brain cells after acute exposure to low-level radiofrequency electromagnetic radiation. Int. J. Radiat. Biol. (In press)

Location Washington DC (USA)

Project leader (s) To be determined. Proposals under review

Full address

Email	
Funding Agency	Wireless Technology Research, LLC.
Main topic	Perform tests on RFR (837 MHz) using standardised tests for the identification of genetic hazards.
Dates (start-end)	Will start in the Autumn of 1996 and last 15 months
Exposure systems	TEM cell characterised with the FDTD method. For more information, see "Potential Public Health Risks from Wireless Technology: Risk Evaluation Research, Progress, Priorities and Request for Proposals" WTR, July 95.
Biological models	Included in the *in vitro* test battery will be the following mutation assays: *Salmonella typhimurium* (Ames) assay, *Escherichia coli* WP2*uvr*A reverse mutation assay, and the L5178Y TK± mouse lymphoma forward mutation assay. In addition, the test battery will include a chromosome aberration assay in human whole blood lymphocytes.
Results	
Publications	
Collaborations within programme	Two laboratories will be chosen to use the same protocol
outside programme	

Location	Washington DC (USA)
Project leader (s)	VERSCHAEVE, TICE, LAI
Full address	• Luc VERSCHAEVE: VITO, Environment Division, Boeretang 200, Mol, 2400 Belgium. • Raymond TICE: Integrated Laboratory Systems, PO Box 13501, Research Triangle Park, NC 27709, USA. • Henry LAI: Center for Bioengineering, University of Washington, Seattle, WA 98195, USA.
Email	verschal@vitooosf1.vito.be hlai@u.washington.edu
Funding Agency	Wireless Technology Research, LLC.

Main topic	Perform tests on radiofrequency radiation (837 MHz) using the single cell gel and micronucleus assays on human lymphocytes *in vitro*.
Dates (start-end)	Will start in the Summer–Autumn of 1996 and last 12 months.
Exposure systems	TEM cell characterised with the FDTD method. For more information, see "Potential Public Health Risks from Wireless Technology: Risk Evaluation Research, Progress, Priorities and Request for Proposals" WTR, July 1995.
Biological models	
Results	
Publications	
Collaborations within programme	Three laboratories chosen to use the same protocol
outside programme	

Location	Washington, DC (USA)
Name(s) of project leader(s)	ZOOK
Full Address	George Washington University Medical Center 2300 I Str NW Washington, DC 20037 (USA)
Email	
Funding Agency	Motorola
Main Topic	*In vivo* and *in vitro* testing of the MIRS signal
Dates(start-end)	July 1990 –1998
Exposure systems and protocols	Near-field head exposure for animals
Biological models	Rats and two cell lines
Results	None yet
Publications	None yet
Collaborations within programme	
outside programme	

Location	Washington DC (USA)
Project leader (s)	LITOVITZ
Full address	Department of Physics and Department of Biology, Catholic University of America, Washington, District of Columbia 20064, USA.
Email	Tlitovitz@aol.com
Funding Agency	EMX Corp. and the Catholic University of America
Main topic	Role of modulation and coherence in the induction of bioeffects by 835 MHz radiofrequency fields
Dates (start-end)	
Exposure systems and protocols	Crawford cell placed in an incubator. Power density was approximately 10 W m^{-2}. Various types of modulation including, 60 Hz AM, 60 Hz FM, and 50 Hz square wave modulation (SQM), as well as cw microwave radiation. An analogue phone AMPS (Advanced Mobile Phone System) and a digital phone AMPS (Digital AMPS) which is TDMA, were also used as sources of microwave radiation. Incoherent ELF noise field was superimposed on cell cultures which had been set up for microwave exposure
Biological models	Activity of ODC in L929 murine cells in culture was the biological marker.
Results	CW and FM fields induced no changes in ODC activity. However, all the AM fields induced significant changes in ODC activity: the analogue phone FM signal caused no effects, and the digital phone AM signal caused a significant increase in ODC activity. Superposition of an incoherent ELF field could completely block the bioeffects of an AM microwave field.
Publications	T.A. Litovitz, M. Penafiel, J.M. Mullins and D. Krause. ELF magnetic noise fields inhibit the effect of cellular phone radiation on the activity of ornithine decarboxylase. Poster B-2-2 at the 18th Annual Meeting of BEMS, Victoria, Canada, June 1996.
Collaborations within programme	
outside programme	