In the last twenty years, hundreds of experiments have been carried out on animals to assess cancer-related risks of exposure to extremely-low-frequency (ELF) and radiofrequency (RF) electromagnetic fields. Most of the work has been performed at frequencies related to the generation of electricity at 50/60Hz and mobile telephony at around 1GHz. Results obtained on cancer-related models are described in this brief review in terms of the risk evaluation that is necessary for the establishment of exposure guidelines and standards.

Overall, it remains true that there are no known well-documented effects leading to health risks for weak induced currents at ELF and “non-thermal” RF fields levels.

**Introduction**

There has been considerable interest and controversial debate in recent years concerning the bioeffects of electromagnetic fields (EMF). This is due to some still-unanswered questions about the effect on health of increasing levels of exposure of the population to EMF. However, the number of experiments, articles, reviews, and databases has risen significantly. The quality of the research has improved vastly and the knowledge is now based on a wide body of data so that ICNIRP, IARC and WHO are or will soon be able to evaluate the carcinogenicity and health risks of EMF.

This review is concerned mainly with animal models of cancer. It is divided in two parts related to the ELF and RF frequency ranges. It is intended to be complimentary to the talk to be given at the Seoul WHO meeting in terms of content and mode of presentation. Laboratory studies on animals play an essential role in evaluating the integrated response of various systems of the body, particularly the nervous, endocrine and immune systems. These systems are largely responsible for homeostasis which maintains the internal environment. When challenged by external stimuli, the interdependent response of these systems cannot be fully defined through in-vitro experiments. However, phenomena seen in experimental animals do not necessarily imply a health risk for humans. In particular, an effect found in only one animal species may be specific to that type of animal and not relevant to humans. Animal studies provide the opportunity to test whether lifetime exposure to well-characterised RF causes cancer, something that is impossible to do using human volunteers. Research on animals can also demonstrate influences of RF exposure on susceptibility to cancer promotion and progression.

**Extremely-low-frequency fields**

A major research effort was launched world-wide to determine the possible bioeffects of magnetic and electric fields at extremely low frequencies (f < 300 Hz, mainly 50/60 Hz corresponding to electricity generation and distribution). Following years of scattered projects, this research activity has become better co-ordinated on the international level, largely thanks to the EMF programme of WHO.

The most recent and comprehensive review on ELF bioeffects is that of the RAPID programme published in 1998. In 2002, IARC is going to published a monograph on the carcinogenicity of ELF fields. However the conclusions of that monograph are already available.

**Exposure systems**

In the last twenty years, a great number of experiments have been performed in laboratories world-wide to assess the biological effects of ELF magnetic and electric fields. This has led to the design and building of several types of exposure systems for in vivo work. The goal was to expose the animals to well-characterised fields under well-defined environmental factors.

In view of the mechanisms of interaction of fields with biological organisms (mainly induced currents), the effects of the magnetic field, which penetrates the body, have been the main focus of the research projects, with fields strength usually at or below 100 μT. In contrast, electric fields do not penetrate the organism because of its conductivity, but strong electric fields induce polarisation of the cell membrane leading to specific effects such as electroporation, which are studied in specific exposure systems. This is also true for direct stimulation of nerves and other excitable cells using electrodes.

There has been many improvements in the design of exposure systems in recent years and it can be stated that most of the key exposure parameters described below are well-characterised and controlled. However, the standardisation of the set-ups is only achieved within some of the multi-centre research programmes. Large-scale studies on long-term effects of ELF magnetic fields on animals have been published in recent years. Large facilities have thus been built and run for exposure of hundreds of rodents over their lifetime (reviewed by Stuchly et al.). Great care is being taken for controlling all environmental factors.
**Genotoxicity**

Effects have been found in different organisms and in particular rodents. The work performed by Lai and Singh is worth mentioning. These investigators used the "comet assay" to detect DNA damage in brain cells from ELF-exposed rats. Increases in DNA double- and single strand breaks were detected after in vivo exposure to a 60 Hz magnetic field at 0.1-0.5 mT. These authors also indicated that the magnetic-field-induced DNA strand breaks were caused by free radicals since a treatment of the animals with free radical scavengers blocked the effects. In a subsequent investigation, they also found that the magnetic-field apparently induces DNA-protein and DNA-DNA cross-links in a manner similar to the chemical mitomycin C. These investigations certainly need confirmation and further investigation. There have been a number of criticisms (also on similar research on RF fields) that merit further attention.

**Carcinogenesis**

The controversial issues deduced from epidemiological investigations have spawned many laboratory experiments to determine whether EMF can initiate, promote or co-promote cancer in animal models. There is no evidence that ELF magnetic fields cause tumours ("initiation"), with the possible exception of lymphomas arising after exposing rats at high-strength fields for three generations but there are some inconsistent indications that EMF exposure might in some circumstances suppress or enhance tumour development/growth. Overall, no convincing experimental evidence has been found to support the hypothesis that exposure to ELF magnetic fields increases the risk of cancer. This conclusion is well supported by the results of a number recent large scale studies of animal carcinogenesis including those using transgenic animals, which have generally been more carefully conducted than some of the earlier studies reporting either positive or negative effects.

Rodents, particularly mice, have been used extensively in studies of adult leukaemogenesis; in spite of the absence of a good animal model of the most common form of childhood leukaemia, i.e., acute lymphoblastic leukaemia. Most studies report a lack of effect of ELF magnetic fields on leukaemia or lymphoma in rodents. These include several recent, large-scale studies of spontaneous tumour incidence in normal and transgenic mice, and of radiation-induced lymphoma and leukaemia in mice. Further studies found no effect on the progression of transplanted leukaemia cells in mice or rats.

Rat mammary carcinomas represent a standard laboratory animal model in the study of human breast cancer. Three recent large-scale studies of rats showed that lifetime magnetic-field exposure had no effect on the incidence of spontaneous mammary tumours. The evidence concerning EMF effects on chemically-induced mammary tumours is more equivocal. Two studies suggested that exposure to ELF EMF increase the incidence or growth of chemically-induced mammary tumours in female rats. However, the work of one laboratory was inadequately described and there was considerable inter-experimental variability in the results from the other laboratory. Two more recent studies have not been able to corroborate these findings. Further experimental investigation may be warranted to resolve this uncertainty.

Whilst there is no good animal model of spontaneous brain tumour, a recent, large scale study reported a lack of effect of exposure to power frequency magnetic fields on chemically-induced nervous-system tumours in female rats. In addition, the low incidence of brain cancers in three recent large-scale rat studies was not elevated by magnetic field exposure.

Studies of pre-neoplastic liver lesions and chemically-induced skin tumours have been almost uniformly negative. In addition, there is no convincing evidence of increased malignant conversion. In particular, in three recent large-scale studies of ELF magnetic-field effects on spontaneous tumour incidence in rodents, the overall proportion of malignant tumours tended to be evenly distributed between exposed and control animals and there was no evidence of a significant trend in dose-response relationship.

**Reproduction and development**

Studies have been carried out of the reproductive and developmental effects of exposure to ELF electric and magnetic field effects using chick and mammalian species. With regard to the studies of EMF effects during the first 2-3 days of development, the data are inconclusive. Positive effects have been reported but attempts at replication have mostly been unsuccessful; in addition, a number of studies found no effect. Studies using mammalian species are more relevant to possible effects on humans and overall, the data do not support the hypothesis that ELF EMF exposures result in reproductive toxicity. Most studies of the effects of exposure to power frequency electric fields on the development of rodents and miniature swine were negative. Similarly, exposure had little effect on rodent reproduction and development, although several studies noted an increase in the incidence of minor skeletal anomalies or variants.

**Endocrine system**

Most animal studies of endocrine function concern the pineal gland and melatonin, because of concerns related to cancer. Fewer studies have been carried out of ELF electromagnetic field effects on the pituitary hormones or those of other endocrine glands. Some, but not all, studies of power frequency EMF effects on rat pineal and serum melatonin levels report that exposure to power frequency electric or magnetic fields resulted in suppression. The evidence from a series of more recent studies by another group reporting that circularly polarised magnetic fields suppress night-
time melatonin levels was sometimes weakened by inappropriate comparisons between exposed animals and historical controls. The data from other experiments was equivocal but mostly negative. The evidence for an effect of exposure to ELF EMF on melatonin levels and melatonin-dependent reproductive status in seasonally breeding animals, Djungarian hamsters and Suffolk sheep, is mostly negative. No convincing effect on melatonin levels has been seen in a study of non-human primates chronically exposed to ELF EMF.

Conclusion on ELF

Most reviews indicate that ELF magnetic do not produce reproducible effects on animals. However, there is still some uncertainty about DMBA models.

Further work is also needed to test a recent hypothesis which is related to the possible effects of contact currents experienced in residential environments: these currents may affect hematopoesis and be thus related to childhood leukaemia, for which there is so far no accepted mechanism.

Radiofrequency fields

The rapid development of mobile telephony in the last ten years has led to a large research effort in the RF range, aimed at assessing the risks related to both mobile telephones and base stations. This followed the allegations in the courts and media that mobile telephones are a cause of cancer and the public objections to the siting of TV, radio and mobile telephony antenna because of a fear of cancer. Animal testing has contributing significantly to this research: at the present time, there are 95 of such studies, completed or on-going, listed in the WHO EMF database. Several reviews and institutional reports have summarised the main findings.

Exposure systems

Several new exposure systems have been built and validated in the recent years for head-only, head-mainly or whole-body exposure. The quality of the systems has improved vastly and nowadays the exposure is well-characterised and uniform.

Genotoxic effects

The energy of RF photons is too weak to break bonds and thus cannot affect DNA directly. However, there have been investigations of potential epigenetic effects (indirect) at low-level.

Micronuclei: No effect was seen on blood cells in mice exposed at 2.45-GHz for 18 months at a whole-body SAR of 1 W/kg. Few other such studies have been performed in vivo.

Chromosomal aberration: Most experiments on whole animals have shown no increase in chromosomal aberration after exposure, even at high intensities corresponding to a rise in body temperature.

DNA damage: An increase in the number of DNA breaks was reported in the brain cells of rats exposed for two hours to pulsed or continuous-wave 2.45-GHz microwaves using the “comet” assay. However, several replications studies have since failed.

Mutation: A large number of studies on animals have consistently failed to demonstrate mutation of somatic cells after exposure to RF microwaves even at high levels.
Cancer

Spontaneous tumour incidence: There were no effects observed in several rodent studies in normal animals but possible effects in transgenic mice as reported by the Repacholi group using transgenic mice prone to develop lymphomas. Replication of this study and extension with more complete follow-up and improved dosimetry is currently under way in Australia and Italy. Another In case of replication, one will need to further assess the relevance of these findings for human health. Other authors have reported a lack of effect of RF exposure on cancer incidence in mice prone to mammary tumours.

Promotion studies: The many co-promotion studies that have been performed using chemically-induced tumours have been consistently negative. There are several more such studies under way.

Progression of injected tumours: The few studies on injected tumours have been negative.

Melatonin: There are so far too few studies on melatonin levels in animals to draw firm conclusions. However, most of these studies were negative.

Conclusions on cancer: Some caution is required before dismissing effects on cancer completely as positive results were found in a few studies.

Acute effects on the nervous system

Gene expression
Consistent changes have been seen only with heating but studies with transgenic worms suggest otherwise. Further work on HSP expression is clearly needed as evidenced also in recent in vitro results.

Blood-brain barrier (BBB) permeability
results of studies on the permeability of the BBB have mainly negative but some positive effects have been reported and further work is on-going in several laboratories.

Conclusions
Regarding data obtained on cancer in animal models using mobile telephone signals, there is very limited evidence of low-level effects overall. Further work is on-going that should clarify the remaining controversies.

1 International Commission on Non Ionizing Radiation Protection
2 International Agency for Research on Cancer
5 http://www.iarc.fr/pageroot/PRELEASES/pr136a.html
12 as found in one study which needs confirmation: Fam, W Z, and Mikhail, E L. Lymphoma induced in mice chronically exposed to very strong low-frequency electromagnetic field. Cancer Let., 105, 257-269 (1996).
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- National Radiological Protection Board, UK http://www.nrpb.org.uk/
- Forschungsgemeinschaft Funk e.V., Research Association for Radio Applications, Germany http://www.fgf.de/
- COST 244bis : Biomedical effects of electromagnetic fields http://www.radio.fer.hr/cost244/main/mainpage.htm


