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In vivo studies on possible effects of radiofrequency electromagnetic fields (RF-EMF), especially as used by mobile radio

A literature study on long-term studies in experimental animals (carcinogenicity studies)



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Dear readers,

As a second written paper based on the lectures held during the 10-year celebration of the Research Association for Radio Applications (Forschungsgemeinschaft Funk e.V. – FGF), issue no. 19 of the “Edition Wissenschaft” presents the literature survey by T. Tillmann and J. Buschmann, Ph.D.s, on long-term experimental studies performed in animals. Both scientists work for the Fraunhofer Institute of Toxicology and Experimental Medicine. The focus of this paper are carcinogenicity studies. In the public, it is often claimed that there is no or insufficient information available from long-term experiments investigating biological effects of electromagnetic fields (EMF). The authors investigated this allegation, putting special emphasis on “low-energy” EMF effects (i.e. below the valid protection limits for humans according to the 26th BImSchV; often also called to as “athermal” or “non-thermal” effects).

Cordially,
Gerd Friedrich

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In vivo studies on biological effects of radiofrequency electromagnetic fields: Survey and prospects

Electromagnetic fields (EMF) fulfil numerous criteria for being seen as dangerous to humans: They are not perceptible by our sense organs; for the most part, they are generated and emitted by impressive technological equipment, and they transport energy. A great number of studies has already been performed in response to this highly emotional situation. However, a critical review of these studies shows that the objective to contribute to a more rational debate for different reasons was not always reached. Therefore, the goal of this lecture is to first give a short overview of the most relevant experimental studies investigating long-term effects in test animals. As an example of such studies, our own tests examining the influence of pulsed radiofrequency EMF on the prenatal development of rats will be presented.

Based on available studies, different approaches and test methods will be discussed. Under the paragraph 'prospects' we will try to describe an experimental strategy which seems to be the most promising for future research efforts.

1. Literature survey

The studies discussed in this paper exclusively deal with long-term effects, since these are of special relevance to human health. Long-term effects are defined as effects

occurring after repeated field exposure and/or an observation period of 4 weeks or longer. This selection is derived from toxicological testing, e.g. tests performed on chemicals.

In the following, some of the studies will be briefly presented: Adey et al. (1999) found a seemingly "tumor-protective" effect of an NADC signal on spontaneous and chemically induced tumors of the central nervous system (CNS) in rats. However, this effect could not be reproduced in a follow-up study which showed no effects of field exposure at all (Adey et al. 2000). Unfortunately, only tests on CNS tumors were performed here. The tests of Chagnaud et al. (1999) did not show any effects of two-week exposure of rats to GSM signals on chemically induced tumors. Exposure periods were too short, though, and the cohort size too small to come to safe conclusions.

In a methodologically sound study, Chou et al. (1992) detected a significant increase in the occurrence of malignant tumors in rats due to field exposure at 2450 MHz. This finding was qualified by the authors, since the number of benign tumors remained the same and the increase found in the exposed group was also still within historical control data. Frei et al. (1998) found no effects of

field exposure at 2450 MHz using two different field strengths on tumorigenesis in mice.

In a much-cited study by Repacholi et al. (1997), the authors identified a significant increase in a specific tumor type (lymphomas) after exposure of transgenic mice at 900 MHz. Results still have to be reproduced, and the study can be doubted due to methodological reasons. Therefore, it was replicated in Australia. The publication of Utteridge et al. has been available since August (2002); it did not succeed in confirming the results of Repacholi.

Salford et al. (1993) found no effects of field exposure at 915 MHz on the development of induced brain tumors in rats. But, regrettably, tests investigated only one single tumor type. A methodologically very well-described study by Toler et al. (1997) indicated no effects of field exposure at 435 MHz on tumor incidence in mice.

In summary, it is made clear by the available literature that experimental studies performed to-date on longterm effects in animals, especially on teratogenicity (induction of congenital malformations) and fertility (reproductive potential), as well as carcinogenicity (cancer initiation), often lead to contradictory results.

But despite these contradictions in available data regarding the

endpoint of teratogenicity/fertility, the conclusion seems justified that occurring effects obviously are thermal and that athermal effects, on the other side, are not very probable.

With regard to the endpoint of carcinogenicity, even more inconsistencies are seen which is partially due to methodological problems. Scientifically sound conclusions on potential health hazards to humans based on animal experiments therefore seem impossible to be drawn at the moment, even though the majority of the studies do not suggest any such effects.

2. Our investigations

For a better understanding of experimental studies in animals, two investigations by ourselves on the influence of pulsed radiofrequency EMF will be described in more detail. The first study examined whether exposure of pregnant rats to a typical GSM field in the range of the human threshold value (5.5 W/m^2) would affect prenatal development of the offspring. None of the examined parameters, however, provided evidence for such effects. A follow-up study tested a substantially higher field strength under improved exposure conditions inside a waveguide, through still without thermal effects (60 W/m^2). Although results do not prove any clear effect, there was a distinct (albeit not statistically significant) increase mainly in embryo losses in the exposed group. As a matter of fact, however, many of the parameters examined in this study go beyond historical control data determined by our laboratory both in control and – even more

pronouncedly – in the exposed group, which may be due to different holding conditions inside the applied waveguides. Thus, these effects possibly are in a grey area. When comparing both studies, we can see that exposure within human thresholds did not affect any of the endpoints examined in animal experiment. If accepting effects occurring under the conditions of our maximum field strength – which does not provoke thermal effects yet – as ‘borderline effects’, the level of ‘no observed effect’ is found in the range between the two tested values.

This practical example illustrates the problems arising in study interpretation; methodological conclusions can be drawn from this for future study performance. These mainly comprise the inclusion of a cage or shelf control as well as the simultaneous use of several groups exposed to different strengths. Moreover, during planning and performance of such studies, investigators have to consider advantages and disadvantages of the use of freely moving animals or of animals that are restrained during exposure.

3. Prospects

When comparing the different approaches, two main groups of studies can be distinguished: Studies aimed at testing a specific hypothesis, and studies mainly serving as a means to do ‘global’ risk assessment. The former often are markedly academic basic research efforts, which often are of high scientific value and are performed using very sensitive model systems. However, portability to the targeted

human organism often is limited, and it is highly difficult (above all when negative results are obtained investigating single hypotheses) to make conclusions about ‘general’ health risks to humans. The second group of studies uses a distinctly toxicological approach in the sense of applied science: Using different test methods, the groups of test animals are exposed to different field strengths to examine as many potentially health-relevant endpoints as possible. Due to the large number of test parameters, this approach – that can best be described as ‘apical’ – allows for an extrapolation of results to humans and can contribute to health risk assessment. However, due to their ‘broad-spectrum’ character, such studies often are less profound than those of the first group, which is why they are not always sensitive enough for exploring specific health risks. A promotion of the dialogue between both groups of researchers could release significant synergies: If, on the one side, results achieved in basic research could be reproduced in applied tests, and if, on the other side, findings from applied studies could be confirmed by mechanistic approaches, the framework for risk assessment would be much improved. Regarding investigations into possible health effects of EMF, the Research Association for Radio Applications (FGF) is predestined to play an important role as a moderator and mediator between the two research schools also in the future. By such efforts, existing gaps of knowledge could more effectively be closed, and the aim to create a less emotional style of discussion based on experimental data could be reached more quickly.

Thomas Tillmann and Jochen Buschmann

In vivo studies on possible effects of radiofrequency electromagnetic fields (RF-EMF), especially as used by mobile radio

A literature survey of long-term experimental studies in animals (carcinogenicity studies)

Introduction

Modern society is characterized by an ever increasing demand for communication without boundaries, wireless data exchange and constant reachability. Besides a large number of terrestrial radio networks, satellite telephone systems (THURAYA, IRIDIUM, INMARSAT) have been used for worldwide mobile communication for quite some time; for decades, GPS (Global Positioning System) satellites have been emitting signals for navigation or localization. A variety of radio, television and communication signals provide worldwide blanket coverage from an orbit near to the earth.

Mobile computers (laptops) and the internet have long since conquered workplaces, households and the sphere of our spare time, as well. Not only phone calls via mobile phones, but also (mobile) data transfers of all kinds (information, entertainment, music, etc.) are made possible worldwide by new transfer

technologies with ever increasing transfer rates.

Local networks are increasingly installed at workplaces and in private households providing wireless communication or mobile data access (e.g. by Blue Tooth (BT), or Wireless LAN Technology (WLAN)). The most recent (third) mobile radio generation is soon to be introduced; applying radiofrequency electromagnetic fields, it will transfer images, sound and graphics with data transfer rates of up to 2.5 Mbps to (nearly) everywhere. New powerful technologies (e.g. UMTS: Universal Mobile Telecommunications System) with fine-mesh network density, i.e. with a large number of new transmitters (base stations), have to be established in order to meet the demand for unlimited, fast and mobile information services available everywhere.

Just this subdivision into small network parcels, i.e. the growing number of (visible) base stations (operating each with less power),

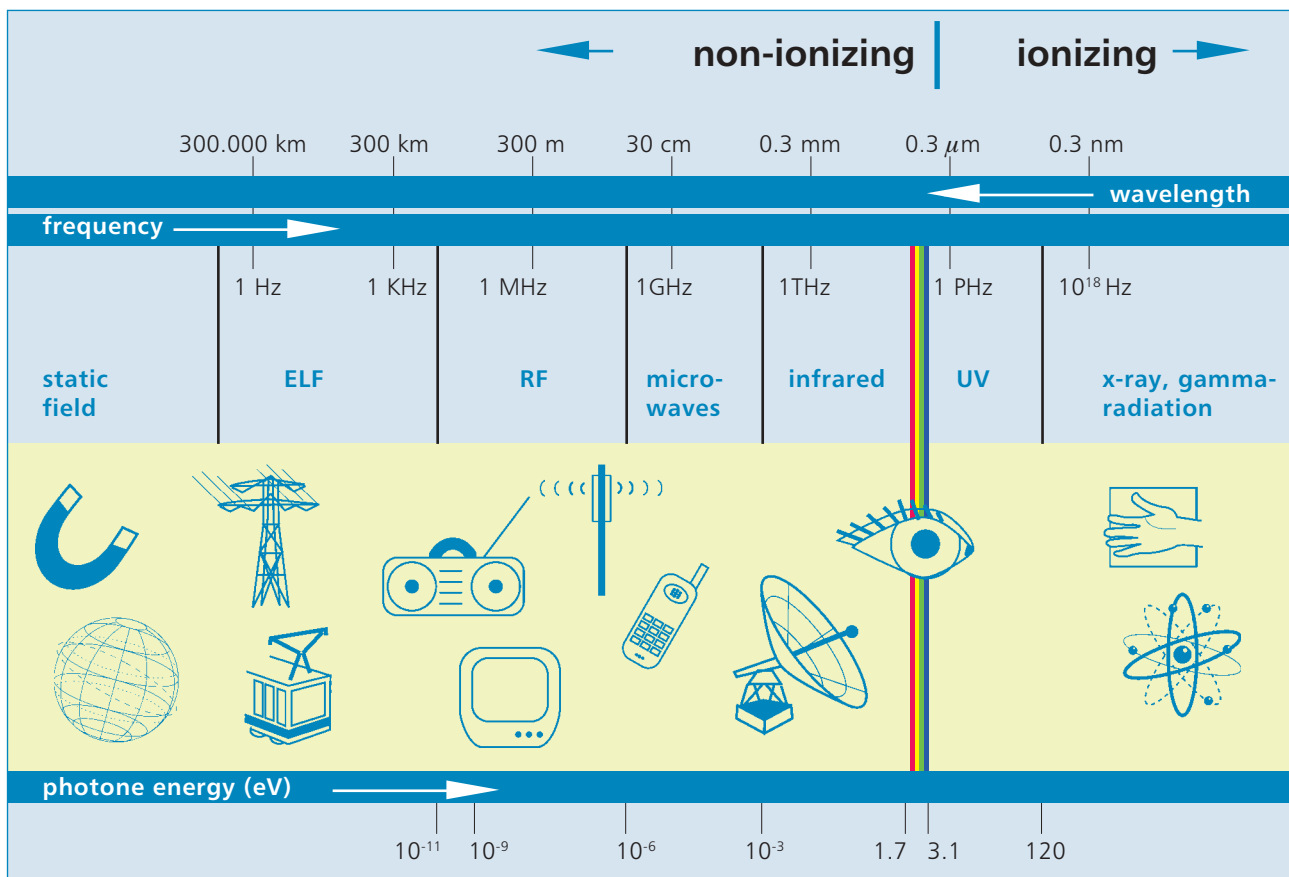
was the trigger of the current discussion about health risks to humans from chronic EMF exposure led in the public.

On the other hand, there is a meanwhile fairly confusing mass of electromagnetic signals from high-power transmitters (uncritically) used for various applications. Electromagnetic fields (RF-EMF) continuously emitted by frequency- or amplitude-modulated radio broadcasting, a large number of television channels, radar and various traditional (directional) radio applications are ubiquitous. In households and at workplaces, we also use a great number of (shielded) devices in part generating strong RF fields (microwave ovens, TV, video and computer monitors, electrical heating, etc.). Public discussion about a potential *environmental pollution* by electromagnetic fields (EMF), the so-called 'electrosmog', today nearly exclusively evolves around base stations of widespread mobile radio networks and the vastly used mobile

phones. Obviously, aspects such as different transmission powers, pulsation, modulation, etc., of fields (nearfield or farfield characteristics) play a minor role in this discussion; instead, the increased number of base stations per se (transmitters) is seen as a cause of concern. Incidentally, EMF meet numerous criteria classifying them as being dangerous to humans: they cannot be perceived by our sense organs; they are partially generated and emitted by impressing technological equipment; and they transfer energy. Defined by wavelength or frequency, the whole electromagnetic spectrum (fig. 1) can be classified, according to the energy transferred into ionizing and non-ionizing radiation,

comprising the most different types of radiation and technical applications – from high cosmic radiation (gamma radiation), nuclear radiation, x-rays, UV light (ionizing radiation) via the visible light and infrared radiation to the radiofrequency (RF) and low-frequency range. The power supply network (50 Hz), radio broadcasting, television, radar, directional (radio relay links) and mobile radio are only a few examples of EMF technologies applied in the non-ionizing RF range where – compared to ionizing radiation – very small energies (< 12 eV) are transferred. These energies are too low even to break chemical bindings. Therefore, at first it seemed almost

incomprehensible that this low-energy electromagnetic radiation was associated in the public with neoplastic changes, e.g. brain tumors in humans, since non-ionizing radiation per se is too low-energetic to (directly) break chemical bindings and thereby e.g. to lead to specific genotoxic alterations (mutations) in the DNA. Besides single case studies, however, also epidemiological studies, some in vitro studies and an Australian animal experimental study, which found an increase in hematopoietic tumors in mice after EMF exposure, have led to uncertainty in the public. In response to this highly emotional situation, a great number of investigations has already been performed or launched. However, a



critical survey of these studies shows that the aim of assessing human health risks from chronic electromagnetic field exposure has not always been possible to achieve for various reasons.

Therefore, the goal of this paper will be to provide a (critical) survey of the most relevant experimental studies investigating RF long-term effects in animals and to present examples of currently ongoing RF-EMF investigations. Finally, in a chapter on future prospects, we will try to present an experimental strategy which seems to be the most promising approach to apply in the future.

Preface

All cited scientific publications are found in peer-reviewed journals and exclusively deal with experimental studies on long-term effects in animals, since these probably are of special health relevance to humans. Long-term effects are defined as effects occurring after repeated field exposure and/or animals observation periods of 4 weeks or longer. In vitro studies with a shorter exposure or observation period also will be included as examples if they are of special relevance to carcinogenesis studies.

Usually, for description of EMF exposure of animals, the specific absorption rate (SAR), averaged as the whole body absorption rate, is given. This frequency-dependent quantity expresses the energy absorbed per volume unit in the tissue. Dependent on water content, conductivity, body geometry and resonances, the SAR is irregularly distributed across the body so that locally limited considerably higher SAR peaks – so-called ‘hot spots’ – can occur. In addition to averaged whole body SARs, especially these local SARs seem to be relevant to the interaction of EMF with biological structures; however, they are rarely included in the corresponding publications. Also, dosimetrical studies performed in dead mice have demonstrated the imprecision of average whole body exposure values. Moreover, they could show how different tissues can reach very different temperature levels leading to the known consequences (Swicord et al. 1999).

As thermal EMF effects are sufficiently known, this study will (as far as possible) exclusively deal with studies investigating non-thermal

long-term effects in animals.

We should bear in mind the difficulties potentially arising when extrapolating (mass/size) SARs obtained from results of EMF-tested animals across the different species (animal/human), not least from physiological discrepancies in thermoregulation.

A detailed evaluation of applied exposure technology (field strength, field homogeneity, absorption, modulation, pulsation, etc.) which is not always fully described, especially in older publications, and of the determined or calculated SAR average or maximum values (local, whole body) cannot be part of this survey study. We will indicate the corresponding references (Valberg 1995, Gauger et al. 1999).

Carcinogenesis and genotoxicity

Through the phases of initiation, promotion and progression after a latency of years to decades, the multiphase process of carcinogenesis leads from the initial transformation of normal cells to a clinically manifest tumor. The first stage of this development (initiation) is characterized by direct damage of the cell genome (e.g. caused by ionizing radiation) or indirect alterations provoked by metabolites (e.g. radicals). If repair processes fail, immunological control mechanisms can lead to cell death (apoptosis, necrosis), or the genetic damage/alteration (in the cell) is permanent (mutation). Initially, the damaged cell is still controlled by the normal tissue, but already during promotion phase, proliferation by clonal multiplication of the transformed cell(s) is stimulated. The changed genome thus disseminates to the daughter cells (preneoplastic foci) and, at first, so-called benign tumors develop. The term 'progression phase' stands for the progressive transformation of benign tumors into malignant ones which are characterized, among other things, by progressive autonomy and an increased metastatic potential.

In the past, non-ionizing electromagnetic radiation repeatedly has been suspected to favour tumorigenesis or in some way to intervene in the different steps of cancer development, though a direct alkylating effect of low-energy RF-EMF (< 12 eV) on the DNA could arithmetically be excluded. However, studies of the working group of Bohr (Bohr et al. 1997; Bohr & Bohr

2000) have given evidence for an excitation of resonant oscillations in chain molecules, e.g. for certain proteins and DNA molecules, within the RF signal range. Allegedly, they may lead to structural changes and chain breaks also in the non-thermal EMF range, thus being a potential (genotoxic) EMF interaction mechanism. Especially evidence gained in epidemiological LF-EMF studies has been taken as an impetus to perform numerous in vitro EMF studies which were aimed at clarifying the suspected carcinogenicity of EMF fields and/or at elucidating the potential mode of action. In this context, some studies on cellular genomes have been repeatedly cited and interpreted as evidence for RF-EMF

genotoxicity, since DNA changes after failed intracellular repair – so it is claimed – later can manifest as mutations.

In this context, repeatedly the studies of Lai and Singh (1995, 1996) are cited which report a statistically significant dose-related increase in chromosomal alterations (DNA single-/double-strand breaks) in brain cells of rats after one-time RF-EMF whole body exposure (2 hours, 2450 MHz, SAR: 0.6 and 1.2 W/kg). Malyapa and colleagues (1997a, 1998), however, could not reproduce the DNA strand breaks, neither in vitro nor in vivo, at 2450 MHz (SAR: 0.7 to 1.9 W/kg) nor during tests in the GSM frequency

Literature carcinogenicity 1

Author (year)	Field	Endpoint	Effect?
Adey (1999)	NADC	spontaneous and induced CNS tumors	protection
Adey (2000)	NADC	spontaneous and induced CNS tumors	- tumor type
Chagnaud (1999)	GSM	chemically induced tumors (2 weeks)	- tumor type
Chou (1992)	2450	benign and malignant tumors	increased malignance; histological control; benign; reproducible?

Literature carcinogenicity 2

Author (year)	Field	Endpoint	Effect?
Frei (1998)	2450	mammary tumor development in tumor-prone strain	- tumor type!
Higashikubo (1999)	FMCW CDMA	induced CNS tumors	- tumor type!
Imaida (1998)	TDMA	chemically induced liver tumors	- tumor type!

Carcinogenesis

range (835.62 MHz, FMCW modulated and 847.74 MHz, CDMA modulation, resp.) with a SAR of 0.6 W/kg in fibroblast and glioblastoma cells (Malyapa et al. 1997b). Sarkar and colleagues (1994) could prove DNA changes (point mutations, base sequence alterations) in brain and testes of Swiss mice after daily 2-hour exposure over 120, 150 and 200 days (2450 MHz, SAR: 1.18 W/kg). Takahashi et al. (2002), on the other hand, did not find evidence for an increase in mutagenicity after 4-week EMF exposure (1500 MHz, 90 min/day, 5 days/week) in the brain of mice (local SAR: 0, 0.67, 2 W/kg). Although micronucleus tests performed in bone marrow and

peripheral erythrocytes of C3H/HeJ mice indicated a significant increase in the number of micronuclei after 18-month exposure (20 hours/day, 7 days/week, 2450 MHz, SAR: 1 W/kg), incidence rates of both groups (sham-exposed and exposed mice) were within the spontaneous range of historical controls (Vijayalaxmi et al. 1997, 1998). The cytogenetic RF-EMF studies done by Maes and colleagues often are quoted. The authors could not find any evidence for a direct genotoxic effect of the different applied electromagnetic fields (2450 MHz, 935.2 MHz) after exposure of up to 2 hours using the sister chromatid exchange test (SCE), but detected a slightly increased SCE rate in the

GSM field in combination with the cytostatic mitomycin-C (Maes et al. 1993; Maes et al. 1997). In vitro studies performed by the same working group (Maes et al. 1996) showed an increased genotoxic effect (SCE test) in lymphocytes in combination with mitomycin-C following 2-hour exposure to a GSM far field (954 MHz, SAR: 1.5 W/kg). However, this evidence of EMF genotoxicity could not be confirmed by more recent tests done in human lymphocytes in the GSM field (900 MHz, 2 hours, SAR: 0.4, 2, 3.5, 5.5 and 10 W/kg), neither in combination with mitomycin-C, nor were additional cytogenetic GSM effects shown by combining GSM field exposure with subsequent (ionizing) x-ray radiation (1 Gy) (Maes et al. 2001).

Micronucleus tests of Bisht et al. (2002) performed in cultivated C3H 10T1/2 cells demonstrated no significant differences when comparing them to sham-exposed cells after 3, 8, 16 or 24 hours of FDMA field exposure (835.62 MHz, SAR: 3.2 or 5.1 W/kg) or CDMA exposure (847.74 MHz, SAR: 3.2 or 4.8 W/kg), whereas Tice and colleagues (2002) after 24 hours exposure of cultivated lymphocytes to four characteristic RF signals (837 MHz, 12.5 kHz FM; 837 MHz, 217 Hz TDMA; 837 MHz, 217 Hz CDMA; 1909.8 MHz, 217 Hz GSM) with specific absorption rates of 5 and 10 W/kg every time found a significantly increased number of changed micronuclei. Overall, the large number of genotoxicity studies investigating cellular systems do not present a consistent picture; certainly, thermal effects of exposure cannot always be excluded. Also, the sensitivity of the methods used or their validity regarding the

Literature carcinogenicity 3			
Author (year)	Field	Endpoint	Effect?
Repacholi (1997)	900	Lymphoma in transgenic mice	increase, methodology!, non-reproducible
Salford (1993)	915	Specially induced brain tumor	- tumor type
Toler (1997)	435	overall tumor development!	-

Literature carcinogenicity – summary
Inconsistent data:
<ul style="list-style-type: none"> Contradictory results Lack of 'guideline' studies
Methodological problems:
<ul style="list-style-type: none"> Negative results at limited study size Positive results: replicability
Health risks to humans:
<ul style="list-style-type: none"> To this date not safely deductible Not supported by majority of studies Zero hypothesis is not provable

whole organism often seem doubtful. Please refer also to current reviews dealing with the topic of genotoxicity of RF mobile radio signals (Brusick et al. 1998, Verschaeve & Maes 1998; IEGMP 2000; Repacholi 2001). In the past, results of these in vitro studies though often enough were an impetus to verify their biological relevance to the whole organism by additional animal experiments.

Literature survey

In general, studies on health-relevant effects of mobile radio (RF) electromagnetic fields have to be distinguished by whether they use near-field (mobile phone) or far field exposure (base station), which differ by a large number of physical parameters (field strength, pulsation, modulation type, transmission duration, etc.).

Maximum transmission power of GSM mobile phones is 2 W (900 MHz) or 1 W (1800 MHz); the adaptation of transmission power – i.e. only the minimum power needed is emitted – being an important

characteristic of mobile radio networks. Contrary to the at more or less non-directional radiation of mobile phones, base stations preferably are equipped with directional antennas bundling energy (6 to 14 W) for boosting signals in a preferred direction and continuously emitting a far field of different intensity and irregular pulse character.

The technology currently applied most in Europe is the GSM (Global System for Mobile Communications); other systems such as DCS 1800 (Digital Personal Communications System), DECT (Digital European Cordless Telecommunications), and TETRA (Trans European Trunked Radio) are also used. The carrier frequencies of these systems are in the ranges of 350 to 1000 MHz and 1800 to 2200 MHz.

In Germany, mobile radio uses carrier frequencies of 890 to 960 MHz in the D-net and of 1710 to 1800 MHz in the E-net. The systems used for data transfer in the United States and in some Asian countries are called – depending on the user access technique – CDMA (Code Division Multiple Access), FDMA

(Frequency Division Multiple Access) and TDMA (Time Division Multiple Access). Applied frequencies are between 450 to 1900 MHz. The above mentioned European systems also use TDMA techniques for the simultaneous transfer of several calls (time-slot technique) – which are the ‘reason’ for the occurring low-frequency (217 Hz) pulsation (‘bursts’) of the radiofrequency carrier. The wide range of current technologies used worldwide by mobile radio, or their different signal characteristics in different networks (carrier frequency, pulsation, near- and far field, net capacity utilization, transfer rate, etc.) illustrate the difficulties arising with regard to portability or comparability of EMF studies that apply even to very slightly divergent signals.

Prenatal EMF exposure and hyperthermia	
Effects after exposure	Effects after hyperthermia
Decreased fetal weight, delayed ossification	Decreased fetal weight
Malformation of extremities, palate clefts (mouse)	Malformations: extremities, eye, facial, cranial
Decreased brain weight	
Pre/postimplant losses	pre/postimplant losses
Maternal weight gain	
Maternal mortality!!!	
Reflex development	

EMF carcinogenicity studies in animals

As early as at the beginning of the seventies, animal long-term experimental studies in animals investigating potential carcinogenic effects also of pulsed radiofrequency electromagnetic radiation were performed (Prausnitz & Süsskind 1962; Spalding et al. 1971; Skidmore & Baum 1974, Baum et al. 1976). They did not provide evidence for health-relevant effects of exposure, though. Moreover, they used unclear exposure parameters and, in part, observed thermal effects of exposure (Preskorn et al. 1978; Roberts & Michaelson 1983).

Mouse studies

After 28 days of unpulsed RF-EMF exposure (CW, 2450 MHz, 8 hours/day, whole body SAR: 21 W/kg) of female CD1 mice, McRee et al. (1981) found no evidence for genotoxic effects of field exposure when testing the sister chromatid exchange in bone marrow cells compared to sham-exposed mice. Effects of chronic unpulsed 2450 MHz field exposure on tumor incidence in C3H/HeA mice were examined by Szmigielski and colleagues (1982). Female mice, characterized by a high spontaneous mammary tumor rate, were exposed from the 6th week of life up to an age of 12 months to EMF (2 hours/day, 6 days/week) and were palpated for lumps every fortnight. Compared to sham-exposed animals, there was an accelerated EMF dose-dependent development of lumps, i.e. a premature palpable manifestation. The study was not blinded, there were no histological tests, and

thermal effects (SAR: 2 to 8 W/kg) could not be excluded; so results are to be interpreted with caution.

Toler and colleagues (1997) used a pulsed RF signal for chronic whole body exposure of female C3H/HeJ mice. The animals, which show a high spontaneous mammary tumor rate, were kept for 21 months (22 hours/day, 7 days/week) in a pulsed electromagnetic field (435 MHz, 1 kHz PW, SAR: 0.32 W/kg). The surviving females – as well as the dead or moribund animals that had been sacrificed – were completely necropsied and histopathologically compared to a group of sham-exposed animals. EMF-exposed and sham-exposed mice showed comparable survival rates; there were no differences between the groups regarding mammary tumor incidence, latency and growth rates, and there were comparable tumor spectra with similar tumor incidences.

Frei and co-authors (1998a, b) as well used C3H/HeJ mammary tumor-prone mice for their 18-month study applying an unpulsed RF-EMF signal (CW exposure: 2450 MHz, 7 days/week, 20 hours/day, SAR: 0.3 to 1 W/kg). The animals were subjected to thorough histopathological tests. Comparing them to sham-exposed control animals, the authors could not find any evidence for effects on the tumor spectrum or the mammary tumor rate, tumor latency periods, tumor growth rate or survival rate of the animals due to field exposure.

The study of Jauchem et al. (2001) who also used C3H/HeJ mice, which were exposed over 3 months (2 min/week) to pulsed, high-energetic ultra wideband signals (UWB), shall only be mentioned briefly. Although this study included

RF range emissions, the applied technology otherwise had no mobile radio characteristics. An influence of exposure on mammary tumor development was not detected. Special relevance among the long-term studies on EMF carcinogenesis is given to the study of Repacholi and colleagues (1997). For the very first time, offspring of transgenic $E\mu$ -Pim 1 female, characterized by a high spontaneous lymphoma rate, and C57BL males were exposed to a typical GSM far field in this study. Over a maximum of 18 months, the heterozygotic females were daily exposed to EMF (7 days/week, 1 hour/day; 900 MHz, 217 Hz pulsed) inside their cages (5 animals/cage), and lymphoma rates were compared to those of sham-exposed animals. According to the authors, the calculated whole body SAR ranges were between 0.13 and 1.4 W/kg. During the 18-month experiment, macropathological examinations were performed in all animals that had died or been sacrificed. 22 animals of the control group and 43 in the treatment group showed macroscopic evidence of lymphoma development. The authors thus postulated a significant increase ($p < 0.001$) in lymphoma incidence (22% versus 43%) from field exposure. Particularly questionable was the evaluation of study results. For example, not all female mice were histologically examined; and the surviving, clinically healthy animals were sacrificed without any further examinations after the 18-month test period. Lymphoma diagnosis cannot be based on observation made from the outside alone or on macroscopic findings revealed during necropsy (which was not even performed), since (still) clinically healthy mice

without obvious lesions, yet with lymphoma or infiltrations in organs may be overlooked. Neither the exact number of histologically examined mice nor the number of survivals was given so that the reference quantity, i.e. the number of lymphatic animals out of all histologically examined animals, could not be determined. In addition, according to the authors, 14 of the animals that had died (7/7) were too autolytic to be histopathologically examined and thus could also have changed the lymphoma incidence found in the experiment. The percentage of 7% (14/201) of autolytic and thus non-evaluated animals in this study seems rather high. In carcinogenesis studies performed under standardized GLP study conditions, results would not be seen as valid, if more than 10% of the animals had not been fully examined.

Additionally, the use of hybrid offspring ($E\mu$ -Pim1 x C57BL/6Ntac) in this study is to be criticized, since no historical comparison data (body weight development, life time, spontaneous tumor rate, etc.), which could help in the evaluation of test conditions and result evaluation or discussion, are available.

An explanation for the short daily whole body EMF-exposure (2 x 30 min) is also lacking, so that a longer daily field exposure of the mice inside their cages or a 24-month study according to the NTP/IARC standard using much applied, acknowledged mice strains (e.g. B6C3F1, CD1, CBA) do make sense. Ultimately, also the unclear exposure parameters or largely varying exposure conditions – the authors speak of SAR ranges of 0.008 to 4.2 W/kg and average values of 0.13 to

1.4 W/kg – have been a cause of criticism. Thus, due to the overall design, test performance and the unclear evaluation, the study seems only partially be suited to be used for assessing health risks of chronic EMF exposure.

In 2002, again an Australian group (Utteridge et al.) published results of a RF-EMF study of a design that, in part, corresponded to that of the 'Repacholi study'. Female heterozygotic offspring of transgenic $E\mu$ -Pim 1 females and C57BL males, as well as non-transgenic wild-type females with a similar genetic background were exposed every morning, except on weekends (1 hour/day, 5 days/week), to a GSM-modulated signal (898.4 MHz, 217 Hz pulsed) while being restrained in holding tubes. The study included 4 EMF dose groups (SAR: 0.25, 1, 2, 4 W/kg), a sham-exposed group and a (negative) cage control group of 120 heterozygotic and 120 wild-type females each, as well as an EMF sham-exposed positive control group (ethylnitrosourea, ENU 50 mg/kg body weight) of 30/30 females each. The mice were kept under standard laboratory conditions for a maximum study period of 24 months. Since EMF exposure took place in a separate room, also the cage control group (besides the (sham-)exposed mice) was moved/stressed every weekday (but not restrained) in order to create similar test/environmental conditions.

1198 of the 1200 sham-exposed and exposed mice were necropsied. The histopathological examination was performed more or less in a tissue spectrum limited to hematopoietic/lymphatic alterations (thymus, spleen, lymph nodes, bone marrow, small intestines and colon, brain,

lungs, heart, liver, kidneys, eyes and macroscopically visible changes). In addition to the routine H&E stain test, immunohistochemical examinations/stain tests (B- or T-cell lymphocyte markers, resp.) in lymphatic tissues were conducted. Compared to sham-exposed control animals, statistical evaluation of survival rate, body weight development, clinical health as well as of the examined tumor spectrum of transgenic mice or wild-type females showed no effects of EMF treatment.

Due to their using 4 EMF dose groups, the study of Utteridge and colleagues is much more than a mere replication of the controversial Repacholi study. The additional use of non-transgenic (wild-type) mice principally is recommendable; nevertheless, a "defined" strain with available exact historical data would have further enhanced the validity of this study. In this context, histopathological results of transgenic/non-transgenic cage controls would be useful, which unfortunately are missing in the publication. The validity of this study is limited both by the size and the tendency of histopathological tests focusing on neoplastic, lymphatic changes (no complete organ spectrum) and the unusual presentation of tumor incidences (lymphoblastic, non-lymphoblastic lymphomas, neurological and other tumors). Daytime(s) of daily exposure(s) is/are not mentioned in the publication, but from the number of exposure systems (15 à 40 animals), we can surmise that there were two exposures per day (1200 animals); related data are lacking, as well as details on the homogeneity of the two animal part deliveries (subsets) which obviously

were received one month apart. The unclear conditions of the four exposure types are a further cause of objection against this study: The authors note that exposure dosimetry remained unchanged over the whole study period, although mean values of body weights varied between 24 g to 39 g (transgenic E μ -Pim 1 mice) and 22 g to 44 g (wild-type); also, individual mice of a weight up to 60 g were exposed. Seen that SAR calculation was performed at the beginning of the study (22 or 24 g initial average body weight) and dosimetry remained unchanged the course of the study, the animals possibly were exposed to considerably smaller SARs.

Comparability of results of the Utteridge study obtained with transgenic E μ -Pim1 mice with the investigations by Repacholi et al. (1997) is strongly limited, particularly due to the fact that Utteridge and colleagues exposed mice restrained in tubes (versus cage exposure) for one hour (versus 2 x 30 min in the morning/evening), 5 days a week (versus 7 days/week) over a maximum of 24 months (versus 18 months) to four EMF dose ranges.

Rat studies

The 4-week EMF investigation by Dasdag et al. (2003) done in Sprague-Dawley rats shall only be mentioned to complete the picture. 8 animals each were (sham-) exposed to a commercially available mobile phone (20 min/day, 7 days/week, 4 weeks, GSM, 890 to 915 MHz) which was mounted at a distance of 0.5 cm below the cages. Since adaptation of the transmission power could not be measured exactly, the authors give a whole

body SAR of 0.52 W/kg at maximum transmission power. Out of a number of study endpoints, only the animals' testes were examined histopathologically. Group inhomogeneities were not found in this study.

Eleven years ago, Chou et al. (1992) published a comprehensive study examining effects of lifelong (25 months, 7 days/week, 21.5 hours/day) pulsed (8 Hz) radiofrequency (2450 MHz) EMF exposure on male SD rats (Sprague-Dawley). The specific absorption rate (SAR) of 0.4 W/kg was determined once at the beginning of the study in animals of a weight of 200 g. It was shown to considerably decrease, though, at a constant field exposure inside the waveguide with increasing body weight of the animals. The histopathological tests did not detect any statistically verified differences between tumor incidences of the exposed and the sham-exposed animals; the total of malignant neoplasia in the group of laboratory rodents exposed lifelong, however, was significantly increased.

The conclusiveness of results obtained by adding up (different) neoplastic changes in different organ systems or systems of non-comparable histopathological (cellular) origin according to neoplasia dignity alone is very limited. As also mortality of exposed rats compared to control animals was unchanged, the biological relevance of this (artificial) sum seems more than questionable. A comparison of (malignant) tumor-bearing exposed animals and other Sprague-Dawley rats also kept under SPF conditions (historical control animals), showed no statistically significant differences between incidences, so that Chou and colleagues did not claim to have

found any EMF-induced neoplastic effects in their study, either.

Vijayalaxmi and co-authors (2003) examined tumorigenesis and/or genotoxicity by the micronucleus test in F-344 rats after a two-year mobile radio field exposure (1.6 GHz). Fischer rats were exposed from the 19th day of pregnancy (in utero until weaning) for 2 hours daily (7 days/week) to a far field – typical iridium signal (whole body SAR: 0.036 to 0.077 W/kg) and, while restrained in holding tubes, exposed restrained in holding tubes with their heads to a characteristic (near field) iridium satellite phone signal (2 hours/day, 5 days/week, brain SAR: 0.16 to 1.6 W/kg) beginning at the age of 35 day and over a period of 2 years. Whereas histopathological examinations (tumor pathology) are not finished yet, the results of the micronucleus tests done in bone marrow erythrocytes are already available. The 2-year RF-EMF exposure of the animals did not provide any evidence for genotoxicity of long-term exposure, instead showing similar micronuclei incidences in bone marrow cells of cage control animals and 1.6 GHz-exposed or sham-exposed rats.

Animal studies on EMF promotion/co-carcinogenicity

Experimental studies on potential tumor promotion and/or co-carcinogenesis of RF-EMF in animals examine tumor manifestation or development in a known model, e.g. after tumor initiation by a known carcinogen (ENU, DMBA, x-ray radiation) or after inoculation of tumor cells into a receptor animal, and compare groups of initiated and exposed (possibly promoted) test animals to initiated but 'non-promoted' control animals. A (strict) separation from studies on tumor progression seems artificial and is especially difficult regarding inoculation tests using known tumor cell lines.

Mason and colleagues (2001) examined effects of very short RF-EMF exposure on DMBA (dimethylbenzanthracene)-induced tumors in SENCAR mice. One-time (1 W/cm², 10 seconds) and repeated (333 mW/cm², 10 s, 2/week, 12 weeks) 94 GHz exposure (CW) without mobile radio characteristics showed no effects on skin tumor development in this model.

Chagnaud et al. (1999) as well selected short exposure periods (total 20 hours) for their study performed in Sprague-Dawley rats. 20, 40 or 75 days after subcutaneous application of benzo(a)pyrene, the animals were exposed over 2 weeks to a GSM signal (900 MHz, 217 Hz pulsation, 2 hours/day, 5 days/week). The palpable lump manifestation and development within the skin of short-term exposed rats was not any different from that of sham-exposed animals and thus must not further be

discussed in this long-term study survey on EMF carcinogenesis.

Mouse

The chronic effect of unpulsed 2450 MHz field exposure on tumor incidence in BALB/C mice was examined by Szmigielski and colleagues (1982). Males were initiated by benzo(a)pyrene (BAP) brushed on the skin (every second day over 5 months) and exposed for 5 months (2 hours/day, 6 days/week). The macroscopic examination of the skin after 8 and 10 months, resp., revealed an EMF dose-dependent increase in the number of lumps as well as accelerated lump development.

The same working group also published studies on the possible association of simultaneous and prior EMF exposure with BAP-induced skin tumors in BALB/C mice (Szudzinski et al. 1982). BAP solution was applied over 6 months to the skin, while the males were exposed to EMF (CW, 2450 MHz, SAR: 2, 4, 6 W/kg, 6 days/week, 2 hours/day) either simultaneously (groups 1, 2) or even 1, 2 or 3 months prior to skin brushing (groups 3 to 5). Every 2 weeks, the skin was clinically examined and changes were rated according to their macroscopic morphology (degrees 0 to 6). In comparison to a sham-exposed group, the authors detected premature (macroscopic) occurrence of skin alterations across all treatment groups. Since neither test was blinded, findings were detected and graded only macroscopically, and since thermal (SAR: 2 to 8 W/kg) or stress-related effects could not be excluded, the results of these early RF studies have to be interpreted with great caution. Wu and colleagues (1994) examined

effects of chronic 2450 MHz field exposure on colon tumor development in BALB/C mice. A total of 115 mice were used, subdivided into a DMH (dimethylhydrazine) treatment group and a control group, as well as two DMH groups which were additionally either EMF-exposed or treated with TPA (12-O-tetradecanoylphorbol-13-acetate). After tumor induction by DMH, the animals, restrained in tubes were exposed over 5 months to an EMF (3 hours/day, 6 days/week, 2450 MHz, CW, SAR: 10 to 12 W/kg). Colon and macroscopically visible lumps were inspected light-microscopically. Study endpoints (colon tumor incidence, size and multiplicity) showed no EMF-induced effects. Heikkinen and colleagues (2001) examined the effects of chronic mobile radio exposure on tumorigenesis initiated by x-ray radiation in female CBA/S mice. The animals were x-rayed three to four times at weekly intervals with 1.33 Gray each (or 0.4 Gy and 0.93 Gy time; 4 Gy whole body dose) and subsequently exposed over a total of 78 weeks to EMF (1.5 hours/day, 5 days/week). 50 animals each restrained in tubes, i.e. orientated perpendicularly to the longitudinal axis of the electrical field, were either sham-exposed or exposed to a NMT (Nordic Mobile Telephone) signal (CW, 902.5 MHz, SAR: 1.5 W/kg), or to a GSM signal (902.4, 217 Hz pulsation, SAR: 0.35 W/kg). In addition, the study used a cage control group, i.e. the animals of this group were neither exposed to x-rays and EMF nor daily 'handled' (disturbed, stressed). Feed and water consumption, body weight development and survival rate of the animals only showed differences between the groups of restrained (sham-)exposed animals

and the cage control group, i.e. the comparison between the three x-ray and EMF (sham-) exposed mouse groups did not indicate any statistically significant discrepancies. The study was completed by clinical and hematological tests, organ weight determination (thymus, liver, spleen and kidneys) and an extensive histological evaluation (blinded study, additional external experts). The statistical evaluation of neoplastic change incidence showed differences between the cage control and the x-rayed or restrained EMF-exposed animals; however, an additional EMF effect in the exposed (PW or CW) animals versus sham-exposed animals was not detected. After initiation of carcinogenesis by x-ray radiation, two characteristic mobile radio signals, unpulsed NMT and pulsed GSM, were applied to restrained mice. The comprehensive examination was subdivided into four parts (subsets). Partially, three or four x-ray part treatments were applied; data on these are lacking, especially on the fact whether there were differences between individual groups. Some data on techniques of organ preparation and on the tumor nomenclature applied are also lacking. Historical data, for example on longevity or the spontaneous tumor spectrum, are hard to find for CBA/S mice, so that the overall quality of the study is difficult to judge; only a direct comparison of subsets with cage controls and/or sham-exposed animals could be performed. A tumor promoting EMF effect could not be found in this study; however, the investigation contains some minor flaws and therefore is not fully usable for risk assessment. The effects of field exposure to a pulsed Japanese standard mobile

radio signal (PDC, TDMA, 1.5 GHz, 50 Hz pulsation, whole body SAR: 0.084 W/kg, 90 min/day, 5 days/week) on DMBA (7.12-dimethylbenz(a)anthracene)-induced skin tumors in the mouse was examined by Imaida and co-authors (2001). During the 10th week of life, all ICR females were treated once with DMBA at a concentration of 100 µg DMBA in 100 µl acetone that was brushed on the shorn skin; the mice restrained in tubes were then (sham-) exposed over 19 weeks to an EMF (starting one week after DMBA initiation). Moreover, the study design comprised a DMBA cage control group and a positive control group (DMBA-TPA) which were additionally treated weekly with the promotor 12-O-tetradecanoyl-phorbol-13 acetate (TPA). Study endpoints were a hormone analysis (melatonin, corticosterone, ACTH), skin thickness at the site of the treatment, the number of tumors, skin tumor types as well as organ weight determination and histopathological examination of the liver, spleen, kidneys and suprarenal glands. Hormone analysis in the serum and/or plasma performed in 4 to 6 animals per group indicated no differences. Comparison of skin thickness in 10 animals each of (sham-) exposed and cage control mice provided no evidence for proliferation at the site of the treatment. In 96.6% of the positive control animals (DMBA-TPA), skin tumors developed with a multiplicity of 18.8 ± 13.4 lumps over the 20-week study period, whereas the untreated DMBA cage control group developed a papilloma, and the (sham-)exposed DMBA/EMF groups did not develop any tumors. So the authors could not detect a promot-

ing effect of EMF on DMBA-induced skin tumors. In addition, lymphoma incidence and/or lymphoma infiltration were explored in the liver and kidneys of the animals. There were no differences between treatment groups in this respect, either. For an evaluation of hormone analysis results (stress hormones and melatonin), the time span between the last (sham-) exposure (19 weeks) and necropsy (20th week) is essential; unfortunately, it is not indicated. Data on organ weights and the results of histopathological examination of the selected organs are not given. The lymphoma incidence given by the authors which is based on the examination of liver and kidneys alone, seems insufficient. The comparison of skin thickness and the statistical analysis with regard to a promoting EMF effect performed in one or no tumor in the cage control or EMF (sham-) exposed animals, resp., demonstrate that this study lacks the relevance necessary to use it for drawing conclusions on tumor-promoting EMF effects.

Rat

The working group of Imaida also examined the possible promoting effect of a pulsed RF-EMF on chemically induced liver tumors (Imaida et al. 1998a, b). 2 weeks after initiation by diethylnitrosamine (DEN, 200 mg/kg body weight, ip), male Fischer rats restrained in tubes were exposed to Japanese standard mobile radio signals over six weeks (PDC, TDMA, 929.2 MHz or 1.44 GHz, 50 Hz pulsation, whole body SAR: 0.58 to 0.8 W/kg [929.2 MHz], or 0.45 to 0.68 W/kg [1.44 GHz], 90 min/day, 5 days/week). A week later (3rd week after DEN application), 2/3 partial hepatectomy was

performed in all animals. Maximum local SARs in the animals' livers were 1.9 to 2 W/kg.

Number and size of glutathion-S-transferase (GST)-positive areas (foci) of the liver, which are seen as preneoplastic changes, were compared across all animals 8 weeks after DEN initiation (6 weeks EMF exposure). In both tests, the authors could not find any differences between sham-exposed and exposed rats (livers), so that a promoting influence of RF-EMF on chemically induced carcinogenesis in the liver could be excluded.

The potential influence of an amplitude-modulated mobile radio signal (NADC) on the incidence of spontaneous or transplacental brain tumors induced by ethylnitrosourea (ENU) was examined by Adey and colleagues (1999) in four groups of Fischer 344 rats. Maternal animals were treated once iv with 4 mg ENU/kg body weight on the 18th day of pregnancy, and offspring (or offspring of an untreated control group) was (sham-) exposed, beginning on day 19 (in utero) until weaning (day 21), to radiofrequency electromagnetic radiation with far-field characteristics. Beginning on the 35th day of life, the young animals were exposed/sham-exposed over 22 months for 4 days per week to a characteristic near-field signal (836.55 MHz, TDMA signal). To this end, the rats were kept for two hours in an exposure carousel with a central antenna and exposed alternately over 8 cycles of 7.5 minutes each (field on/off), i.e. for a total of one hour. The average near-field whole body SAR was calculated by the authors to be 1.8 W/kg (females, 236 g body weight) and 2.3 W/kg (males, 462 g body weight). After 22 months, the

surviving animals were sacrificed, necropsied and macroscopically examined. Unfortunately, only the H&E sections of the CNS were evaluated. Animal mortality being comparable in all groups, the study never – neither in the ENU test animal group nor in untreated controls – revealed any evidence for a (brain tumor) initiating or promoting effect of EMF exposure; considering all study time windows, exposed rates showed a (statistically non-significant) tendency towards a lower CNS tumor incidence.

In a follow-up study, Adey and colleagues (2000) examined the effects of two-year frequency-modulated RF-EMF field exposure (836.55 MHz and 12.5 kHz) on the spontaneous and ENU-initiated CNS tumor rate in 540 Fischer rats. After one-time ENU treatment (4 mg ENU/kg body weight, iv) of the maternal animals on the 18th day of pregnancy, litters were exposed daily beginning on the 19th day (in utero) until weaning (21st day of life), for 2 hours to a far field, and again beginning on day 31/33 of life over their whole lifetime to a typical near-field signal. For this, male and female F344 rats were restrained in exposure carousels (10 animals/carousel, orientated radially around a central antenna) on 4 days per week for 2 hours per day, and exposed intermittently. Local SARs in the animals' brains were calculated by the authors to be 1 W/kg (females, 236 g body weight) to 1.2 W/kg (males, 450 g body weight), thus, according to the authors, being within the local (brain) SAR range of phone users (humans). The offspring of sham-treated and ENU-initiated maternal animals either were (sham-) exposed to EMF or

used as a cage controls for comparing CNS tumor incidence across 6 groups (à 90 rats: 45 m/f).

After 24 months, the surviving animals were sacrificed and, like the animals that had died or were killed moribund, necropsied and macroscopically examined. Standardized CNS preparations (serial slices) were made and microscopically evaluated. In none of the test animal groups, mortality, tumor type, tumor incidence and the number of neoplasia were changed by the 2-year EM exposure, neither in untreated animals nor in offspring of ENU-initiated Fischer rats.

A comprehensive RF-EMF study on the initiation/promotion of brain tumors and other neoplasms performed in 900 offspring of ENU-treated maternal animals was published by Zook & Simmens (2001). On day 15 of pregnancy, Sprague-Dawley females were treated (initiated) iv with 0, 2.5 or 10 mg/kg ENU, and litters were randomized into 15 treatment groups of 60 animals each (30 m/f). Over a period beginning with the 2nd month of life until a maximum age of 24 months, the animals were exposed to a 860 MHz field (FMCW, PW 11.1 Hz pulsation, 6 hours/day, 5 days/week). The animals were restrained in tubes orientated radially around a central antenna; the local SAR in the brain was 1 W/kg. In addition to the CW/PW EMF exposure groups, the offspring of the three ENU dose groups also was divided into sham-treatment and cage control groups. The extensive (immuno)histological evaluation (peer-reviewed, i.e. validated by external experts) comprised the brain (18 to 26 slices per animal), hypophysis, spinal cord, trigeminus nerve, lungs, liver, spleen, heart,

Literature on fertility/teratogenicity 1			
Author (year)	Field	Endpoint	Effect?
Akdag (1999)	9450	number of sperms (thermal)	-
Lebovitz (1987)	1300	sperm parameters	slight decrease
Berman (1980)	2450	sperm production	- even in the thermal range
Nakamura (2000)	2450	ovarial and placental blood circulation hormonal level during pregnancy	decrease, reproduction?

Literature on fertility/teratogenicity 2			
Author (year)	Field	Endpoint	Effect?
Jensh (1983)	2450	behavioural effects on offspring	-
Jensh (1982)	915	malformations, fetal weight	-
Berman (1978) (1982) (1984)	2450	fetuses and young animals	decreased weight, decrease in ossification, thermal
Thalau (2002)	survey study on embryonic development		few hard data, athermal effects not probable

Literature teratogenicity – summary
Inconsistent data:
<ul style="list-style-type: none"> but less contradictory results than regarding carcinogenicity lack of 'guideline studies'
Methodological problems:
<ul style="list-style-type: none"> thermal effects are in any case teratogenic, therefore exposure has to remain in the athermal range! effects similar to thermal ones in the athermal range fairly improbable
Health hazards to humans
<ul style="list-style-type: none"> -

kidneys, suprarenal glands, thyroid gland, and all macroscopically visible changes found in the animals. Apart from diagnosis (classification according to type/dignity) of all neoplasms, the number and/or multiplicity, volume and localization of brain tumors were evaluated. Compared to historical data (1 to 2%), test evaluation resulted in an unexpectedly high incidence (7.3%) of brain tumors which was explained by the large (standardized) number of tissue slices. Brain tumor incidence alone was distinctly dependent on the ENU dose; an initiating or promoting effect of the two exposure 'patterns' (PW/CW) was found for none of the test parameters. Additionally, lifelong EMF exposure had no influence on the (rest of the) tumor spectrum in any of the groups. This extensive study in Sprague-Dawley rats with lifelong, high weekly exposure (6 hours/day, 5 days/week) seems well-suited for risk evaluation regarding brain tumor development after chronic EMF exposure, that is, for the evaluation of possible neoplastic processes in the CNS (after ENU initiation and EMF promotion). Only the incomplete examinations of the organ/tissue spectrum (11 tissue and macroscopical changes), as well as the unclear extent of histopathological inspection of non-target organs are to be mentioned critically. Chronic GSM field exposure (900 MHz, 217 Hz pulsation) was used by Bartsch and colleagues (2002) in their three studies on the promotion of mammary tumors in female Sprague-Dawley rats. A total of 120 animals aged 51 days was treated once intragastrally with 8.75 mg per animal or with 5 mg/100 g body

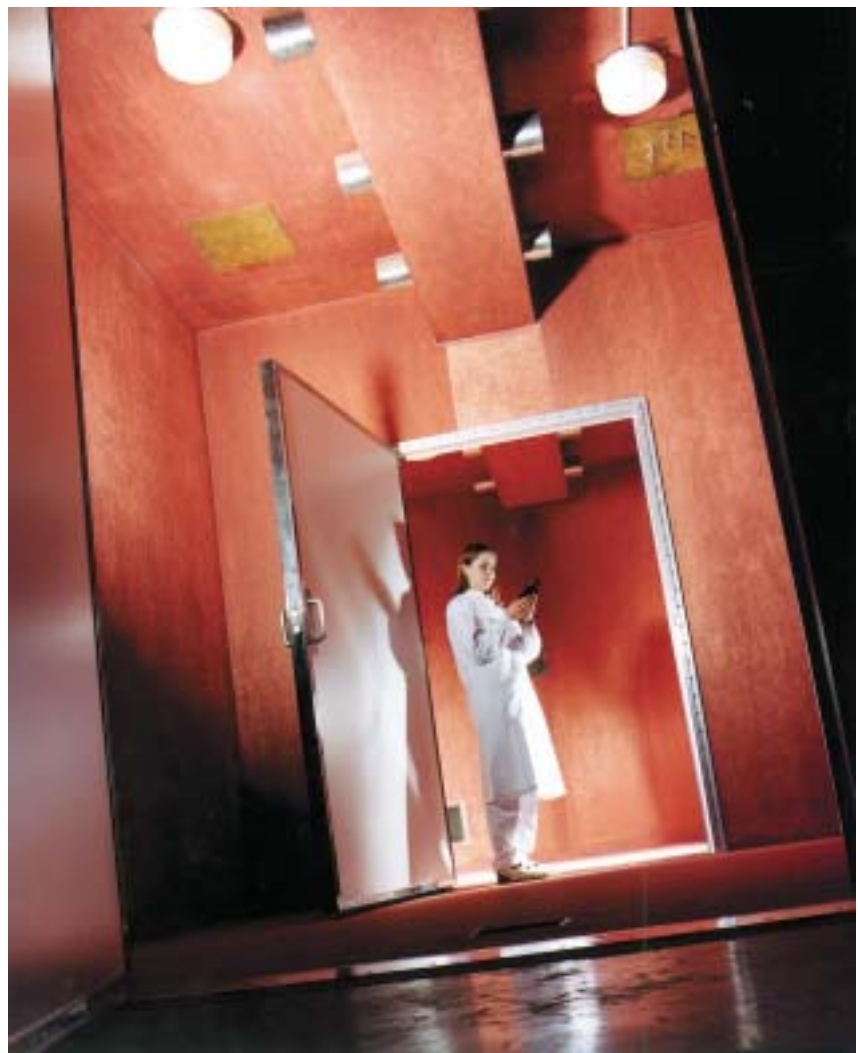
weight of 7,12-dimethylbenz(a)anthracene (DMBA) and exposed lifelong inside their cages (approx. 23 hours/day, 7 days/week). The calculated whole body SARs were 32.5 to 130 mW/kg (150 g body weight), 17.5 to 70 mW/kg (300 g body weight) and 15 to 60 mW/kg (400 g body weight). Mammae were palpated weekly (beginning with week 7), and animals with lumps of more than 1 to 2 cm in diameter were necropsied. The entire mammary area was processed histologically and examined pathologically under blinded conditions under the microscope by an investigator. Though significantly different tumor latencies were detected in the three experiments under these conditions, both in the benign and in the malignant mammary tumors, tumor development in the sham- and in RF-exposed animals did not differ across the (part) studies, and cumulative tumor incidence was identical in both (sham-) exposed groups. Compared to sham-exposure, chronic GSM field exposure did not affect mammary tumor incidence in DMBA-treated female rats in any of the (part) studies. However, varying exposure conditions (SAR ranges) of the growing, freely moving animals, different latencies and tumor incidences found in the three part studies do limit the conclusiveness of this study.

Tumor cell inoculation studies

Results from EMF short-term exposure of Fischer rats were published by Salford and colleagues (1993, 1997). After intracranial inoculation of a neoplastic glioma cell line (RG2/N32), animals were exposed over 2 to 3 weeks to unpulsed and pulsed EMF (7 hours/day, 5 days/week, 915 MHz, CW, or 4, 8, 16, 50 and 217 Hz PW, SAR: 1.7 W/kg). The authors found no evidence for a possible EMF influence on tumor development

(tumor size) in the animals. In our survey of chronic long term tests, this study will not be further considered due to the short duration of exposure.

The effect of unpulsed chronic RF exposure on tumor development after tumor cell application was examined by Szmigielski and colleagues (1982) in male BALB/C mice. In this study, the males were injected intravenously with 2×10^5 L1 sarcoma cells, and subsequently, animals were exposed to an EMF (CW, 2450 MHz, 2 hours/day, 6



Study on embryonic toxicity: Exposure of pregnant rats to a pulsed RF-EMF (900 MHz, 217 pulse) at 4.6 W/m^2 (human threshold) in specially shielded animal test rooms showed no teratogenic, embryolethal or development inhibiting effects.

Experimental studies

days/week, SAR: 2 to 8 W/kg) over a maximum of 3 months. The macroscopic examination of the lungs after 1 and 3 months showed an EMF dose-dependent increase in the visible lung nodules compared to sham-exposed control animals.

The relevance of this study seems small, particularly due to the inexact numbers of applied tumor cells and the insufficient macroscopic evaluation. Thermal effects cannot be excluded either at the given absorption rates.

Santini and colleagues (1988) examined melanoma development in (sham-) exposed C57BL/6J mice after one-time subcutaneous application of 3×10^6 melanoma cells. Per group, 15 animals were used. The lifelong uniform (CW) or pulsed EMF exposure (2.5 hours/day, 6 days/week, 2450 MHz, SAR: 1.2 W/kg) began 15 days prior to tumor cell injection. The average longevity of the females showed no differences: in non-exposed control animals, it was 25.9 ± 6.2 days or 24.4 ± 7.9 days (CW), and 26.6 ± 8.5 days (PW) in the exposed groups.

Additionally, the authors analyzed tumor sizes, which showed to significant discrepancies either between the groups. Due to the selected endpoints (longevity and tumor size), this study overall has a rather small relevance for the assessment of human health risks from EMF exposure, and it seems questionable whether mean melanoma size at a similar (short) longevity of all animals (± 2 to 3 days) and a relatively short duration of exposure (maximum 42 days, 2.5 hours/day) is a sensitive parameter for the identification of EMF effects at all.

Possible RF-EMF influences on the growth of intracranially applied 9L

gliosarcoma tumor cells in restrained Fischer rats were investigated by Higashikubo and colleagues (1999).

Three groups each with different numbers of inoculated tumor cells (2 to 10, 11 to 36, 37 to 100 cells) were used and (sham-) exposed.

Over a time period of 4 weeks prior to/a maximum of 150 days after tumor cell inoculation, the animals were daily (4 hours/day, 5 days/week) exposed to 835.62 MHz (FMCW) or 847.74 MHz (CDMA) signals. Local average SARs in the animals' brains were 0.75 ± 0.25 W/kg. At occurrence of neurological disorders or massive weight losses, the animals were necropsied; the surviving rats were examined after a maximum of 150 days. Animal mortality and the organ weight (brain) were compared across treatment groups after 48-hour fixation in a formalin bath: Mortality was definitely dependent on the number of inoculated tumor cells, whereas FMCW or CDMA exposure had no additional influence on the rats' survival rate. Brain weight was not changed by additional EMF exposure, neither in tumor-bearing nor in 'healthy' animals (inoculated with tumor cells or sham-treated).

The authors conclude from their tests that neurological symptoms are not clinically detectable until tumors have reached a certain tumor size (brain weight increase), (thus having affected longevity of the animals included in this study). The TD50 comparison (number of tumor cells required to induce brain tumors in 50% of the rats) between sham-exposed and EMF-exposed animals especially shows a distinct dependency of tumor development on the number of inoculated tumor cells, whereas an influence of (sham-) exposure was scarcely perceptible:

The authors found a TD50 value of 2 to 3 tumor cells (sham-exposure 3; FMCW 2; CDMA 2.5 cells), so that the parameters of longevity and brain weight do not seem sensitive enough to determine an additional RF-EMF effect in this study with an inoculation rate between 2 and 100 tumor cells.

Prospects

Methodological conclusions for the performance of future investigations can be drawn from this survey of experimental EMF studies. These primarily refer to the inclusion of a sham-treated and a non-treated cage or shelf control, as well as – insofar as possible within the study design – a positive control and the simultaneous use of several groups subjected to different exposure levels (dose groups), a procedure that is well-established in toxicological routine tests on chemicals, pharmaceuticals, etc. This ensures confirmation of possible dose/effect relation. Also, the inclusion of extensive histological diagnostics (according to the IARC/WHO) seems urgently required for covering the whole spectrum of neoplastic changes and e.g. an improved evaluation of shifts in the dignity of neoplastic changes (Chou et al. 1992). Moreover, advantages and disadvantages of using freely moving or restrained animals for exposure are to be considered in planning and performance of such studies. Worldwide, efforts have been intensified to investigate possible health consequences from RF-EMF exposure. Numerous 'new' animal experimental studies have been initiated, as well as replication studies for a (re-) evaluation of available study results. As an example of these studies, the research project PERFORM-A already launched in March 2000 within the Fifth Framework Program (FP 5) of the EU, and the CEMFEC (Combined Effects of Electromagnetic Fields with Environmental Carcinogens) project that began in May 2001, shall be mentioned here. They are aimed at clarifying whether

radiofrequency EMF have carcinogenic or co-carcinogenic effects on the animal species of rats and mice.

Within the European study project PERFORM-A, two carcinogenicity studies each will expose B6C3F1 hybrid mice (at the Fraunhofer ITEM, Hannover) as well as Wistar rats (at the RCC in Füllinsdorf, Switzerland) over two years on, five days per week for, two hours per day to radiofrequency EMF of 902 MHz and 1747 MHz, resp.

In a third part project (at the ARC Seibersdorf, Austria), the influence of a daily 4-hour exposure at 902 MHz performed over six months will be examined in female Sprague-Dawley rats, mammary tumors were previously induced with DMBA (7.12-dimethylbenz(a)anthracene). In this animal model, the influence of radiofrequency EMF on tumor growth, incidence, latency and dignity will be explored.

The fourth part project (at the LCG-RBM near Ivrea, Italy) will try to reproduce the results of the Australian mouse study performed by Repacholi and colleagues who – already in 1997 – claimed to have found a two- to three-fold increase in lymphoma rates in Pim1 transgenic mice after 18-month daily one-hour exposure to an EMF of 902 MHz (see above). The IT'IS foundation in Zurich, Switzerland, is responsible for the construction, the installation and operation of the exposure systems (Ebert et al. 2001). The single exposure units of these systems each consist of two spherical high-grade steel plates. The animals are positioned at the outer rim of these plates and restrained in acrylic tubes. Due to the radial arrangement of exposure tubes, each animal undergoes a

whole body exposure as homogeneous as possible. Per experiment, three dose groups and one sham-exposed control group will be examined.

All animal experiments will be performed blinded under the conditions of Good Laboratory Practice (GLP). Moreover, validation guidelines on carcinogenicity of the EU, OECD and of the American Environmental Protection Agency EPA are considered.

The results of the whole PERFORM-A project will probably be available in 2005.

Also under the Fifth EU Research Program, in vitro and in vivo studies on possible (co-)carcinogenesis of RF-EMF will be performed within the project CEMFEC (Combined Effects of Electromagnetic Fields with Environmental Carcinogens). In contrast to the model of initiation by a carcinogen and subsequent long-term promotional treatment, the CEMFEC project will examine a combined long-term treatment with a known (environmental) mutagen and EMF exposure in order to account for simultaneous lifelong exposure of humans to a combination of chemical and physical (environmental) harmful substances/agencies.

In the in vitro part of the study (at the UGOA, Genova, Italy), cultivated lines of NIH 3T3 fibroblasts and L929 fibrosarcoma cells will be exposed either alone or combined with RF radiation to MX (3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone) or to the herbicide vinclozolin. RF-EMF exposure consists of unpulsed and pulsed RF fields (CW, PW), two field strengths (SARs) and two time periods. A large number of endpoints (enzyme activity, reactive oxygen metabolites,

Summary

membrane potential changes, cell proliferation, cell cycle, proto-oncogenes) associated with non-genotoxic (co-) carcinogenesis will be examined in this in vitro part of CEMFEC (at UGOA, Genova, Italy, and VITO, Mol, Belgium).

The two-year animal experimental part of the study (at the University of Kuopio, Finland) will consist of a combined (synchronized) lifelong exposure of groups of 72 rats each (Wistar females) to RF-EMF (GSM signals) and MX (3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-

furanone) via the drinking water.

The findings obtained from two SAR exposure groups (GSM, 2 hours/day, 5 days/week, SAR: 0.3 W/kg or 1 W/kg) with parallel MX application will be compared to those of the exclusive MX treatment and an untreated cage control.

The STUK – Radiation and Nuclear Safety Authority, Helsinki, Finland, is responsible for construction, installation and operation of exposure systems.

Besides the 'classic' (histopathological) endpoints (at the Fraunhofer

ITEM, Hannover), genotoxicity tests (at the VITO, Mol, Belgium) will be performed during (in the blood) and at the end (in the brain, liver) of the two-year study.

The results of the CEMFEC project are expected to be available in 2004.

Summary studies performed of to-date

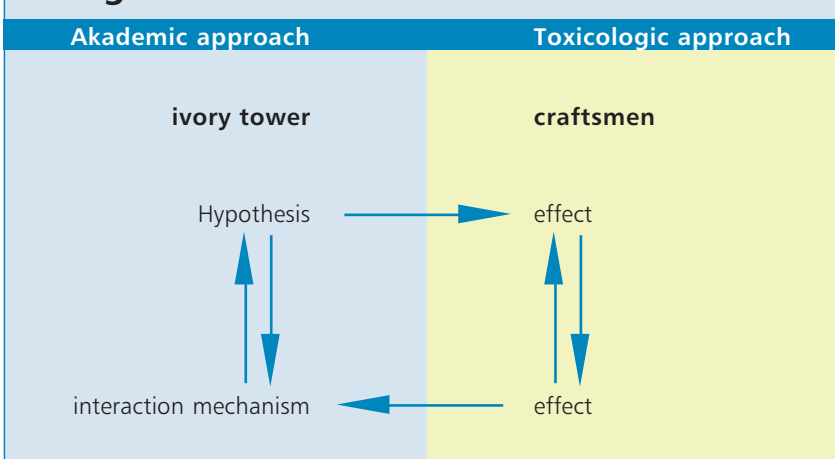
When comparing the different approaches, two basic groups of studies can be distinguished: studies aiming at validating a specific hypothesis, and studies mainly serving as a means for 'global' risk assessment.

The former are strongly academic attempts at basic research, often of high scientific value, and are performed using very sensitive model systems. Extrapolability to the human target organism often is limited, and it is very difficult (above all in case of negative results from the verification of single hypotheses) to draw conclusions on 'general' health risks to humans. The second study group uses a markedly toxicological approach in the sense of applied research: Different test methods are used to examine various groups of test animals exposed to different field strengths, including as many potentially health-relevant endpoints as possible. This approach, best described as 'apical', by the large number of test parameters allows for a fairly good extrapolability of results to humans and therefore as well for an assessment of health risks. However, such studies, due to their 'broad-spectrum' characteristics, often are less profound than those of the first group, thereby not always

Different study concepts

Basic research	applied research
In-depth studies of single hypotheses	„broadband“ studies
Few parameters	numerous parameters
Most sensitive test system	standard test system
Exposure – control	several exposure groups – control
Effect or no effect	dose-effect relation
Limited portability to humans	good portability to humans

Dialogue in research



being sensitive enough for exploring specific health risks.

A promotion of the dialogue between both groups of researchers could release significant synergies: If, on the one side, results achieved in basic research can be reproduced in applied research and, on the other side, findings obtained by applied studies can be confirmed by mechanistic approaches, the framework of risk assessment will be considerably improved.

In summary, we may say that, to date, only a small number of chronic RF-EMF studies have been published and that there still are few studies using characteristic (pulsed) GSM mobile radio signals.

Long-term experimental studies investigating the GSM signal technology widely spread in Germany and Europe, are still rare. Only two experimental carcinogenesis studies – with the above described inconsistencies – and a study on potential promotion of DMBA-induced mammary tumors from GSM exposure have been published. ‘Early’ studies were not always satisfactorily performed or published so that their contribution to an assessment of human health risks from chronic RF-EMF is limited. Especially incomplete, non-standardized histopathological evaluations found in carcinogenesis studies and the partially unclear exposure technology (EMF signal) minimize the relevance of these investigations. Based on such data, a sound scientific assessment of potential health risks from RF-EMF is not possible; however, concrete evidence for such health concerns to date has not been found.

Glossary and abbreviations

Absorption	energy intake (and transformation into heat)
AC	alternating current
ACTH	adrenocorticotrophic hormone
AM	amplitude modulation
Amplitude	maximum value of field strength
Carcinogenicity	cancer initiation
CDMA	Code Division Multiple Access
CW	continuous wave
DC	direct current
DCS	Digital Personal Communications System
DECT	Digital Enhanced Cordless Telecommunication
DNA	de(s)oxyribonucleic acid
ELF	extremely low frequency (below 3 kHz)
EMF	electromagnetic field
ENU	ethylNitrosourea
eV	electron volt
FDMA	Frequency Division Multiple Access
Fertility	reproductive potential
FM	frequency modulation
Frequency	number of wave oscillations per second, expressed in Hertz
GLP	Good Laboratory Practice
GSM	Global System for Mobile Communications
Gy	Gray
H&E	hematoxylin and eosin
Hz	Hertz
IARC	International Agency for Research on Cancer
ICNIRP	International Commission on Non-Ionizing Radiation Protection
ip	intrapertitoneal
iv	intravenous
LF	low frequency
Mbps	megabytes per second
MHz	Megahertz
NADC	North American Digital Cellular
NTP	National Toxicology Program
PW	pulsed wave
PDC	Personal Digital Cellular (Japanese standard, 800 and 1500 MHz)
RF	radiofrequency
SAR	specific absorption rate
TDMA	Time Division Multiple Access
Teratogenicity	induction of congenital malformations
TETRA	Transeuropean Trunked Radio
UMTS	Universal Mobile Telephony System
W	Watt

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