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Indication of cocarcinogenic potential of chronic UMTS-modulated radiofrequency exposure in an ethylnitrosourea mouse model

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Abstract

Purpose: To evaluate putative effects on tumour susceptibility in mice exposed to a UMTS (universal mobile telecommunications system) test signal for up to 24 months, commencing with embryo-fetal exposure.

Material and methods: Animals were exposed to UMTS fields with intensities of 0, 4.8, and 48 W/m^2, the low-dose group (4.8 W/m^2) was subjected to additional prenatal ethylnitrosourea treatment (40 mg ENU/kg body weight).

Results: The high-level UMTS exposure (48 W/m^2), the sham exposure, and the cage control groups showed comparable tumour incidences in the protocol organs. In contrast, the ENU-treated group UMTS-exposed at 4.8 W/m^2 displayed an enhanced lung tumour rate and an increased incidence of lung carcinomas as compared to the controls treated with ENU only. Furthermore, tumour multiplicity of the lung carcinomas was increased and the number of metastasising lung tumours was doubled in the ENU/UMTS group as compared to the ENU control group.

Conclusion: This pilot study indicates a cocarcinogenic effect of lifelong UMTS exposure (4.8 W/m^2) in female B6C3F1 descendants subjected to pretreatment with ethylnitrosourea.

Keywords: *ethylnitrosourea, ENU, UMTS, electromagnetic fields, cellular phone, health effects, cancer, B6C3F1 mice*

Introduction

Communication without constraints, worldwide wireless data exchange, and constant availability by cellular phone are key words of modern society. While the number of cell phone users has been increasing for decades worldwide, the question whether electromagnetic fields (EMF), in particular radiofrequency (RF) signals of wireless communication by cell phones, may affect human health is still a matter of intensive discussion in the public and the scientific community. Although a causal relation of electromagnetic exposure and health was reported or suspected by the authors in only very few scientific investigations – and repetitive studies denied those positive findings without fail – these publications gave rise to some undifferentiated fears in the population. By far the higher number of investigations could not find evidence to support the theory of biological or even health effects from electromagnetic exposure, but these were often ignored in the public.

Particularly with regard to the hypothesis that RF-EMF (radiofrequency electromagnetic field) exposure will increase the risk of cancer development in the following decades of human lifetime, several animal carcinogenicity studies were performed in this field to investigate the possible tumour initiation potential of EMF (reviews by Elder 2003, Dasenbrock 2005, Valberg et al. 2007, Kundi and Hutter 2009).

Based on the multistage theory of carcinogenesis, electromagnetic fields were also suspected to act as a promoting agent in tumorigenesis. Focusing on an assumed promoting/cocarcinogenic RF-EMF effect, another experimental approach is to RF-expose rodents pretreated with ionising radiation (Heikkinen

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et al. 2001, 2003) or with established chemical carcinogens such as DMBA/dimethylbenz-[a]-anthracene (Imaida et al. 2001, Bartsch et al. 2002, Anane et al. 2003, Huang et al. 2005, Yu et al. 2006, Hruby et al. 2008), ENU/ethylnitrosourea (Adey et al. 1999, 2000, Zook and Simmens 2001, 2006, Shirai et al. 2005, 2007) or other agents (Heikkinen et al. 2006).

Tumour-prone (Toler et al. 1997, Sommer et al. 2004) and pre-damaged transgenic (i.e., immune-suppressed) mice with a well-defined neoplastic background have also been used in EMF research (Repacholi et al. 1997, Utteridge et al. 2002, Oberto et al. 2007), and – similar to neoplastic induction by radiation or chemical carcinogens – an influence on tumour latency, spectrum, incidence etc., in those transgenic animals would support the hypothesis of RF-EMF influences on cancer development.

In 2000, an independent expert group on mobile phones (chaired by Sir William Stewart) recommended to limit children's cell phone use as much as possible, since children would be more vulnerable to, e.g., brain tumour development – if the use of cell phones turned out to have health effects – due to their thinner skin and skulls, increased tissue conductivity, developing nervous system, and a long remaining lifetime. Contrarily, Otto and von Mühlendahl (2007), reviewing the role of electromagnetic fields in children's health more recently, found no evidence of a special vulnerability of children and adolescents to EMF compared to adults.

To experimentally prove that EMF increases the risk of brain tumours, however, ethylnitrosourea (ENU) treatment of laboratory animals with simultaneous electromagnetic field exposure is an appropriate approach, as ENU is known to induce neurogenic tumours in laboratory animals.

ENU administration during early pregnancy is a well-established experimental method used in trans-generation carcinogenesis studies with laboratory animals (Tomatis 1979, Diwan and Meier 1974, Vesselinovitch et al. 1979), offering the benefit of maternal treatment (e.g., on day 6 post conception) which should cause no stress to the descendants.

Another advantage of the transgenerational study design is the early start of RF exposure with prenatal initiation as embryo-fetal exposure and pups born in the exposure device and maintained in the EMF with their mothers until weaning. This study design certainly fulfills a lifetime exposure in the truest sense of the word, including the more vulnerable juvenile weeks.

Universal mobile telecommunications system (UMTS) is a modern network technology for mobile communication commonly used in Europe. Although reports dealing with technical aspects of an experimental UMTS exposure were published recently (Ndoumbè et al. 2004, Reinhardt et al. 2007), in vivo studies analysing effects of UMTS exposure per se are rare (Sommer et al. 2007, 2009) and carcinogenicity studies are still lacking.

Ethylnitrosourea-induced carcinogenesis combined with high-frequency electromagnetic field exposure was previously used in local RF head exposure studies (Shirai et al. 2005, 2007) (Japanese standard cellular phone exposure technique: TDMA/time division multiple access system, 1439 MHz, or W-CDMA/wide-band code division multiple access, 1950 MHz) in two 2-year studies (1.5 hours/day [h/d], 5 days/week [d/w] for up to 24 months, organ-averaged SAR [specific absorption rate] in the brain: up to 2 W/kg). However, no effects on ENU-induced brain tumorigenesis in F344 rats have been found.

Furthermore, Zook and Simmens (2001, 2006) found no evidence that pulsed-wave (pw) or continuous-wave (cw) exposure to 860 MHz radiation (6 h/d, 5 d/w for up to 24 months, 1 W/kg brain-averaged SAR) had an impact on the induction or promotion of tumours including neoplasms of the central nervous system in the offspring of Sprague Dawley rats treated with ENU.

In contrast, lifetime RF exposure (836.55 MHz, TDMA signal, 2 h/d, 4 d/w for up to 22 months) of Fischer 344 rats revealed a tendency to a lower spontaneous and ENU-related CNS tumour incidence (Adey et al. 1999). However, the follow-up study with a similar study design (i.e., maternal ENU treatment) using a frequency-modulated signal (836.55 MHz $\pm$ 12.5 KHz deviation) showed no EMF-related effects on brain tumorigenesis (Adey et al. 2000). Unfortunately, the value of most of these experimental EMF/ENU studies is limited, because histopathological examination was performed only for the central nervous system.

In a pilot study we analysed the tumorigenic potential of long-term RF-EMF exposure in healthy vs. ENU pre-treated B6C3F1 mice, assuming that indications of a cancer-initiating and/or cocarcinogenic (promoting) effect of UMTS exposure should be covered by this study design.

Methods

The study was approved according to the German Animal Welfare Act by the local authority at the Bezirksregierung, Hannover, Germany. The animal experiment was performed blind to all scientists involved except for the staff of the Bergische Universität Wuppertal (BUW) who constructed and installed the exposure device and monitored the daily RF exposure.

Animals, environment, and conduct of the study

Young adult C57BL/6N (females) and C3H/HeN (males) mice, 7–8 weeks of age at delivery, were purchased from Charles River Deutschland, Sulzfeld, Germany, to produce B6C3F1 descendants at the Fraunhofer Institute for Toxicology and Experimental Medicine (ITEM).

After the acclimatisation period in the animal facility, healthy parental animals were randomised by weight into groups using a computer-program (Provantis 7, Instem Computer Systems, Stone, UK) and were mated at 10 weeks of age (ratio: 3 f/1 m, day 0 p.c. [post conception] determination by vaginal plug control).

(Sham-)exposure of the plug-positive maternal mice started on day 6 p.c., while the maternal ENU treatment (40 mg ENU/kg body weight intraperitoneal; ENU supplier: Sigma-Aldrich Chemie GmbH, Taufkirchen, Germany) was carried out on day 14 p.c.

Each treatment group consisted originally of up to 20 maternal mice and their litters. After the first week of lifetime, litter standardisation (allocation by chance after sexing the descendants) was performed and afterwards per cage 3 female offspring and their mothers were maintained per cage up to the weaning time point (Figure 1). After weaning, maternal mice were removed from the cages. The carcinogenesis study was conducted using the 3 remaining female descendants per cage. The above-mentioned number of 60 F1 mice was reduced in two groups (Table I) due to 1–2 non-pregnant maternal mice, as the premature/early exposure start required a pregnancy diagnosis on day 6 p.c.

In total, five treatment groups were used in the study: three were housed in different decks (and different RF power density groups) of the exposure device (one of them with additional maternal ENU treatment), and two control groups (positive control with ENU treatment and an untreated cage control group) were also maintained in the same animal room (monitored standard laboratory conditions: temperature: 20 $\pm$ 2°C, relative humidity: 40–80 %, 12-h light/dark cycle, air exchange rate: 10–15 times per hour) in the conventional area of the animal facility.

Mice were housed in Makrolon® (polycarbonate) cages (type II: 350 cm^2) or in client-specific trapezoidally shaped polycarbonate cages (ground area: 373 cm^2; both cage types supplied by E. Becker & Co. GmbH, Castrop-Rauxel, Germany), specially

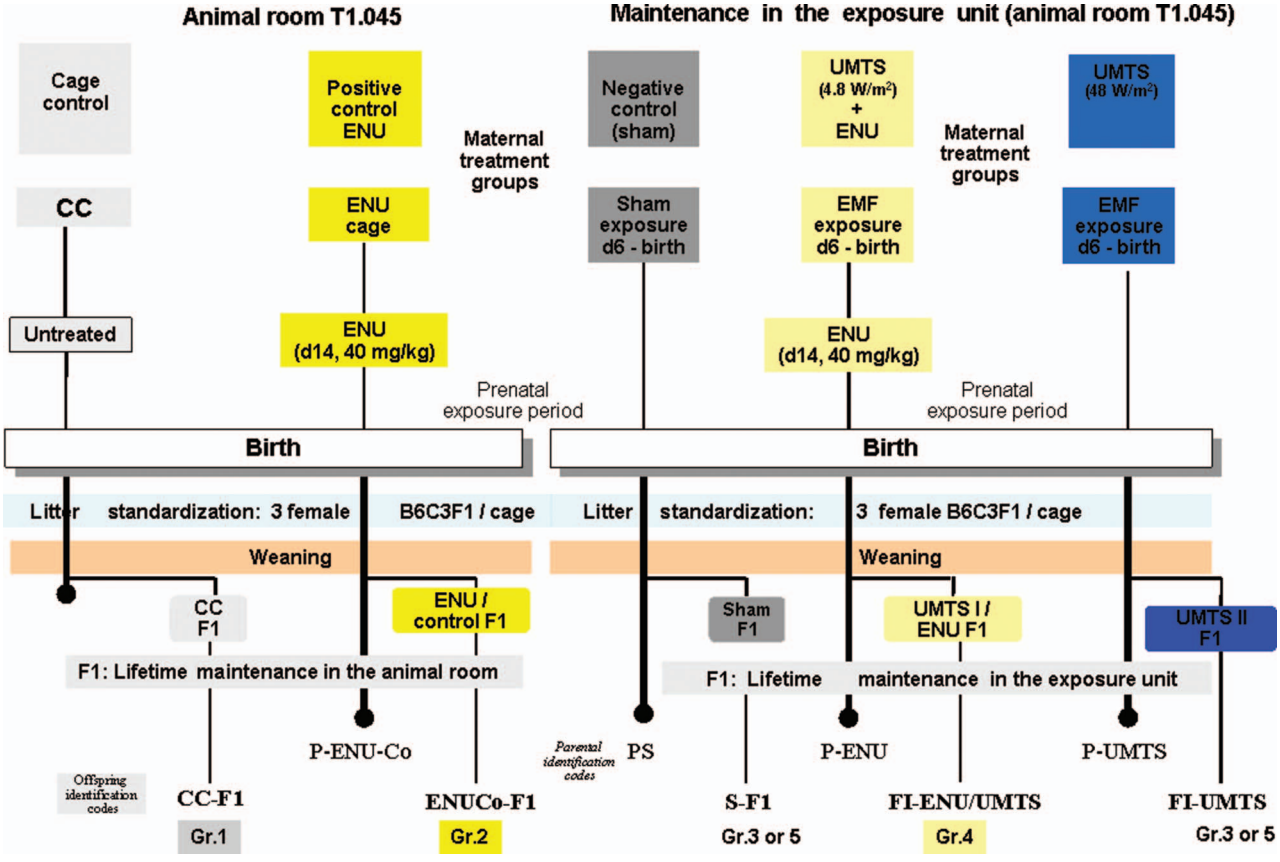

Figure 1. Study design.

constructed for space-saving maintenance in the exposure device (Figure 2). Absorbent softwood was used as bedding material in the cages ('ssniff bedding 3/4', ssniff Spezialdiäten GmbH, Soest, Germany). A pelleted chow, identified as 'ssniff V1534', was used as standard diet during the course of the study, with the exception of the six-week breeding period, when an enriched diet, identified as 'ssniff V1124', was offered, both supplied by ssniff Spezialdiäten GmbH, Soest, Germany. Drinking water from the Hannover city water supplier (Stadtwerke Hannover, Hannover, Germany) was offered fresh weekly in Makrolon® bottles *ad libitum*.

All mice were checked at least once a day for clinical symptoms, morbidity, or mortality. In addition, the health status of the animals was monitored by sampling sentinel mice during the total course of the study. Starting at five weeks lifetime, individual body weights were recorded to the nearest 0.1 g weekly during the first 13 weeks and then every four weeks until study termination. All weight data were collected by on-line data acquisition (Provantis 7).

UMTS exposure system

The test signal was delivered by a generic UMTS signal generator GUS 6960S (GMT@Uni Wuppertal, Wuppertal, Germany) and amplified in a BEKO HLV-500 power amplifier (BEKO Elektronik, Dachau, Germany). The latter had been developed on behalf of BUW, since in 2005 high-power amplifiers with high linearity and large crest factors needed for UMTS signals were not available on the market.

The generic UMTS test signal with a carrier frequency of 1966 MHz (according to Ndoumbè et al. 2004) including features of real UMTS signals was applied for 20 h/d (4 h were dedicated to the daily animal caretaking) on 7 d/w for up to 24 months. Based on radial waveguides of cylindrical shape, exposure of the mice was performed in a three-decker exposure device (sham: 0 W/m^2, low: 4.8 W/m^2, high: 48 W/m^2) (Figure 3), housing up to 60 animals per deck (three females per cage). The customer-specific stainless steel construction was also supplied by E. Becker & Co GmbH. For optimisation of the exposure field distribution the segments with the cages were equipped with self-made high-impedance side panels and with a flat absorber lining the inner surface of the outside wall (ECCOSORB SF-U 2.0 SA, Emerson & Cuming Microwave Products N.V., Westerlo, Belgium).

Selection of power levels was based on experimental data of a thermal dose range finding (DRF) study, a six-week UMTS pre-study, and on the technical features of the available power amplifier. Using the UMTS-modulated signal and a highly linear power amplifier (nominal cw output power of 400 W represents the technical limit at the time of delivery due to available UMTS transistors), the highest time-averaged power density that could be achieved without distortion of the signal was 48 W/m^2. Considering the large crest factor (ratio of maximum to average signal power) of the UMTS signal of approximately 8 dB, this corresponds to a maximum power density in the random peaks of the UMTS signal of about 300 W/m^2. Consequently, the

Figure 2. UMTS exposure device with two opened exposure segments. Note the specifically constructed trapezoidal polycarbonate cages with several ventilation holes. Water supply was assured by the externally mounted water bottle and a drinking nipple made of glass penetrating into the cage through a tube dimensioned as 'waveguide beyond cut-off', scale bar 50 cm.

Figure 3. Three-decker UMTS exposure device for mice. Scale bar 50 cm.

average power density of 48 W/m^2, which is well below the thermal range as determined in the thermal DRF study, was selected as 'high dose'. The 'low dose' was determined by applying a factor of 1/10.

During the total course of the study, one to maximum four mice per cage (mother + 3 pups) were maintained and exposed simultaneously in the device. In order to analyse the exposure conditions for this variable number (1–4) of growing (body weight approx. 2–55 g), freely moving mice inside each cage (numerous configurations, positions, and postures), multiple field measurements and dosimetric calculations were performed. A brief summary of the technical exposure conditions in this lifetime study is given in Table II. Technical details of a similar radial waveguide exposure setup are given by Reinhardt et al. (2007).

During the complete course of the study, exposure levels and temperatures in the device were monitored, recorded, and analysed on a daily basis. The blinding of the levels in the UMTS exposure or sham exposure units was disclosed by the BUW team after finalisation of the histopathological examination.

Pathology

Each animal was subjected to complete necropsy. Any animal judged to be moribund was humanely euthanised by an overdose of carbon dioxide and subsequent bleeding. All animals found dead were necropsied immediately. The physical condition of each animal prior to euthanasia and all macroscopically visible tissue alterations detected during necropsy were described in detail in a necropsy protocol. Fixation of the lung lobes was carried out by careful intratracheal instillation of formalin, while all other tissues were immersion-fixed in 10% buffered formalin, trimmed (Ruehl-Fehlert et al. 2003, Kittel et al. 2004, Morawietz et al. 2004) and embedded in paraffin. Skulls and other bones with macroscopic findings were decalcified in equal portions of sodium citrate (20%) and formic acid (45%) prior to embedding. Embedded tissues were sectioned (3–4 μm-thick sections) and stained with hematoxylin and eosin (H&E).

Histopathological examination was performed including brain, lungs, liver, spleen, kidneys, mesenteric lymph nodes, and any gross lesions detected. The tissue slides were examined by light microscopy and observations were recorded with an on-line computer program (P.L.A.C.E.S. 2000.1, Instem Computer Systems, Stone, UK).

Neoplasms and pre-neoplastic lesions were diagnosed and classified according to the international nomenclature of the World Health Organisation/ International Agency for Research on Cancer (WHO/IARC 2001).

Statistical evaluation

Differences between groups were considered statistically significant at the level of $P < 0.05$. Statistical examinations were performed using the analysis of variance as a global test. Whenever the group means differed significantly according to the analysis of variance, the means of the groups were compared using Dunnett's modification of the *t*-test. Survival data of the animals were analysed using the Kaplan-Meier log-Rank test. Statistical analysis of the neoplastic lesions was performed separately for each tumour type. Incidences of benign and malignant neoplasms of the same cell type were considered both separately and in combination (McConnell et al. 1986). To compare the incidences of histopathological findings in either direction the two-tailed Fisher test at a level of $P < 0.05$ was used.

Results

Ethylnitrosourea pre-study

Seen that dissimilar susceptibilities of different mouse strains and huge differences due to the time point of dosing are mentioned in the literature (e.g., Diwan and Meier 1974, Vesselinovitch et al. 1979), a six-week ENU pre-study was carried out in female C57BL/6N mice (40 mg ENU/kg body weight, intraperitoneal (i.p.) on day 14 p.c.). B6C3F1 hybrids were born and housed with their mothers until weaning, and there was no apparent ENU influence with regard to litter size or mortality.

Thermal pre-studies

Using one exposure per day (2 GHz, cw signal, 2 h/d) with a stepwise increased cw power density (0, 20, 30, 50, 60, 80, 100, 120, 140, 160, 180, 200, 210, 220, 250, 260 W/m^2) in one radial waveguide of the three-decker exposure system, rectal temperature measurements ($n \geq 10$ mice, 2 mice per cage) simultaneously performed directly after termination of the RF exposure revealed regular body temperatures ($37.1 \pm 0.3^\circ$C to $37.7 \pm 0.6^\circ$C) regardless of the RF power density applied. A second series of daily exposures (0–260 W/m^2), with rectal temperature measurements performed 15 min after the end of the exposure, disclosed a clearly decreased mean body temperature (e.g., $36.2 \pm 0.3^\circ$C for 250 W/m^2 and above) on the high-exposure days.

To test the UMTS exposure unit with newborn animals (i.e., unknown heat load of the pups), a six-week UMTS pre-study until weaning of the F1

generation was performed with 12 maternal mice (mating for 3–4 days, ratio: 3 f/1 m) using a UMTS exposure (48 W/m^2) and a sham exposure group. After litter standardisation (week 1) and after weaning (week 3) the UMTS exposure using three female descendants per cage was continued for one week, showing no abnormalities.

In addition, rectal body temperature measurements in 10 (trained) adult female mice directly after two days of UMTS exposure (48 W/m^2, 20 h/d) revealed no measurable temperature increase.

UMTS exposure

During the two-year study period, complete (i.e., 20 h/d) RF exposures were performed on 97.5 % of the planned 730 target days. Continuous monitoring of exposure levels and temperatures in the device revealed no abnormalities. A brief summary of the technical exposure conditions for the variable number (1–4 per cage) of growing, freely moving mice (numerous configurations, positions, and postures) in this lifetime study is given in Table II.

In addition, numerical calculations of the whole-body SAR as a function of the body mass based upon anatomical mice models placed in the EMF field of a realistic radial waveguide model (Figures 4 and 5, one mouse, lateral or frontal wave impact) revealed maximum whole-body SAR values for body weights between 12 and 16 g at 1966 MHz.

Health status

Serological examinations ($n = 32$) of sentinels, routinely performed during the entire course of the study, did not show antibodies against viruses such as MHV/mouse hepatitis virus, Reovirus Type 3, Sendai virus, TMEV/Theilers' mouse encephalomyelitis virus, PVM/pneumonia virus of mice, MVM/minute virus of mice, Rotavirus, or against Mycoplasma pulmonis. Bacteriological ($n = 14$) and parasitological examinations ($n = 32$) during the study revealed no abnormalities. Clinical observation of the mice indicated an undisturbed animal study.

Body weight

Starting with similar mean body weights, the mice in the different groups displayed comparable body weight developments within the first months of the study, although the cage controls showed always the highest values (Figure 6). After about one year, body weights of the two groups with maternal ENU treatment stagnated and decreased compared to the others, whereas the cage controls, sham- and UMTS-exposed mice developed similar body weights until the end of the study.

Mortality

At around 12 months' lifetime, mortality of the two F1 groups with maternal ENU treatment started to increase compared to the others. As mortality exceeded 75 % in both ENU groups, the survivors were necropsied (week 75) according to the recommendations of OECD (Organisation for Economic Co-operation and Development) Guideline No. 451 'Carcinogenicity Studies'. Statistically the two descendant groups with maternal ENU treatment revealed similar mortalities (Kaplan-Meier log-Rank test). Incidences of mortality (including sacrifices of moribund animals for ethical reasons) in the three remaining groups were also comparable (Kaplan-Meier): 46–49 % of the female mice in these groups were alive after 24 months' lifetime and RF exposure.

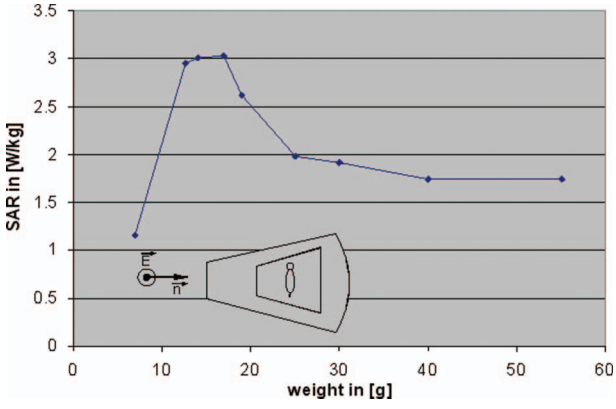

Figure 4. Numerical calculation of the whole-body SAR versus body mass for a single mouse in the radial waveguide with electrical field vector $\vec{E}$ and with lateral impact of direction $\vec{\eta}$.

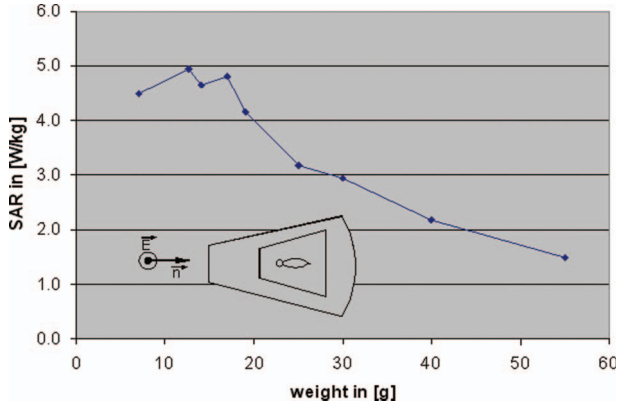

Figure 5. Numerical calculation of the whole-body SAR versus body mass for a single mouse in the radial waveguide with electrical field vector $\vec{E}$ and with frontal impact of direction $\vec{\eta}$.

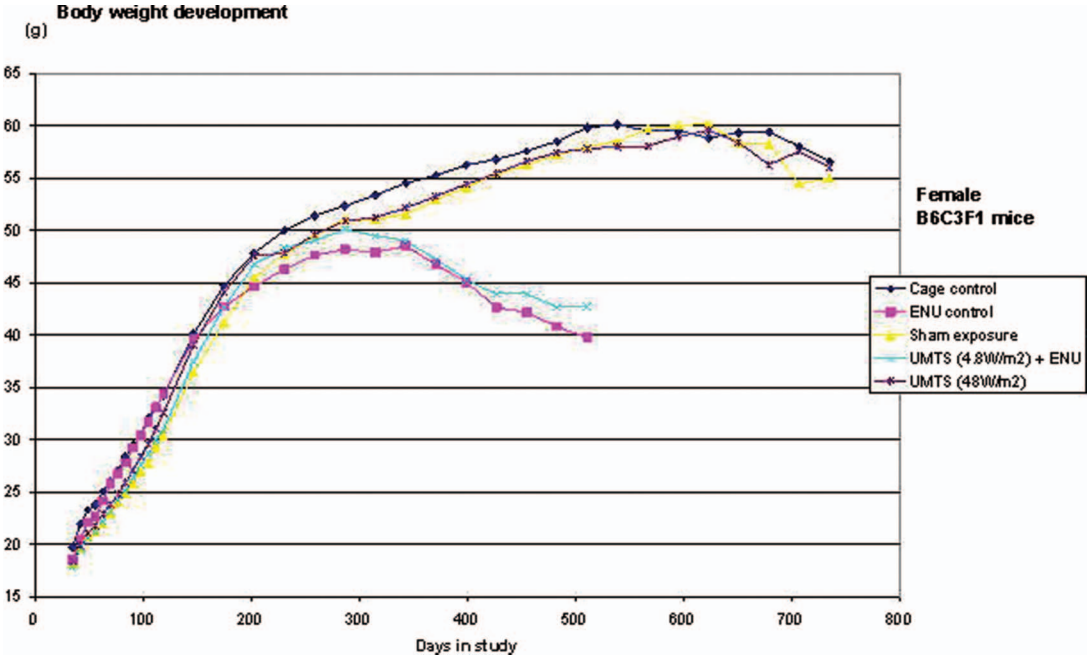

Figure 6. Body weight development of the five treatment groups (mean values in g).

Table I. Treatment groups of the F1 animals.

Group	UMTS exposure	ENU treatment	Number of mice
Cage control	–	–	60
ENU control	–	40 mg ENU/kg body weight	60
Sham exposure*	–	–	54#
UMTS + ENU	4.8 W/m^2	40 mg ENU/kg body weight	60
UMTS*	48 W/m^2	–	57#

*With regard to sham or UMTS exposure, the study was performed in a blinded way; #As the study was conducted with 54 and 57 F1 mice per group, one or two cages (3 females per cage) in the exposure unit were left without animals.

Table II. UMTS exposure summary data (48 W/m^2).

No. of mice per cage (related to study stage)	Whole-body SAR [W/kg]	Standard deviation [%]
1 mature female (30 g)	3.84	48.8
1 mature female (30 g)	4.48	40.8
and 3 pups (2 g each)	0.62	45.6
3 young females (12.5 g each)	5.76	46.0
3 old females (55 g each)	1.19	41.0

Average values and standard deviations of the calculated whole-body SAR (power density 48 W/m^2) in typical study phases (dissimilar number of mice per cage, different body masses). Each value represents up to 12 different postures/configurations of the freely-moving mouse/mice in a cage.

Histopathology

Table III gives an overview of the observed neoplastic and pre-neoplastic lesions in the target organs of all treatment groups. After up to two years of lifetime, B6C3F1 female mice of the cage control, sham exposure, and UMTS 'high-dose' groups revealed comparable tumour incidences in the protocol organs. With respect to tumour behavior (benign or malignant), tumour multiplicity, or tumour metastasising potential (originating from the protocol organs), there were no differences between the UMTS 'high-dose' and sham exposure groups. The only exception found was a markedly increased number of pre-neoplastic liver foci in the UMTS 'high-dose' group as compared to the cage controls (34/56 vs. 20/60) and the sham control group (18/54).

As expected, tumour incidence and tumour spectrum in the B6C3F1 mice were increased by maternal ENU treatment causing markedly higher incidences of lung and liver neoplasms in the two ENU-treated groups as compared to the cage controls and the other groups. In addition, brain tumours were observed exclusively in several ENU-treated mice, with seven tumours such as mixed glioma, oligodendroglioma, or meningioma in the ENU control group and one oligodendroglioma and one astrocytoma in the ENU/UMTS group (Table III).

Furthermore, analysis of the neoplastic and pre-neoplastic lesions in the two ENU groups using two-tailed Fisher test revealed some remarkable findings.

Table III. Incidences of neoplastic and pre-neoplastic lesions of the protocol organs.

Lesions	Cage control	ENU	Sham control	UMTS [4.8 W/m^2] + ENU	UMTS [48 W/m^2]
Animal totals	(60)	(60)	(60)	(60)	(60)
Cerebrum	[60]	[60]	[54]	[58]	[55]
Mixed Glioma [M]	**0** (0%)	**1** (2%)	**0** (0%)	**0** (0%)	**0** (0%)
Oligodendroglioma [M]	**0** (0%)	**3** (5%)	**0** (0%)	**0** (0%)	**0** (0%)
Oligodendroglioma [B]	**0** (0%)	**2** (3%)	**0** (0%)	**1** (2%)	**0** (0%)
Astrocytoma [B]	**0** (0%)	**0** (0%)	**0** (0%)	**1** (2%)	**0** (0%)
Meningioma [B]	**0** (0%)	**1** (2%)	**0** (0%)	**0** (0%)	**0** (0%)
Lungs	[60]	[60]	[54]	[58]	[56]
Bronchiolo-Alveolar Carcinoma(Ta) [M]	**2** (3%)	**33***** (55%)	**0** (0%)	**45***** (78%)	**1** (2%)
Bronchiolo-Alveolar Adenoma(Ta) [B]	**3** (5%)	**27***** (45%)	**2** (4%)	**36***** (62%)	**2** (4%)
Bronchiolo-Aveolar hyperplasia	**1** (2%)	**3** (5%)	**0** (0%)	**8*** (14%)	**1** (2%)
Liver	[60]	[60]	[54]	[58]	[56]
Hepatocellular Carcinoma(Ta) [M]	**15** (25%)	**31**** (52%)	**6** (11%)	**30**** (52%)	**9** (16%)
Hepatocellular Adenoma(Ta) [B]	**46** (77%)	**30**** (50%)	**37** (69%)	**49** (84%)	**46** (82%)
Hepatoblastoma(Ta) [M]	**3** (5%)	**1** (2%)	**1** (2%)	**1** (2%)	**2** (4%)
Hemangiosarcoma(Ta) [M]	**1** (2%)	**0** (0%)	**1** (2%)	**0** (0%)	**2** (4%)
Hemangioma(Ta) [B]	**1** (2%)	**0** (0%)	**1** (2%)	**0** (0%)	**2** (4%)
Focus/foci of hepatocellular alteration	**20** (33%)	**17** (28%)	**18** (33%)	**30** (52%)	**34**** (61%)
Bile duct hyperplasia	**0** (0%)	**1** (2%)	**0** (0%)	**1** (2%)	**0** (0%)
Kidneys	[60]	[60]	[54]	[58]	[56]
Renal Tubule Carcinoma [M]	**0** (0%)	**1** (2%)	**0** (0%)	**2** (3%)	**0** (0%)
Renal Tubule Adenoma [B]	**0** (0%)	**1** (2%)	**0** (0%)	**0** (0%)	**1** (2%)
Spleen	[60]	[60]	[54]	[58]	[56]
Hemangiosarcoma [M]	**0** (0%)	**0** (0%)	**1** (2%)	**0** (2%)	**1** (2%)
Hemangioma [B]	**0** (0%)	**0** (0%)	**0** (0%)	**1** (2%)	**0** (0%)
Stromal Hyperplasia	**0** (0%)	**1** (2%)	**0** (0%)	**0** (0%)	**0** (0%)
Hematop./Lymphoret. Tissue[$]	[60]	[60]	[54]	[58]	[56]
Lymphoma [M]	**24** (40%)	**4** (7%)	**17** (32%)	**4** (7%)	**16** (29%)
Histiocytic Sarcoma [M]	**2** (3%)	**3** (5%)	**3** (6%)	**1** (2%)	**0** (0%)

Figures in [brackets] represent the number of animals from which this tissue was examined microscopically.
No neoplastic or preneoplastic lesion in cerebellum, gall bladder and mesenterial lymph nodes.
[B] Benign tumour/[M] malignant tumour.
Significance of difference in a pairwise Fisher's test between cage control and treatment groups: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.
[$]The incidences of neoplasms of the hematopoietic/lymphoreticular tissue refer to the limited number of protocol organs and macroscopic lesions examined.

The tumour rates of the liver (51/58 vs. 44/60) and lung (50/58 vs. 42/60) were obviously increased in the ENU/UMTS group as compared to the ENU control group (Table IV). Moreover, incidences of hepatocellular adenoma(s) (49/58 vs. 30/60) and bronchiolo-alveolar carcinoma(s) (45/58 vs. 33/60) were significantly increased in the ENU groups after lifetime UMTS exposure (Table V).

In respect to bronchiolo-alveolar carcinoma(s) (39/58 vs. 18/60) and hepatocellular adenoma(s) (38/58 vs. 16/60), tumour multiplicity was significantly increased in the ENU/UMTS group as compared to the ENU control group (Table VI).

The incidence of metastasising lung carcinoma(s) in the two ENU groups was doubled (15/58 vs. 7/60) by the long-term UMTS exposure of the mice (Table VII).

The incidence of pre-neoplastic foci of hepatocellular alteration also increased significantly in the

Table IV. Tumour incidences in lungs and liver, ENU groups only.

Treatment *Lesions*	ENU	UMTS [4.8 W/m^2] + ENU
Animal totals	(60)	(60)
Lungs	[60]	[58]
Bronchiolo-Alveolar Adenoma(Ta) [B] And/ Or Carcinoma(Ta) [M]	**42** (70%)	**50*** (86%)
Liver	[60]	[58]
Hepatocellular Adenoma (Ta) [B] And/Or Carcinoma(Ta) [M]/ Hepatoblastoma [M]	**44** (73%)	**51** (88%)

Figures in [brackets] represent the number of animals from which this tissue was examined microscopically.
[B] Benign tumour/[M] malignant tumour.
Significance of difference in a pairwise Fisher's test between ENU and UMTS/ENU group: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Table V. Tumour incidences in lungs and liver (benign/malignant), ENU groups only.

Lesions	ENU	UMTS [4.8 W/m^2] + ENU
Animal totals	(60)	(60)
Lungs	[60]	[58]
Bronchiolo-Alveolar Carcinoma(Ta) [M]	**33** (55 %)	**45*** (78 %)
Bronchiolo-Alveolar Adenoma(Ta) [B]	**27** (45 %)	**36** (62 %)
Liver	[60]	[58]
Hepatoblastoma [M]	**1** (2 %)	**1** (2 %)
Hepatocellular Carcinoma(Ta) [M]	**31** (52 %)	**30** (52 %)
Hepatocellular Adenoma(Ta) [B]	**30** (50 %)	**49***** (85 %)

Significance of difference in a pairwise Fisher's test between ENU and UMTS/ENU group: $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.
[B] Benign tumour/[M] malignant tumour.
Figures in [brackets] represent the number of animals from which this tissue was examined microscopically.

Table VI. Tumour incidences in lungs and liver (multiplicity), ENU groups only.

Lesions	ENU	UMTS [4.8 W/m^2] + ENU
Animal totals	(60)	(60)
Lungs	[60]	[58]
Multiple Bronchiolo-Alveolar Carcinomata [M]	**18** (30 %)	**39***** (67 %)
Single Bronchiolo-Alveolar Carcinoma [M]	**15** (25 %)	**6** (10 %)
Multiple Bronchiolo-Alveolar Adenoma(Ta) [B]	**9** (15 %)	**17** (29 %)
Single Bronchiolo-Alveolar Adenoma [B]	**18** (30 %)	**19** (33 %)
Liver	[60]	[58]
Multiple Hepatoblastomata [M]	**1** (2 %)	**0** (0 %)
Single Hepatoblastoma [M]	**0** (0 %)	**1** (2 %)
Multiple Hepatocellular Carcinomata [M]	**7** (12 %)	**15** (26 %)
Single Hepatocellular Carcinoma [M]	**24** (40 %)	**15** (26 %)
Multiple Hepatocellular Adenomata [B]	**16** (27 %)	**38***** (66 %)
Single Hepatocellular Adenoma [B]	**14** (23 %)	**11** (19 %)

Significance of difference in a pairwise Fisher's test between ENU and UMTS/ENU group: $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.
[B] Benign tumour/[M] malignant tumour.
Figures in [brackets] represent the number of animals from which this tissue was examined microscopically.

ENU/UMTS group as compared to the ENU control group (30/58 vs. 17/60). As examples of a rare lesion, two cases of bronchiolo-alveolar carcinoma metastasising into the brain (Figure 7) were diagnosed exclusively in the ENU/UMTS treatment group.

Table VII. Incidences of metastasising tumours in lungs and liver, ENU groups only.

Lesions	ENU	UMTS [4.8 W/m^2] + ENU
Animal totals	(60)	(60)
Lungs	[60]	[58]
Metastasising Bronchiolo-Alveolar Carcinoma(Ta) [M]	**7** (12 %)	**15** (26 %)
Non-Metastasising Bronchiolo-Alveolar Carcinoma(Ta) [M]	**26** (43 %)	**30** (52 %)
Liver	[60]	[58]
Metastasising Hepatoblastomata [M]	**1** (2 %)	**0** (0 %)
Non-Metastasising Hepatoblastoma [M]	**0** (0 %)	**1** (2 %)
Metastasising Hepatocellular Carcinoma(Ta) [M]	**11** (18 %)	**10** (17 %)
Non-Metastasising Hepatocellular Carcinoma(Ta) [M]	**20** (33 %)	**20** (33 %)

Significance of difference in a pairwise Fisher's test between ENU and UMTS/ENU group: $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.
[M] Malignant tumour.
Figures in [brackets] represent the number of animals from which this tissue was examined microscopically.

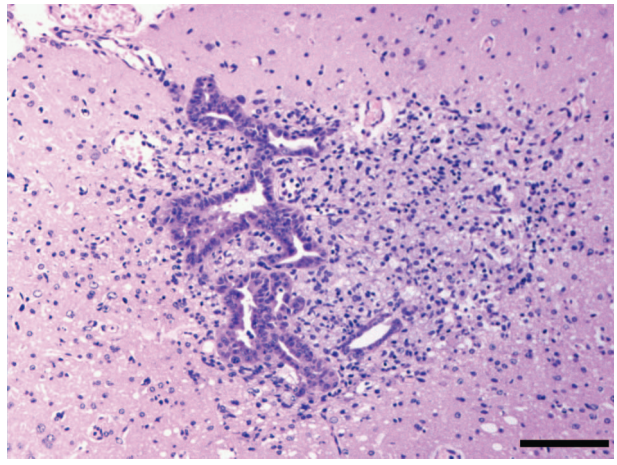

Figure 7. Cerebrum, metastasis from primary tumour in the lung (bronchiolo-alveolar carcinoma). Female B6C3F1 mouse, ENU/UMTS treatment, H&E stain, scale bar 50 μm.

Discussion and conclusion

Health impairment from exposure to electromagnetic fields is still a matter of controversial discussions worldwide. Besides epidemiological investigations retrospectively analysing the EMF exposure, i.e., from wireless communication technologies/cell phone use, several animal studies have been performed exposing rodents non-thermally to radio-frequency EMF of various characteristics (namely different frequencies, SAR values, field orientations etc.) with diverse study end points over varying periods of time.

To our knowledge, experimental studies using UMTS exposure per se are rare and most RF-EMF cancer studies are focused either on a suspected initiating or a promoting/cocarcinogenic exposure effect. In this study, both these aspects have been addressed simultaneously. In addition, experimental studies often have the disadvantage of a relatively late study start at several weeks of age and therefore, in contrast to the present study, do not expose the juvenile animals as early as possible.

Based on electromagnetic field characteristics of the third generation of wireless communication systems in Europe – UMTS – this paper describes a one-generation study with lifetime exposure starting as early as possible in the developing organism, namely prenatally as embryo-fetal exposure, meaning that B6C3F1 hybrids were born in the electromagnetic exposure device and maintained within EMF for up to two years' lifetime.

Continuous temperature monitoring in the exposure device and series of body temperature measurements were performed prior to the start of the study. In the thermoregulatory region, the animals are able to compensate an additional heat load (i.e., from RF) through physiologic regulation to maintain a constant body temperature (Ebert et al. 2005). In several pre-studies, this thermoregulatory mechanism was verified by demonstrating a constant body temperature during exposure and by a temperature fall directly after the end of the exposure/heat load (e.g., 2 GHz, 250 W/m^2 cw exposure). A non-thermal EMF exposure can thus be stated for the power density of 48 W/m^2 applied to the high-dose group in our study as well as for the 4.8 W/m^2 intensity used in the ENU/UMTS group. In addition, the six-week UMTS pre-study (exposure start on day 6 p.c., 1966 MHz UMTS signal, 48 W/m^2, 20 h/d) revealed no effects on litter size or neonatal mortality until four weeks post partum. Rectal body temperature measurements in adult B6C3F1 mice after two days of exposure (UMTS signal, 48 W/m^2, 20 h/d) indicated a 'non-thermal' exposure level in the UMTS study set-up as well.

Furthermore, the long-term exposure was conducted with only approximately one-fifth of the power density (48 W/m^2) of the maximally tested 260 W/m^2 electromagnetic field, and the exposure level of 4.8 W/m^2 in the ENU mouse model with lifetime UMTS exposure was again reduced to one tenth. However, rectal temperature measurements in the pregnant maternal mice, newborn pups, and young mice were not performed during the study.

Histopathological examination demonstrated similar tumour incidences for the UMTS exposure at 48 W/m^2, sham exposure, and cage control groups. On the other hand, different incidences of liver and lung neoplasms (see Tables IV–VII) were diagnosed in the two ENU groups with increased tumour incidences in the ENU group subjected to additional lifetime UMTS exposure at 4.8 W/m^2. Bearing in mind the risk of false-positive results when multiple comparisons are conducted (Haseman 1983), highly significant increases such as in hepatocellular adenoma(s) cannot be ascribed to chance alone. Furthermore, histopathological analysis (i.e., by two-tailed statistical testing) for each tumour type separately and comparison of benign and malignant lesions of the same cell type both separately and in combination is recommended by international guidelines (i.e., U.S. Environmental Protection Agency [EPA 2005]). Nevertheless, the interrelationship of these (significant) findings must be emphasised and special care should be taken in weighting these results.

A very high incidence of liver tumours was diagnosed in all groups including controls. In the control groups, the liver tumour rate was higher than expected as spontaneous occurrence and exceeded respective historical control data (Haseman et al. 1999, Dasenbrock et al. 2005, Tillmann et al. 2007). As possible source a *Helicobacter hepaticus* infection was suspected (Stout et al. 2008), and subsequent analysis of deep frozen sera (retained samples) confirmed the presence of *Helicobacter* antibodies in the parental mice at delivery and in the offspring generation at various time points during the study. In addition, special stainings (Steiner's modification of the Warthin-Starry silver staining) of preserved randomly sampled liver tissue also demonstrated helical microorganisms in the liver parenchyma of the B6C3F1 mice.

Scoring for *Helicobacter* species during health supervision for a long time was not performed routinely by laboratory animal suppliers and in research facilities, and one should assume (in particular) a high number of unrecognised *Helicobacter* infections in mouse colonies. Recently, Pritchett-Corning and colleagues (2009) reported a *Helicobacter* prevalence in about 20% of European laboratory mouse samples ($n > 90{,}000$) over a five-year period, whereas Taylor et al. (2007) and Bohr et al. (2006) demonstrated *Helicobacter* species in 79 % and 87.5 % of the tested colonies/mouse lines in Europe. Since an influence of *Helicobacter* hepaticus infection on liver tumorigenesis was recently confirmed by others (Stout et al. 2008) and also as a precaution, all liver data of this study were excluded from interpretation so as to avoid the discussion of an influence of *Helicobacter* presence in all groups of the study (additional but confounding factor) and/or to avoid the debate on a comparison with the huge number of historical (tumour) data collected in laboratory animal studies with a (possible) unrecognised *Helicobacter* infection.

Even without consideration of the liver pathology data, however, microscopic examination of the lungs revealed a distinct promoting/increasing effect of chronic UMTS exposure in this ENU mouse model concerning tumour incidence (Table IV), tumour malignancy (Table V), tumour multiplicity (Table VI) and the metastasising potential (Table VII) in the ENU/UMTS group as compared to the ENU controls. This UMTS exposure effect observed in our study must definitely be clarified, as RF-EMF-related effects have been suspected for decades. Even if it is unlikely that just one mechanism, if any, should be responsible for all the reported biological effects associated with (non-thermal) electromagnetic field exposure, a recent review by Hardell and Sage (2008) listed a large variety of such effects, and these included not only neurological effects, neurodegenerative diseases, immune system deregulation, allergic and inflammatory responses, miscarriage, and cardiovascular effects, but they also provided evidence of genotoxic effects, impact on childhood leukemia, breast cancer and brain tumour incidences from RF-EMF. In summary, the authors considered it justified to conclude that EMF exposure can change gene and/or protein expression. On the other hand, the authors stated that this evidence was based on very few early 'omics' studies and must be clarified. As a possible biological mechanism of this EMF-related effect the intracellular formation of free radicals is given, which could damage macromolecules (e.g., DNA). The claim put forth by physicists that the transported/emitted energy of all non-ionising radiation (e.g., cell phone exposure) is too weak (<12 eV) to directly break down chemical compounds or to damage DNA would be rebutted by identification of a specific catalytic biochemical pathway. All theories of a mode of action of electromagnetic field exposure, however, so far are hypothetical and unproven. Therefore, positive findings related to EMF exposure such as the enhanced lung tumorigenesis in UMTS-exposed and ENU-pretreated mice in our study must be confirmed by additional studies and their possible mechanism by EMF exposure, if any, must be verified with care.

Today, experimental studies with chronic UMTS exposure are still rare, and published papers do not reflect all aspects that are necessary for comprehensive risk evaluation. Having in mind that a sound (well-founded) carcinogenicity study for testing chemicals, i.e., according to OECD guideline No. 451, should be conducted in male and female animals with at least three different treatment (RF intensities) groups plus controls and without the limitations resulting from other well-known (budget-related) shortcomings in this study (limited space in the exposure unit, technical feasibility: one sex, one ENU/UMTS exposure level exclusively, restricted extent of histopathological examinations), this mouse experiment with long-term UMTS exposure must be considered as a pilot study.

In contrast, this study outline may help to fill the gap of long-term EMF exposure in juvenile individuals, as laboratory animal studies using commercial sources/breeders may often have the disadvantage of a late exposure start (i.e., after weaning, delivery, and a quarantine period).

In conclusion, although the authors are aware of limitations in the design of this pilot study (i.e., one gender, one 'dose' group, limited number of protocol organs), the histopathological results point at a distinct cocarcinogenic effect of chronic UMTS exposure in this ENU mouse model, whose mechanism has to be verified. While a ten times higher exposure intensity (i.e., 48 W/m^2) alone was non-effective with regard to mouse tumorigenesis, the possible link, if any, between RF exposure and carcinogenesis as demonstrated in this ENU mouse model needs to be confirmed. It would currently be far from reputable, however, to use these limited results (cocarcinogenic effects of UMTS exposure in ENU-induced mouse tumorigenesis) for predicting health effects of cell phone exposure in humans.

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